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(57) Abstract: The invention provides a pharmaceutical composition comprising sildenafil or a pharmaceutically acceptable salt thereof admixed with excipients in a multicomponent pharmaceutical composition, wherein a first component is adapted to deliver sildenafil rapidly to promote fast onset of action, and a further component is adapted to deliver the sildenafil from dose to dose, wherein the sildenafil is delivered from dose to dose within the therapeutic window.



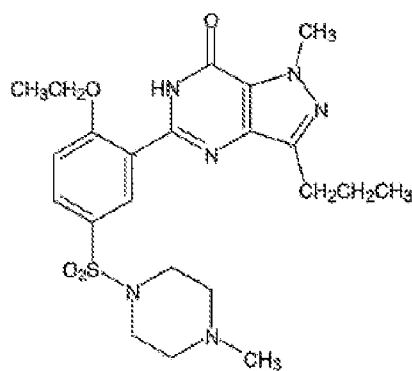
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## NEW PHARMACEUTICAL FORMS OF SILDENAFIL

The present invention relates to novel forms and formulations of sildenafil. In particular, the present invention relates to the use of such forms and formulations of sildenafil in the treatment of male sexual dysfunction.

Sildenafil is generically described in US patent 5,250,534 as a selective cGMP PDE inhibitor useful in the treatment of cardiovascular disorders.

Sildenafil free base i.e. 5-{2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, is specifically described in US patent 6,204,383 B1 as an agent with pharmaceutical utility in the treatment of male sexual dysfunction. Sildenafil free base has the following structure:



We have found phenol co-crystals improve solubility profile of sildenafil to bring about rapid onset of action. The phenol co-crystals improve solubility at all levels of pH therefore improving the performance of the drug during fasted and non-fasted stomach conditions.

Example 1 illustrates the preparation of solid sildenafil by the evaporation of a solution in a mixture of dichloromethane and methanol. Examples 2 and 6 describe a solution of sildenafil iodide in dichloromethane, but this is not isolated as a solid product.

The citrate salt of sildenafil (sildenafil citrate) is currently marketed as Viagra® in numerous countries including the USA and the European Union.

The following patents describe various uses, compositions, formulations, and combinations containing sildenafil. These patents are incorporated herein by reference. US Patents 6,743,799, 6,743,443, 6,740,793, 6,740,306, 6,737,070, 6,735,470, 6,734,186, 6,730,786, 6,730,689, 6,730,674, 6,730,505, 6,723,345, 6,713,487, 6,713,295, 6,706,892, 6,706,720, 6,706,691, 6,706,682, 6,706,283, 6,699,991, 6,696,495, 6,696,072, 6,693,122, 6,689,118, 6,686,349, 6,689,338, 6,683,080, 6,682,716, 6,673,987, 6,673,841, 6,673,778, 6,670,386, 6,669,961, 6,667,398, 6,667,060, 6,660,756, 6,656,935, 6,656,452, 6,656,385, 6,650,943, 6,649,606, 6,645,965, 6,645,954, 6,645,528, 6,645,466, 6,644,309, 6,642,274, 6,642,244, 6,638,937, 6,635,638, 6,635,274, 6,634,576, 6,632,419, 6,630,504, 6,627,632, 6,627,234,

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6,077,841, 6,075,028, 6,066,735, 6,051,594, 6,043,252, 6,037,346, 6,013,663, 6,007,824,  
5,981,563, 5,958,926, 5,955,611, 5,874,437, 5,858,694 are incorporated herein by reference.

In particular all information concerned with preparing the sildenafil active moiety from readily available starting materials is incorporated in full. In addition, it should be appreciated that  
30 all information concerning the incorporation of sildenafil into a formulation is herein incorporated by reference as is information on the use of such formulations in medical therapy.

Sildenafil is the active ingredient in Viagra® which is a potent inhibitor of PDE receptors in particular the subtype 5 which is associated with male erectile dysfunction. Sildenafil is a potent muscle relaxant associated with the arterial walls in the cardio vascular system.  
35 Sildenafil also antagonises other PDE sub types such as PDE 2 and 6 which are associated with cardiac contractility and blue haze respectively.

Whilst Viagra is a very potent and selective drug its pharmacological profile is far from ideal. It is slow in its absorption through the gut wall and therefore it can take 1 to 2 hours for onset of action since it's delivered in a bolus from a swallow tablet it is absorbed all at once and is then metabolized quickly and expelled from the body leaving a deficit in the blood stream and causing potency to drop and then disappear long before the next dose is due. This is a real problem for sufferers of erectile dysfunction trying to plan their sexual encounter to be coincidental with having sufficient medicine in their blood stream but not such a vast excess that unwanted side effects occur such as blue haze and cardiac contractility.

There is a need for a technical solution to this long standing problem and one which solves all three problems at the same time i.e., rapidity, longevity from dose to dose and one which delivers the drug within the therapeutic window between dose to dose. A product line extender having such superior properties would be an obvious commercial success. The fact that no such product has ever been made or described is testament to the fact that there are no obvious solutions to this issue.

A first step in solving this problem is finding variants of the product, i.e. rapidity longevity and maintenance within the therapeutic window from dose to dose which possess physical and chemical characteristics which are conclusive to addressing one or more of the problems associated with PDE 5 inhibition such as rapidity of action duration of effect and sustenance within the therapeutic window for prolonged periods of time from dose to dose.

Co-crystals of many substances are known, co-crystals impart properties of the co-crystal partner (co-crystal former, or co-former) on the target molecule. There is no rational reason why one product forms co crystals whilst others do not even if a target molecule is miss selected it is not possible to pre judge the compounds which would form co crystals and to second guess what those co crystals partners might be. Sildenafil is commercially available as the citrate salt and is therefore a good choice as a starting material. Other salts of sildenafil have been disclosed in the art however none have been tested for rapidity or duration of effect or for any tendency to be within the therapeutic window from dose to dose.

It has been surprisingly found that one class of salts lends itself to forming superior adduct with sildenafil and which adducts possess superior properties. These are the fatty acid salts.

It has also been surprisingly found that specific formulation technologies can be used in conjunction with co-crystals of phenolic compounds and or fatty acids of sildenafil to engineer a superior product possessing superior properties as outlined above, that is to say a more rapidly acting product having a PK profile within the therapeutic window from dose to dose, Information on formulations technologies, co crystals with sildenafil and fatty acid salts of sildenafil are provided herein

Accordingly, the present invention relates to various aspects.

In one aspect, the invention provides co-crystals of sildenafil with a group of phenolic compounds. In particular, the invention provides a co-crystal, which co-crystal comprises sildenafil and a co-crystal former, which co-crystal former is a compound which comprises a phenol moiety. The co-crystal former may be a compound of formula (I) as defined herein.

5 Another aspect relates to fatty acid salts of sildenafil optionally in the form of co-crystals.

The invention provides a salt of sildenafil with a long chain fatty acid. The salt may be amorphous or crystalline. The long chain fatty acid typically has formula  $R-C(O)OH$  wherein R is  $C_{6-24}$  alkyl or  $C_{6-24}$  alkenyl.

10 Another aspect relates to a pharmaceutical composition comprising sildenafil and/or a pharmaceutically acceptable salt or co-crystal thereof admixed with excipients in a multicomponent pharmaceutical composition, wherein a first component is adapted to deliver sildenafil rapidly to promote fast onset of action, and a further component is adapted to deliver the sildenafil from dose to dose wherein the sildenafil is delivered from dose to dose within the  
15 therapeutic window.

The pharmaceutical composition of the invention may comprise sildenafil and/or a pharmaceutically acceptable salt or co-crystal thereof admixed with excipients in a multicomponent pharmaceutical composition, wherein a first component is adapted to deliver sildenafil rapidly to promote fast onset of action, a second component is adapted to deliver the sildenafil  
20 from dose to dose, and a third component wherein the sildenafil is delivered from dose to dose within the therapeutic window.

In one embodiment the pharmaceutical composition of the invention comprises a first component which is adapted to deliver the sildenafil rapidly to promote a fast onset of action, and a second component which is adapted to deliver the sildenafil from dose to dose, and  
25 which is further adapted to deliver the active ingredient from dose to dose within the therapeutic window. The pharmaceutical composition may be a dosage form, typically a solid dosage form, for instance a swallow tablet.

The invention further provides a pharmaceutical composition comprising sildenafil or a pharmaceutically acceptable salt thereof, which may be as further defined herein (for instance, as in the immediately preceding paragraph) wherein the pharmaceutical composition is  
30 in the form of a swallow tablet.

Typically the dosage form, for instance a tablet (swallow tablet), comprises two components:

a first component which is adapted to deliver the sildenafil rapidly to promote a fast  
35 onset of action, and

a second component which is adapted to deliver the sildenafil from dose to dose, and which is further adapted also to deliver the active ingredient from dose to dose within the therapeutic window.

In the pharmaceutical compositions described herein (including in the dosage forms and swallow tablets) which comprise a first component and one or more further components (for instance a second component, or both a second component and a third component) the first component typically comprises from 10% to 30% by weight, for instance 20% by weight, of the total amount of sildenafil in the composition. The balance of sildenafil is present in the one or more further components. For instance, the balance of sildenafil may be present in a second component, or where second and third components are present, the balance of sildenafil is usually distributed between the second and third components. The total amount of sildenafil in the pharmaceutical compositions described herein (including in the dosage forms and swallow tablets), is often 100mg, 50mg or 25 mg.

In the pharmaceutical compositions described herein (including in the dosage forms and swallow tablets) which comprise a first component and a second component, the first component typically comprises from 10% to 30% by weight, for instance 20% by weight, of the total amount of sildenafil in the first and second components, and the second component typically comprises from 90% to 70% by weight, for instance 80% by weight, of the total amount of sildenafil in the first and second components. The percentage by weight here refers to the percentage by weight of sildenafil free base which the particular form of sildenafil provides (i.e. weights are quoted on a "free base" basis).

Accordingly, in some embodiments, the total amount of sildenafil in the first and second components (which again refers to the total amount of sildenafil free base which the particular form or forms of sildenafil in the first and second components provide) is 100 mg, and the first component comprises from 10mg to 30mg of sildenafil and the second component comprises from 90mg to 70mg of sildenafil. The first component may for instance comprise 20mg of sildenafil and the second component may comprise 80mg of sildenafil.

In other embodiments, the total amount of sildenafil in the first and second components is 50 mg, and the first component comprises from 5mg to 15mg of sildenafil and the second component comprises from 45mg to 35mg of sildenafil. The first component may for instance comprise 10mg of sildenafil and the second component may comprise 40mg of sildenafil.

In other embodiments, the total amount of sildenafil in the first and second components is 25 mg, and the first component comprises from 2.5mg to 7.5mg of sildenafil and the second component comprises from 17.5mg to 22.5mg of sildenafil. The first component may for instance comprise 5mg of sildenafil and the second component may comprise 20mg of sildenafil.

The sildenafil in the first component may be sildenafil free base. Alternatively, the sildenafil in the first component may be a pharmaceutically acceptable salt of sildenafil. It may for instance be sildenafil citrate. Alternatively, it may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the first component may be in the form of a co-crystal of sildenafil. For all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

The sildenafil in the second component is often a pharmaceutically acceptable salt of sildenafil. Sildenafil citrate is one preferred choice for the second component. Alternatively, the sildenafil in the second component may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the second component is sildenafil free base. In yet another embodiment, the sildenafil in the second component is in the form of a co-crystal of sildenafil, for instance a co-crystal of sildenafil with a compound which comprises a phenol moiety. For all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

The first component typically comprises from 10mg to 35mg, for instance from 10mg to 30mg, or for instance from 20mg to 25mg, of sildenafil. The first component may for instance comprise 20mg of sildenafil. The first component may alternatively comprise 25 mg of sildenafil. The sildenafil in the first component may be sildenafil free base. Alternatively, the sildenafil in the first component may be a pharmaceutically acceptable salt of sildenafil. It may for instance be sildenafil citrate. Alternatively, it may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the first component may be in the form of a co-crystal of sildenafil. For all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

The second component typically comprises from 40mg to 100mg of sildenafil, for instance from 40mg to 90mg of sildenafil, or, for example, from 50 mg to 80 mg of sildenafil. The second component may for instance comprise 80mg of sildenafil. The second component may alternatively comprise 50mg of sildenafil. The second component in some embodiments comprises from 70mg to 90mg of sildenafil, for example 80mg of sildenafil. The sildenafil in the second component is often a pharmaceutically acceptable salt of sildenafil. Sildenafil citrate is one preferred choice for the second component. Alternatively, the sildenafil in the second component may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the second component is sildenafil free base. In yet another embodiment, the sildenafil in the second component is in the form of a co-crystal of sildenafil, for instance a co-crystal of sildenafil with a compound which comprises a phenol moiety. For all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

Thus, the first component may comprise from 10mg to 35mg of sildenafil and the second component may comprise from 40mg to 100mg of sildenafil. The first component may

for instance comprise from 10mg to 30mg of sildenafil, and the second component may comprise from 40mg to 90mg of sildenafil. The first component may for instance comprise from 20mg to 25mg of sildenafil, and the second component may comprise from 50mg to 80mg of sildenafil. The first component may comprise about 20mg of sildenafil and the second component may comprise about 80mg sildenafil. Alternatively, the first component may comprise about 25mg of sildenafil and the second component may comprise about 50mg sildenafil.

The first component may be adapted to deliver sildenafil rapidly, wherein the adaptation is that the first component comprises sildenafil admixed with excipients in a manner which promotes rapid, preferably immediate, release of the sildenafil.

The first component may comprise sildenafil admixed with excipients, which may be conventional excipients, which promote immediate release.

The first component may for instance comprise from 10mg to 35mg, for example from 10mg to 30mg, or from 20mg to 25 mg, of sildenafil with such excipients which promote immediate release. It may for instance comprise 20mg, or 25mg, of sildenafil with such excipients which promote immediate release. The excipients may be conventional excipients. The sildenafil in the first component may be sildenafil free base. Alternatively, the sildenafil in the first component may be a pharmaceutically acceptable salt of sildenafil. It may for instance be sildenafil citrate. Alternatively, it may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the first component may be in the form of a co-crystal of sildenafil. For all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

The second component of the pharmaceutical composition of the invention may comprise sildenafil with excipients, for instance conventional excipients, which promote modified release.

The second component may for instance comprise from 40mg to 100mg, for example from 40mg to 90mg, or from 50mg to 80mg, of sildenafil with such excipients which promote modified release. It may for instance comprise 50mg, or 80mg, of sildenafil with such excipients. The second component may for instance comprise from 70mg to 90mg, of sildenafil, for instance 80mg sildenafil citrate, with such excipients. The excipients may be conventional excipients. The excipients which promote modified release in the second component may be polymers. The sildenafil in the second component is often a pharmaceutically acceptable salt of sildenafil. Sildenafil citrate is one preferred choice for the second component. Alternatively, the sildenafil in the second component may be a fatty acid salt of sildenafil. In another embodiment, the sildenafil in the second component is sildenafil free base. In yet another embodiment, the sildenafil in the second component is in the form of a co-crystal of sildenafil, for instance a co-crystal of sildenafil with a compound which comprises a phenol moiety. For



all these forms of sildenafil, the dosage of sildenafil, quoted on a free base basis, may be as defined above.

Another aspect of the invention provides sildenafil adapted in a multi component dosage form, such as a tablet, said dosage form being adapted in a first way to provide rapid release of sildenafil into the bloodstream, said dosage form being adapted in a second way to further provide a maintenance dose of sildenafil within the therapeutic window, and the dosage form being adapted in a third way to provide a modified or delayed release format of the sildenafil product which lasts from dose to dose.

The exact dose of each component is dependent on the choice of formulation but in general the choice of each component will be made so that the amount of active ingredient in each component delivers the right amount of drug product to ensure rapidity, longevity from dose to dose and maintenance of dose within the therapeutic window.

As a rule of thumb the total amount of sildenafil in a formulation is at least 20mg and usually 50mg to 100mg.

A preferred aspect of the invention is a product (usually a multi component dosage form, such as a tablet) which comprises:

sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as further defined herein;

a fatty acid salt of sildenafil, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and a delayed release component, comprising a bolus dose of sildenafil. Often, the sildenafil in the bolus dose is in the form of sildenafil citrate.

Another preferred aspect of the invention is a product (usually a multi component dosage form, such as a tablet) which comprises:

from 2.5mg to 25mg sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as further defined herein;

from 2.5mg to 25mg sildenafil in the form of a fatty acid salt of sildenafil as defined herein, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and

said delayed release component, comprising a bolus dose of sildenafil. The bolus dose of sildenafil may be from 20mg to 95mg sildenafil. The sildenafil in the bolus dose may be in the form of sildenafil citrate.

Another preferred aspect of the invention is a product (usually a multi component dosage form, such as a tablet) which comprises:

from 2.5 to 5mg sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as further defined herein;

from 2.5 to 15mg sildenafil in the form of a fatty acid salt of sildenafil as defined herein, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and

5 said delayed release component, comprising a bolus dose of sildenafil. The sildenafil in the bolus dose may be in the form of sildenafil citrate. The bolus dose may for example be from 10mg to 80mg sildenafil, for instance 20mg sildenafil.

Another preferred aspect of the invention is a product (usually a multi component dosage form, such as a tablet) which contains: 5mg of sildenafil co-crystals with a phenol to deliver rapidity, 15mg of sildenafil fatty acid adapted using time release technology to deliver sildenafil between onset of action and kick in of a bolus amount of delayed release component, and a bolus amount of delayed release component of sildenafil which is suitably 20mg.

Except where specified otherwise, all sildenafil doses are cited on a free base basis. Thus if the sildenafil is in the free base form, the term "80mg sildenafil", as used herein, refers to 80mg sildenafil free base. However, if the sildenafil is in the form of the citrate salt, 15 the term "80mg sildenafil" as used herein means 112mg of sildenafil citrate (if the mass of the sildenafil citrate is rounded to zero decimal places). Similarly, if the sildenafil is in the free base form, the term "20mg sildenafil", as used herein, refers to 20mg sildenafil free base. However, if the sildenafil is in the form of the citrate salt, the term "20mg sildenafil" as used herein means 28 mg of sildenafil citrate (if the mass of sildenafil citrate is rounded to zero 20 decimal places).

### **Brief Description of the Figures**

Fig. 1 shows powder X-ray diffractograms of the initial batch of sildenafil (P42) as received (upper diffractogram) and the published P42 form: QEGTUT anhydrous form (lower 25 diffractogram).

Fig. 2 shows powder X-ray diffractograms of the initial P42 batch as received (upper diffractogram) and after grinding (lower diffractogram).

Fig. 3 shows powder X-ray diffractograms of P42 polymorphs P42 Form I (upper diffractogram) and P42 Form II (lower diffractogram).

30 Fig. 4 shows powder X-ray diffractograms of P42 polymorphs P42-A (first and top diffractogram), P42-B (second diffractogram), P42-C (third diffractogram), P42-D (fourth diffractogram) and P42-E (fifth and bottom diffractogram).

Fig. 5 is a diagram summarising the different behaviours of forms of P42.

35 Fig. 6 shows powder X-ray diffractograms of the following new multicomponent forms of P42: P42-I-A (first and top diffractogram), P42-I-B (second diffractogram), P42-III (third diffractogram), P42-IV-A (fourth diffractogram), P42-IV-B (fifth diffractogram), P42-V-A (sixth and bottom diffractogram).

Fig. 7 shows powder X-ray diffractograms of the following new multicomponent forms of P42: P42-VI-B (first and top diffractogram), P42-VI-C (second diffractogram), P42-VI-D (third diffractogram), P42-VI-E (fourth diffractogram), P42-VII (fifth diffractogram), P42-VIII (sixth diffractogram) and P42-IX (sixth and bottom diffractogram).

5 Fig. 8 shows the dissolution profile of 25mg Viagra tablets in 0.01M hydrochloric acid.

Fig. 9 shows the dissolution profile of 50mg Viagra tablets in 0.01M hydrochloric acid.

10 Fig. 10 shows the dissolution profile of 100mg Viagra tablets in 0.01M hydrochloric acid.

Fig. 11 shows the dissolution profile in 0.01M hydrochloric acid of the sustained-release core development formulation no. 16CF25/026 comprising sildenafil citrate, as described in Example 67.

15 Fig. 12 shows the dissolution profile in 0.01M hydrochloric acid of the immediate-release development formulation no. 16CF25/027 comprising sildenafil citrate, as described in Example 67.

Fig. 13 shows the dissolution profile of 25mg Viagra tablets in pH 4.5 phosphate buffer.

20 Fig. 14 shows the dissolution profile of 50mg Viagra tablets in pH 4.5 phosphate buffer.

Fig. 15 shows the dissolution profile of 100mg Viagra tablets in pH 4.5 phosphate buffer.

25 Fig. 16 shows the dissolution profile in pH 4.5 phosphate buffer of the sustained-release core development formulation no. 16CF25/026 comprising sildenafil citrate, as described in Example 67.

Fig. 17 shows the dissolution profile in pH 4.5 phosphate buffer of the immediate-release development formulation no. 16CF25/027 comprising sildenafil citrate, as described in Example 67.

30 Fig. 18 shows the dissolution profile of 25mg Viagra tablets in pH 6.8 phosphate buffer with 0.125% CTAB.

Fig. 19 shows the dissolution profile of 50mg Viagra tablets in pH 6.8 phosphate buffer with 0.125% CTAB.

Fig. 20 shows the dissolution profile of 100mg Viagra tablets in in pH 6.8 phosphate buffer with 0.125% CTAB.

35 Fig. 21 shows the dissolution profile in pH 6.8 phosphate buffer with 0.125% CTAB of the sustained-release core development formulation no. 16CF25/026 comprising sildenafil citrate, as described in Example 67.

Fig. 22 shows the dissolution profile in pH 6.8 phosphate buffer with 0.125% CTAB of the immediate-release development formulation no. 16CF25/027 comprising sildenafil citrate, as described in Example 67.

5 Fig. 23 shows the dissolution profile in 0.01M hydrochloric acid of the immediate-release development formulation no. 16CF25/033 comprising sildenafil free base, as described in Example 68.

Fig. 24 shows the dissolution profile in pH 4.5 phosphate buffer of the immediate-release development formulation no. 16CF25/033 comprising sildenafil free base, as described in Example 68.

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### **Detailed Description of the Invention**

Information on how to make and use the invention is provided herein. The references mentioned herein are also incorporated herewith. The pharmacological test methods are also incorporated.

15

The term “alkyl”, as used herein, refers to a linear or branched chain saturated hydrocarbon radical. A “C<sub>n-m</sub> alkyl” refers to an alkyl having from n to m carbon atoms. Thus, an alkyl group may be a C<sub>1-25</sub> alkyl group, a C<sub>1-24</sub> alkyl group, a C<sub>6-24</sub> alkyl group, a C<sub>1-10</sub> alkyl group, a C<sub>1-6</sub> alkyl group or a C<sub>1-4</sub> alkyl group. Examples of a C<sub>1-10</sub> alkyl group are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl or decyl. Examples of C<sub>1-6</sub> alkyl groups are methyl, ethyl, propyl, butyl, pentyl or hexyl. Examples of C<sub>1-4</sub> alkyl groups are methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. If the term “alkyl” is used without a prefix specifying the number of carbons anywhere herein, it has from 1 to 4 carbons.

20

The term “alkenyl”, as used herein, refers to a linear or branched chain hydrocarbon radical comprising one or more double bonds. A “C<sub>n-m</sub> alkenyl” refers to an alkenyl having from n to m carbon atoms. Thus, an alkenyl group may be a C<sub>2-25</sub> alkenyl group, a C<sub>2-24</sub> alkenyl group, a C<sub>6-24</sub> alkenyl group, a C<sub>2-10</sub> alkenyl group, a C<sub>2-6</sub> alkenyl group or a C<sub>2-4</sub> alkenyl group. Examples of a C<sub>2-10</sub> alkenyl group are ethenyl (vinyl), propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl or decenyl. Examples of C<sub>2-6</sub> alkenyl groups are ethenyl, propenyl, butenyl, pentenyl or hexenyl. Examples of C<sub>2-4</sub> alkenyl groups are ethenyl, i-propenyl, n-propenyl, s-butenyl or n-butenyl. Alkenyl groups typically comprise one or two double bonds.

30

The term “co-crystal” (or “co crystal” or “cocrystal”) as used herein means a solid that is a crystalline single phase material comprising two or more different molecular and/or ionic compounds which are neither solvents nor simple salts (S. Aitipamula et al. “Polymorphs, Salts, and Cocrystals: What’s in a Name?”, Cryst. Growth Des., 2012, 12 (5), pp 2147–2152). The two or more different molecular and/or ionic compounds in a co-crystal are generally compounds which are themselves solid at room temperature (i.e. solids at 22 °C).

35

They are typically present in the co-crystal in a definite stoichiometric ratio. In the co-crystals of the present invention, one of the two or more different molecular and/or ionic compounds is an API, sildenafil, and another of the two or more different molecular and/or ionic compounds is a co-crystal former. Indeed, the co-crystals of the present invention are pharmaceutical co-crystals. A pharmaceutical co-crystal is a crystalline single phase material comprising an API and one or more unique co-crystal formers, typically in a stoichiometric ratio. Each of the one or more co-crystal formers is a molecular or an ionic compound that is a solid at room temperature. Solvates (including hydrates) of an API that do not further comprise a co-crystal former are therefore not considered to be co-crystals. A pharmaceutical co-crystal may however include one or more solvent (e.g. acetonitrile, or water) molecules in the crystal lattice which comprises the API and the one or more unique co-crystal formers. Co-crystals can be constructed through several types of interaction, including hydrogen bonding (H-bonding), pi stacking, and van der Waals forces. However, co-crystals often rely on hydrogen-bonded assemblies between neutral molecules of an API and another (co-crystal former) component.

The dosage forms of the present invention are proven to work as pde5 inhibitors and find use in the treatment of male erectile dysfunction. Fresh frozen human penis was obtained from IIAM (Pennsylvania). Tissue was thawed at room temperature, the corpus cavernosum was dissected from the penis to yield approximately 2-4 g of tissue and the following isolation protocol was followed. Tissue was coarsely chopped in ice-cold isotonic buffer (35 ml) containing 250 mM sucrose, 1 mM EDTA, 0.5 mM PMSF and 20 mM HEPES, pH 7.2, and the mixture subjected to brief (1 min.) treatment with a Silversen mixer/emulsifier. Homogenates were prepared using homogeniser tubes with Teflon pestles and a soluble fraction was prepared by centrifugation at 100,000 x g for 60 min. at 4°C. 10 ml of high speed supernatant was applied to a Pharmacia Mono Q anion exchange column (1 ml bed volume) equilibrated with buffer containing 1 mM EDTA, 0.5 mM PMSF and 20 mM HEPES, pH 7.2 (chromatography buffer). The column was then washed with 5 bed volumes of chromatography buffer, after which PDEs were eluted using a continuous gradient of 0-500 mM NaCl (total volume 35 ml) and 1 ml fractions collected.

Column fractions were assayed for PDE activity using 500 nM cGMP or 500 nM cAMP as substrate. cAMP PDE activity was also determined in the presence of 1 μM unlabelled cGMP and the PDE activity of selected fractions was determined in the presence of 10 mM CaCl<sub>2</sub> and 10 units/ml bovine brain calmodulin. Appropriate fractions were pooled and stored at 4°C during the course of the study.

Inhibition studies were performed using a substrate concentration of 500 nM throughout. All inhibitors were dissolved in DMSO and concentration-response curves were constructed over the range 3x10<sup>-10</sup> to 1x10<sup>-4</sup> M in half log increments. IC<sub>50</sub> values were calculated using the sigmoidal curve fitting algorithm of bio stat.

Human corpus cavernosum soluble PDEs were separated into three distinct fractions of activity. The first, fraction I, (designated by order of elution) represented the major PDE present and was highly selective for cGMP as substrate. This fraction was found to be insensitive to stimulation by calcium/calmodulin and was classified as PDE<sub>V</sub>. Fraction II hydrolysed cGMP and cAMP, with the latter activity being stimulated in the presence of cGMP, and was classified as PDE<sub>II</sub>, whilst fraction III was cAMP selective and this activity was inhibited in the presence of cGMP, consistent with PDE<sub>III</sub> activity.

In order to further characterise the PDE isoenzymes present in the tissue, studies were performed using a variety of inhibitors. Inhibitor studies with fractions I and II were performed using cGMP as substrate, whilst fraction III studies utilised cAMP. These studies confirmed that fraction I corresponds to PDE<sub>V</sub>, whilst fraction III was clearly identified as PDE<sub>III</sub>; fraction II (PDE<sub>II</sub>) was relatively insensitive to all the inhibitors tested.

In summary, the above investigation identified three PDE isoenzymes in human corpus cavernosum tissue. The predominant PDE was the cGMP-specific PDE<sub>V</sub>, whilst cGMP-stimulated cAMP PDE<sub>II</sub> and cGMP-inhibited cAMP PDE<sub>III</sub> were also present.

The formulations of the present inventions are tested in vitro and found to be potent and selective inhibitors of the cGMP-specific PDE<sub>V</sub>. Thus relaxation of the corpus cavernosum tissue and consequent penile erection is presumably mediated by elevation of cGMP levels in the said tissue, by virtue of the PDE inhibitory profile of the compounds of the invention.

The sildenafil summary shows the in vitro dissolution profiles for the two elements of the formulation, the inner sustained release core with 80mg sildenafil and the outer core which is an ODT with 20mg sildenafil. Guidance is to place the tablet under the tongue for 60 seconds (see caffeine summary where we tested how much caffeine dissolved by doing this as substitute for Viagra) then swallow the tablet. Described herein is our model of how the tablet dissolves based on different pH levels. We assume 20% will go into blood plasma PK from the sublingual element (some will go normal route so even if 30% dissolves not all will go sublingual). This would give us 4mg sublingual which according to other papers could deliver 4 to 5 times the dose in systemic circulation than normal, i.e. same amount as 16-20mg of normal citrate but importantly much quicker, i.e. 15mins. The rest of the tablet will be swallowed and therefore all the ODT dissolves in the stomach so the blood plasma PK will be as Pfizer ODT data the core will then dissolve slowly in the intestine. By our estimates we will deliver the equivalent sildenafil in plasma somewhere around to a normal dose of 100 mg with about 112% to 116% of AUC (so within 505b2 guidelines) modelling and or testing in humans will confirm. A two component tablet is preferred the sildenafil summary shows the in vitro dissolution profiles for the two elements of the formulation.

The present invention relates to novel pharmaceutical formulations, in particular to modified release formulations for the delivery of a therapeutically useful amount of sildenafil. Sildenafil citrate (Viagra®) is currently approved for the treatment of erectile dysfunction in male humans. Sildenafil is generically described in US patent 5,250,534 as a selective cGMP  
5 PDE inhibitor useful in the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis. Sildenafil is specifically described in US patent 6,204,383 B1 as an agent with pharmaceutical utility in the treatment of male sexual dysfunction (MED).

The physiological mechanism of erection of the penis involves release of nitric oxide  
10 (NO) in the corpus cavernosum during sexual stimulation. (NO) then activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing inflow of blood. Sildenafil has no direct relaxant effect on isolated human corpus cavernosum, but enhances the effect of nitric oxide by inhibiting phosphodiesterase type5 (PDE5), which is re-  
15 sponsible for degradation of cGMP in the corpus cavernosum. When sexual stimulation causes local release of (NO), inhibition of PDE5 by sildenafil causes increased levels of cGMP in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum. Sildenafil at recommended doses has no effect in the absence of sexual stimulation.

20 Sildenafil citrate in currently marketed swallow tablets is available in three dosage forms i.e. 25 mg, 50 mg and 100 mg of sildenafil calculated as the free base. For currently marketed swallow tablets, the time for maximum plasma concentrations of sildenafil is between 0.5 and 2 hours when the patient is in a fasting state, but is delayed, on average, by 1 hour when sildenafil is taken with a high fat meal. After the initial variable delay in the onset  
25 of action, a therapeutic effect is maintained for approximately 2 hours, followed by a diminished response for about a further 2 hours.

When administering a conventional swallow tablet from which the active moiety is absorbed into the bloodstream, there is usually a minimum blood plasma concentration which is required to achieve a therapeutic effect. As the blood plasma level increases, so does the  
30 therapeutic effect in a dose-related manner until a maximal therapeutic effect has been achieved. However, when drug blood plasma levels exceed a certain concentration, undesired side-effects become apparent. When drug blood plasma levels drop below a certain concentration there is little or no therapeutic benefit. Drug blood plasma concentrations between these two levels are often referred to as the therapeutic window. Hence, blood plasma levels  
35 outside the therapeutic window are associated with either a lack of efficacy or unacceptable side-effects. For example, it has been reported that high doses of sildenafil can result in the inhibition of other phosphodiesterases, for example PDE 2 and PDE 6. PDE2 has been linked

to the control of cardiac contractility, whereas PDE6 is found in the retina and is involved in the phototransduction pathway of the retina. A common side-effect of sildenafil when delivered by currently marketed swallow tablets is "blue haze", i.e. a transient dose-related impairment of colour discrimination, which is consistent with PDE6 inhibition.

5 Warnings are provided on package inserts for existing sildenafil products against administering sildenafil to patients with pre-existing cardiac conditions.

In summary, currently approved swallow tablets have a number of draw-backs. For example, they suffer from a slow and variable onset of action (i.e. they do not achieve the lower limit of the therapeutic window for a significant and variable period of time). Also,  
10 currently approved swallow tablets have a tendency to produce excessive concentrations of sildenafil (i.e. blood plasma levels may exceed the upper limit of the therapeutic window).

In conclusion, currently approved swallow tablets suffer from a slow and variable onset of action, a short duration of action, and a risk of unacceptable side-effects.

Sildenafil free base i.e. 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-  
15 methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, is specifically described in US patent 6,204,383 B1. Example 1 illustrates the preparation of solid sildenafil by the evaporation of a solution in a mixture of dichloromethane and methanol. Examples 2 and 6 describe a solution of sildenafil iodide in dichloromethane, but this is not isolated as a solid product.

20 Sildenafil is currently marketed as the citrate salt in numerous countries including the USA and the European Union.

Sildenafil citrate is the active ingredient in VIAGRA®, which is approved for use in the treatment of MED. The choice of an improved formulation of sildenafil to deliver a clinically optimal dose of sildenafil is not a matter of routine. Other PDE5 agents have recently  
25 become available on the market for the treatment of MED. These agents include: Cialis®, and Levitra®. These agents have a faster onset of action and longer duration when compared to Viagra®, thereby emphasising the current deficiencies of Viagra®.

In view of the above, there is a clear need to find alternative formulations of sildenafil as compared to the currently marketed form, which deliver a more rapid onset of therapeutic  
30 efficacy and a prolonged duration of therapeutic efficacy within the therapeutic window. Furthermore, there is a need to provide alternative formulations that do not depend so markedly on fasting for a more rapid onset of therapeutic efficacy when compared to the currently marketed product, and which are more suited for use in a relaxed environment, which is appropriate to non-clinical sexual activity.

35 Unlike many other medical conditions, sexual dysfunction is greatly affected and indeed potentiated by stress and other factors including anxiety, uncertainty, time-



restrictions, the need for a controlled or limited diet and a clinical environment.

Hence, maximum benefit for the patient is achieved when therapy takes place in as natural an environment as possible, when there is no pressure to keep to a strict time-

5 freedom from distracting side-effects.

The time interval between dosing and onset of therapeutic efficacy with currently marketed swallow tablets is between 0.5 and 2 hours for fasted healthy male volunteers, and is delayed by a median 60 minutes following a high fat meal. In the general population, this uncertainty is likely to be even greater, and represents a major disadvantage for a stress-free  
10 sexual environment. Hence there is a need for a formulation which provides a rapid and predictable onset of therapeutic effect.

The duration of therapeutic efficacy for conventional swallow tablets is very short and not conducive to relaxed sexual activity. In real-life situations, the opportunity for sexual activity may not always be predictable with any degree of certainty, so the need for strict  
15 time-tables represents a major disadvantage which may cause high levels of counter-productive stress and anxiety. Hence there is a need for a formulation that delivers a therapeutically effective blood plasma level of sildenafil for longer than 2 hours and for up to about 24 hours.

The sharp bolus of sildenafil released into the blood plasma by currently marketed tablets, as described in the art, is undesirable because of the risk of side-effects. The target  
20 population for therapy includes many people of above middle age who are potentially vulnerable to side-effects associated with cardiac contractility, and who may be tempted to increase the dose beyond the recommended level. Furthermore, even clinically non-significant side-effects such as temporary vision impairment represent unwanted distractions which may increase stress and anxiety.

We have surprisingly found that sildenafil formulations can be prepared which provide either a rapid and predictable onset of therapeutic efficacy, or a rapid and predictable onset of therapeutic efficacy combined with a prolonged duration of therapeutic efficacy and a control of excessive blood plasma levels and adverse events. Such formulations are less affected by fasting and are more suited for use in a relaxed environment which is appropriate to  
30 non-clinical sexual activity when compared with the conventional swallow tablets of the prior art.

Whenever mentioned herein, the term predictability is to be understood to mean that the patient should have confidence in the achievement of sufficient sildenafil blood plasma concentrations necessary for the therapeutic effect that enables sexual activity when the opportunity for sexual activity arises, which opportunity inevitably cannot be timed exactly.  
35

Accordingly, the present invention provides a modified release drug delivery dosage form which delivers sildenafil within the therapeutic window either more rapidly than the currently marketed swallow tablets containing sildenafil, or continuously for a long period of time compared to the currently marketed swallow tablets containing sildenafil, or more rapidly and continuously for a long period of time when compared to currently marketed swallow tablets containing sildenafil. Suitably, the modified release formulation of the present invention is a rapid release, or a delayed release, or a prolonged release formulation, or any combination of the aforementioned, optionally combined with a conventional release component.

One published pharmacokinetic study, which is described in the prescribing information associated with the currently marketed swallow tablets, quotes mean sildenafil blood plasma levels in healthy human male volunteers. Hence, as a starting point, one may calculate the blood plasma levels of sildenafil which fall within the therapeutic window in an average human male patient suffering from MED, but otherwise healthy, to be about 50 ng/ml to 500 ng/ml, probably 100 ng/ml to 400 ng/ml, more probably 150 ng/ml to 350 ng/ml, and even more probably 175 ng/ml to 350 ng/ml and most probably between 200 to 325 ng/ml. But, it should be appreciated that interpatient variability results in the therapeutic window varying from patient to patient, and hence in the need for individual dose adjustment in order to achieve the optimal benefits that the present invention provides.

It is clear from all the above information, that the therapeutic window for sildenafil may also be defined in terms of efficacy and side-effect profile. The lower threshold of the therapeutic window is equivalent to the threshold at which an adequate improvement in erectile function is delivered. The higher threshold of the therapeutic window is the threshold at which side-effects become unacceptable. It is apparent that the therapeutic window lies between the thresholds at which a substantially undiminished erectile response is achieved.

It is therefore a feature of this invention that the formulations of this invention are provided in a series of dosing strengths for the purposes of dose titration, i.e. they permit an individual patient to commence with a low dose formulation and increase the dose systematically until an optimal effect is achieved. It is a further feature of this invention that the formulations of this invention are designed to provide a release of sildenafil within the above-defined therapeutic window.

Whenever mentioned herein the term sildenafil is to be understood to include sildenafil in the form of the free base and also in the form of a pharmaceutically acceptable salt. Sildenafil free base is the compound 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one which is the active moiety in Viagra™. The term “pharmaceutically acceptable salt thereof” refers to salts which are physically, chemically and physiologically acceptable for either human or veterinary use.

It should also be understood that sildenafil or a pharmaceutically acceptable salt thereof includes solutions, amorphous forms, and crystalline forms of sildenafil including solvates, hydrates, co-crystals and polymorphs.

Whenever a scientific or patent reference is quoted herein it must be understood that such reference is incorporated herein by reference in full including other references quoted therein.

The term "more rapidly", in the context of rapid release formulations, in the context of this specification, means that a therapeutic blood plasma concentration of sildenafil is achieved more rapidly than with the swallow tablets of the prior art, particularly in the non-fasted state, and more particularly when taken with a high fat meal.

The term "continuously for a long period of time" in the context of this specification means that sildenafil should be released within the therapeutic window over a period of more than 2 and up to 24 hours, for example between 2 hours and 5 hours, preferably between 2 and 10 hours, and more preferably between 0.15 and 24 hours (i.e. from dose to dose).

It should be understood that when the terms "more rapidly" and "continuously for a long period of time" are used together as "more rapidly and continuously for a long period of time" the release of sildenafil should bridge the complete period of time between the onset of therapeutic efficacy implied by the term "more rapidly" and the diminution of the sildenafil blood plasma concentration below the therapeutic window implied by the term "continuously for a long period of time".

The term "rapid release", in the context of "modified release", in the context of this specification, means a formulation by means of which a therapeutic blood plasma concentration of sildenafil is achieved more rapidly than with the swallow tablets of the prior art, particularly in the non-fasted state, and more particularly when taken with a high fat meal.

The term 'delayed release', in the context of "modified release", in the context of this specification, is understood to indicate a formulation that is designed to retard the initial release of drug from the dosage form by a pre-determined interval of time. In the case of sildenafil, delayed release may be understood to mean retardation of release, when compared to the currently approved product which is described as releasing sildenafil between 0.15 and 2 hours when measured in the fasting state, and one hour longer when taken with a high fat meal.

The term "prolonged release", in the context of "modified release", in the context of this specification, may be understood to indicate a formulation that is designed to maintain the release of drug over a period of time that is substantially greater than is achieved in the currently marketed formulation. In the case of sildenafil prolonged release, substantially greater means that the drug is released within the therapeutic window for longer than 2 hours with no

marked diminution of therapeutic effect. Accordingly, sildenafil is released within the therapeutic window over a period of more than 2 and up to 24 hours, for example between 2 hours and 5 hours, preferably between 2 and 10 hours, and more preferably between 2 and 24 hours. Rapid release formulations may be achieved by several different methodologies, which may be used alone or in combination.

For example, rapid release may be achieved by a dosage form of sildenafil comprising a rapidly dispersing wafer containing sildenafil or a pharmaceutically acceptable salt thereof which is placed on the tongue and dissolves in the mouth, for example within the buccal fluids. Suitably the wafer is dispersed and/or dissolved over a period of about 1 to 60 seconds, preferably about 1 to 30 seconds, most preferably about 1 to 10 seconds. Suitably the wafer is made from a freeze-dried compact containing sildenafil or a pharmaceutically acceptable salt thereof, in a matrix of a buccal fluid-dispersible polymer such as gelatine and a polysaccharide such as mannitol. Sildenafil is dissolved or dispersed into a suspension of mannitol and gelatine prior to filling into blister cavities. These liquid filled blisters are then conveyed through a liquid nitrogen freezing tunnel for freezing and then into a freeze dryer where the solvent is removed leaving behind a highly porous wafer loaded with sildenafil. Details of this technology are described in the scientific and patent literature, for example W Habib et al in *Critical Reviews in Therapeutic Drug Carrier Systems*, Vol 17 (1) 61-72 (2000), M J Rathbone, J Hadgraft & M S Roberts in *Modified Release Drug Delivery Systems*, Marcel Dekker, New York, 2003, US Patent No. 4,642,903 and US Patent No 5,738,875 which are incorporated herein by reference.

Alternatively, rapid release of sildenafil may be provided by the blending and compression of sildenafil with water soluble excipients, such as a sugar such as but not limited to mannitol, and an effervescence agent, at low compression forces. The low compression forces lead to the formation of a highly porous tablet which disintegrates rapidly. Rapid disintegration is further aided by the inclusion of the effervescence agent, which in the context of this specification is defined as one or more agents which produce carbon dioxide upon contact with buccal, gastric, or intestinal fluids.

Typically, effervescence is derived by the reaction which takes place between alkali metal carbonates or bicarbonates and organic acids such as citric acid or tartaric acid to release carbon dioxide. Effervescence may also result from the inclusion of a carbonate or bicarbonate alone to react with acidic gastrointestinal fluids. Suitably the porous tablet disperses over a period of about 1 to 60 seconds, preferably about 1 to 45 seconds, most preferably about 1 to 30 seconds. Details of this technology are described in the scientific and patent literature, for example W Habib et al in *Critical Reviews in Therapeutic Drug Carrier Systems*, Vol 17 (1) 61-72 (2000), M J Rathbone, J Hadgraft & M S Roberts in *Modified Release*

Drug Delivery Systems, Marcel Dekker, New York, 2003, US Patent No. 5,178,878 and US Patent No 5,607,697 which are incorporated herein by reference.

5 Alternatively, rapid release of sildenafil may be achieved by blending and compressing sildenafil with a suitable sugar such as but not limited to sucrose which has been melt-spun to form a mass of thin filaments with a high surface area. The resulting tablets are highly porous. Upon contact with buccal fluids, they disintegrate rapidly as the mass of thin filaments dissolves. Details of this technology are described in the scientific and patent literature, for example W Habib et al in Critical Reviews in Therapeutic Drug Carrier Systems, Vol 17 (1) 61-72 (2000) and US Patent No 4,855,326 which are incorporated herein by reference.

10 Alternatively, rapid release of sildenafil may be achieved by blending and compressing sildenafil with a low mould ability saccharide (e.g. such as but not limited to lactose and mannitol) which has been granulated using a high mould ability saccharide (e.g. such as but not limited to maltose and maltitol) as a binder. The resulting tablets possess characteristics which enable them to dissolve rapidly on contact with aqueous fluids, typically within about 15 to 60 seconds, preferably about 1 to 30 seconds, most preferably about 1 to 15 seconds. Details of this technology are described in the scientific and patent literature, for example W Habib et al in Critical Reviews in Therapeutic Drug Carrier Systems, Vol 17 (1) 61-72 (2000) and US Patent No 5,576,014 which are incorporated herein by reference.

20 Alternatively, rapid release of sildenafil may be achieved by blending and compressing sildenafil with a disintegrating agent (e.g. such as but not limited to carboxymethylcellulose) and a swelling agent (e.g. such as but not limited to modified starch, e.g. Sodium Starch Glycolate) to produce a rapidly disintegrable tablet which preferably on contact with aqueous fluids disperses over a period of about 1 to 90 seconds, preferably about 1 to 60 seconds, most preferably about 1 to 30 seconds. Details of this technology are described in the scientific and 25 patent literature, for example W Habib et al in Critical Reviews in Therapeutic Drug Carrier Systems, Vol 17 (1) 61-72 (2000) and US Patent No 5,464,632 which are incorporated herein by reference.

It should be appreciated that such tablets will afford advantages over the existing marketed swallow tablets even if swallowed before complete dissolution in the mouth, since 30 dissolution in the gastric fluids will still allow a faster dissolution of sildenafil than is achievable from conventional swallow tablets.

A further embodiment of the present invention relates to the use of taste masking agents and flavours, or the use of forms of sildenafil, for example a suitable salt form, which have a pleasant or acceptable taste.

35 One way of augmenting the rapid release achievable by a suitable choice of formulation, is to utilise a salt of sildenafil which is very soluble in saliva or in gastric fluid.

Yet another way of augmenting the rapid release achieved by a suitable choice of formulation is to utilise an amorphous form of a salt of sildenafil or sildenafil free base. In addition the amorphous or crystalline form of a salt of sildenafil or sildenafil free base may be dispersed or adsorbed in a thin layer over a high surface area inert substrate. Suitable substrates include but are not limited to: Amberlite® XAD-4, Amberlite® XAD-7, Amberlite® XAD-16, AMBERSORB® 348F, AMBERSORB® 563, AMBERSORB® 572, Activated carbon, Activated carbon Darco®, Activated carbon Darco® G-60, Activated carbon Darco® KB, Activated carbon Darco® KB-B, Activated carbon Norit®, silica gel high purity grades with high pore volume, for example about 0.75 cc/g and average pore diameter 60Å.

It will be appreciated that other materials with comparable properties may also be used as substrates.

A solution of sildenafil or a sildenafil salt may be prepared by dissolving the free base or a suitable salt thereof in a suitable solvent or by contacting stoichiometric quantities of the acid and base components of the salt in water or in a solvent such as but not limited to methanol, ethanol, or dichloromethane or a mixture thereof, for example at a concentration of 1% to 20% by weight. The solution is mixed with the inert substrate as defined above, and the required product is isolated by a by either vacuum evaporation or by spray drying. The resulting product has sildenafil or a salt thereof dispersed or adsorbed in a thin layer over a high surface area inert substrate.

The dissolution of sildenafil salts may also be enhanced by reducing the particle size and hence increasing the surface area, for example by such methods as jet milling, ball milling, controlled spray drying, and supercritical fluid precipitation.

Jet or fluid energy milling, involves the use of high pressure air jets to forcibly collide particles together, suitably within a hollow toroidal mill chamber. The high kinetic energy of the air causes particles to impact with other particles with sufficient energy for fracture to occur. This process is repeated until a desired particle size range is obtained. The product is suitably removed from the apparatus with a particle size classifier.

Ball milling of sildenafil salts involves the use of a hollow cylinder rotated along a horizontal longitudinal axis. Inside the cylinder, grinding beads are loaded to a level of 30 to 50% of the chamber volume together with sildenafil salt powder feedstock. The size of the beads depends upon the material being processed and the size of the mill chamber. The chamber is rotated at a suitable velocity to allow the beads to cascade and grind the sildenafil drug particles to a finer and desired size. A feature of ball milling is that it can be conducted in the dry state, alternatively in a wet state in which sildenafil feedstock is supplied to the milling chamber as a suspension in a fluid.

Drug particles of a fine and defined particle size can be manufactured by means of supercritical fluid precipitation. One suitable procedure is rapid expansion of a supercritical solution (RESS), in which sildenafil drug particles are formed as a result of the rapid expansion of a supercritical fluid containing dissolved sildenafil. A second procedure is gas anti-solvent recrystallisation (GAS) in which the supercritical fluid acts as an anti-solvent and causes sildenafil precipitation from a solution. A third procedure is solution enhanced dispersion (SEDS), which involves the rapid dispersion and mixing of a sildenafil solution with the supercritical fluid, typically in a coaxial arrangement, and the extraction of the solvent into the supercritical fluid, leading to precipitation of fine sildenafil drug particles. Multiple repetitions of these techniques is also one method for producing novel polymorphic forms which may have greater aqueous solubility and hence be more suitable for rapid release formulations.

Detailed descriptions of both jet and ball milling can be found in *Pharmaceutics: the science of dosage forms*, M E Aulton (ed) first edition, 2000, Churchill Livingstone, London, D Ganderton in *Unit Processes in Pharmacy Volume 7*, Heinemann, London, 1968, and M E Fayed & L Otten (eds) in *Handbook of Powder Science & Technology*, second edition, Chapman & Hall, New York, 1997. The procedures described in the above-mentioned references are incorporated herein by reference.

Detailed descriptions of spray drying can be found in K. Masters, *Spray Drying in Practice* SprayDryConsult International ApS, Denmark, 2002, which is incorporated herein by reference.

Detailed descriptions of supercritical fluid processing can be found in M A McHugh & V J Krukonis, *Supercritical Fluid Extraction: Principles & Practice*, Butterworth-Heinemann, Boston, 1994 which is incorporated herein by reference.

Preferably, ultrafine drug particles of sildenafil will have a size profile such that at least 90% by weight of the particles have a maximum diameter no greater than 5 microns. More preferably ultrafine drug particles of sildenafil will have a size profile such that at least 90% by weight of the particles have a maximum diameter no greater than 3 microns. Even more preferably ultrafine drug particles of sildenafil will have a size profile such that at least 90% by weight of the particles have a maximum diameter no greater than 1 micron. Most preferably ultrafine drug particles of sildenafil will have a size profile such that at least 90% by weight of the particles have a maximum diameter no greater than 0.5 microns.

Dispersants and/or other physical stabilisers may be added to prevent aggregation of ultrafine particles and the consequent reduction in the rate of dissolution. Descriptions of suitable dispersants and stabilisers and methods for their use can be found in *Dissolution technology*, L J Leeson and J T Carstensen (eds), APS, Washington 1974, and C.G. Liversedge et

al., Int J Pharm Vol 125, pages 309-313, 1995), which publications are incorporated herein by reference.

Useful stabilisers include polymers and surfactants e.g. hypromellose, hydroxypropylcellulose, mannitol, gelatine, tragacanth, acacia, sorbitan esters, glycerol monostearate, methylcellulose, carboxymethylcellulose, sodium lauryl sulphate, polyvinylpyrrolidone, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, polyethylene glycols, block co-polymers of ethylene oxide and propylene oxide.

Delayed release of sildenafil can be achieved by means of a physical barrier or coating which delays exposure of the active material to the buccal, gastric, or intestinal fluids.

One technique which provides delayed release involves the application of a coating of a fluid resistant barrier to a single dosage unit, or to a multiparticulate dosage unit, for example one composed of beadlets, pellets, spheroids, minitablets and/or granules. These coatings can be designed to dissolve at a specific pH range, for example an enteric coating which dissolves at a pH greater than 5.0. Typical pH-dependent polymers suitable for coating dosage forms (single or multiparticulate) include the following:

cellulose acetate phthalate, which dissolves at pH 6.0-6.4

hydroxypropylmethylcellulose phthalate 50, which dissolves at about pH 4.8

hydroxypropylmethylcellulose phthalate 55, which dissolves at about pH 5.2

polyvinylacetate phthalate, which dissolves at about pH 5.0

methacrylic acid-methyl methacrylate copolymer (1:1), which dissolves at about pH 6.0

methacrylic acid-methyl methacrylate copolymer (2:1), which dissolves at pH 6.5-7.5

methacrylic acid-ethyl acrylate copolymer (2:1), which dissolves at about pH 5.5

hydroxypropylmethylcellulose acetate succinate, which dissolves at about pH 7.0

poly(methylvinylether/maleic acid) monoethylester, which dissolves at pH 4.5 -5.0

poly(methylvinylether/maleic acid)n-butyl ester, which dissolves at about pH 5.4

shellac, which dissolves at about pH 7.0

Alternatively a non-pH-dependant coating may be used, which initially impedes the ingress of aqueous fluid, but subsequently erodes and/or dissolves to expose the active agent to dissolution. Typical non-pH-dependent polymers suitable for coating dosage forms (single or multiparticulate) to provide a fluid resistant barrier which subsequently erodes or dissolves include, but are not restricted to acacia, alginate, amylase, beeswax, carboxymethylcellulose, carnuba wax, cellulose acetate, cholesterol, ethylcellulose, fatty acids, gelatine, glyceryl behenate, glyceryl monostearate, glyceryl monodistearate, glyceryl tripalmitate, hypromellose, hydroxypropylcellulose, hydrogenated vegetable oil, lecithin, methylcellulose, paraffin wax, pectin, polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyglyclide-co-lactide co-polymers, polyvinylpyrrolidone, starch, stearic acid, stearyl alcohol, partially hydrogenated cottonseed oil/soyabean oil (melting at 51-55°C), partially hydrogenated



palm oil (melting at 58-63°C), partially hydrogenated cottonseed oil (melting at 61-65°C), partially hydrogenated soyabean oil (melting at 67-71°C), partially hydrogenated castor oil (melting at 85-88°C), polyethylene glycol 3350 (melting at 54-58°C).

5 Delayed release of sildenafil may also be achieved by a fluid resistant barrier which combines one or more pH-dependant polymers optionally with one or more non-pH-dependant polymers.

10 Examples of delayed release dosage forms include enteric coated tablets or enteric coated multiparticulate formulations, in which drug-loaded multi-particulate spheres are coated with methacrylic acid-methyl methacrylate co-polymers such as Eudragit L100-55, Eudragit L30D-55, or Eudragit FS 30D or Eudragit S100/S12.5. Such formulations will not release sildenafil in the acidic environment of the stomach but only on exposure to the higher pH typically found in the small and large intestine (pH range 5 to 8). An enteric coated tablet illustrating one aspect of this invention may be a single-layer tablet or a multi-layer tablet, such as a bi- or tri-layer tablet, wherein the active agent is present in one or more discrete layers within the compressed tablet form. The discrete tablet layers can be arranged to provide modified or non-modified release of active agent. General descriptions and methods for the preparation of suitable tablets may be found in *Aqueous polymeric coatings for pharmaceutical dosage forms*, J W McGinty (ed), Marcel Dekker, 1989, New York, and in *Microencapsulation and related drug processes*, P Deasy, Marcel Dekker, 1984, New York, which publications are incorporated herein by reference.

20 Similarly, a capsule can be prepared in which the active dose is provided in the form of sildenafil beads and is divided into two or more parts, each part having a non-pH-dependant protective coat of different thickness, which takes a different time to erode. Suitable non-pH-dependent coating materials have already been described above. Further information can be found in J R Robinson & V H Lee (eds) in *Controlled Drug Delivery*, second edition, Marcel Dekker, New York, 1987, V Ranade & M A Hollinger in *Drug Delivery Systems*, second edition, CRC Press, Boca Raton, 2004 and M J Rathbone, J Hadgraft & M S Roberts in *Modified Release Drug Delivery Systems*, Marcel Dekker, New York, 2003 which are incorporated herein by reference.

30 Modified release may also be provided in the form of prolonged release. A prolonged release dosage form may consist of a matrix dosage unit, such as a hydrophilic and/or an erodible matrix, usually in tablet form. Release from such a unit can be controlled by a number of mechanisms, such as dissolution, erosion, diffusion, osmotic pressure or any combination thereof. Embodiment of prolonged release dosage forms may utilise excipients which control sildenafil release by more than one formal mechanism.

35 An erosion controlled prolonged release dosage unit can be achieved by compressing sildenafil with a slowly dissolvable and/or erodable polymeric material into a tablet form.

Release of sildenafil occurs as the polymer dissolves and/or erodes away. Suitable polymers include but are not restricted to glyceryl monostearate, acrylic resins, ethylcellulose, stearyl alcohol, hydroxypropylcellulose, carboxymethylcellulose, hypromellose, methylcellulose, hydroxyethylmethylcellulose, sodium carboxymethylcellulose. Further information can be found in Controlled Drug Delivery, second edition, J R Robinson & V H Lee (editors), Marcel Dekker, New York, 1987, in Drug Delivery Systems, second edition, V Ranade & M A Hollinger, CRC Press, Boca Raton, 2004, and in Modified Release Drug Delivery Systems, M J Rathbone, J Hadgraft & M S Roberts, Marcel Dekker, New York, 2003 which publications are incorporated herein by reference.

A diffusion controlled prolonged release dosage form may be produced by compressing a water-swallowable hydrophilic polymer in combination with sildenafil drug substance. Such systems are often referred to as "hydrophilic matrices" or "swallowable-soluble" systems. Water continues to penetrate the matrix causing the swelling of the hydrophilic polymer. The gelatinous layer that is formed, retards the rate of ingress of water into the matrix and the flux of drug out of the matrix. Sildenafil is released from such matrices either by diffusion through the gel layer or by erosion and/or dissolution of the gel layer. Suitable materials would include any pharmaceutically acceptable excipient which can swell and form a gelatinous mass upon hydration, for example, hydroxypropylmethylcellulose, and xanthan gum. Further information and descriptions of such dosage forms can be found in Controlled Drug Delivery, second edition, J R Robinson & V H Lee (editors), Marcel Dekker, New York, 1987 which publication is incorporated herein by reference.

An osmosis controlled prolonged release dosage form may be produced by compressing sildenafil in combination with an osmagent into a tablet matrix core formulation. This matrix core is then in part coated with a semi-permeable membrane in known manner, utilizing such polymers such as methacrylates, ethylcellulose, and cellulose acetate. Aqueous fluids are drawn by osmosis from the exterior environment across the membrane at a controlled rate into the core, causing dissolution of both sildenafil and the osmagent and increased pressure within the matrix core. The pressure forces the solubilised sildenafil out through a specially created aperture or passageway. Examples of osmagents include but are not restricted to sodium chloride, potassium chloride, lithium chloride, magnesium chloride, magnesium sulphate, lithium sulphate, sodium sulphate, potassium sulphate, citric acid, mannitol, ribose, arabinose, galactose, leucine, glycine, fructose, sucrose, sodium and other bicarbonates. Further information can be found in the scientific and patent literature, for example: Controlled Drug Delivery, second edition, J R Robinson & V H Lee (editors), Marcel Dekker, New York, 1987, Modified Release Drug Delivery Systems, M J Rathbone, J Hadgraft & M S Roberts, Marcel Dekker, New York, 2003, and US Patents 3,760,984, 3,845,770, 3,987,790,

3,916,899, 4008,719, 4,036,227, 4,576,604, 4,578,075, 4,673,405, 4,681,583, 4,693,895, 4,705,515, 4,773, 907, 5,229,133 which documents are incorporated herein by reference.

Prolonged release can also be achieved by applying a porous or semipermeable membrane coat onto a tablet surface by the application of such polymers such as methacrylates, ethylcellulose, and cellulose acetate. Release from such systems can occur by more than one of the mechanisms described above, for example a combination of dissolution, diffusion, erosion, and osmosis. Alternatively, prolonged release can be achieved by coating multiparticulates with semipermeable membranes. The multiparticulates include drug-coated substrates, such as lactose beads, and drug-containing substrates, such as drug-containing lactose spheres.

Hence the compositions of the present invention provide a single modified release formulation of sildenafil or a combination of two or more taken from the various modified and unmodified release forms of sildenafil: rapid release, conventional release, pulsed release, delayed release, and prolonged release. Therefore the compositions of this invention have a component or a combination of components which possess one of the following release characteristics:

- Rapid
- Delayed
- Prolonged
- Rapid + Delayed
- Rapid + Prolonged
- Delayed + Prolonged
- Rapid + Delayed + Prolonged
- Rapid + Conventional
- Delayed + Conventional
- Prolonged + Conventional
- Rapid + Delayed + Conventional
- Rapid + Prolonged + Conventional
- Delayed + Prolonged + Conventional
- Rapid + Delayed + Prolonged + Conventional

One preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided both rapidly and with duration of activity of approximately 2 hours. Such a formulation may comprise a rapid release component combined with a conventional release component at a lower dose than would conventionally be necessary. Such a formulation is useful to a patient who expects an imminent sexual encounter irrespective of recent food intake, and who wishes to avoid distracting or harmful side-effects.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided with an initial delay of 0.15 to 2 hours, and with duration of activity of approximately 4 hours. Such a formulation may comprise a conventional release component at a lower dose than would conventionally be necessary, combined with a delayed release component. Such a formulation is useful to a patient who expects a sexual encounter at a time which is not less than 2 hours in the future, but does not wish to be restricted by recent or imminent food intake, and who wishes to avoid distracting or harmful side-effects.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided both rapidly and with duration of activity of approximately 4 hours. Such a formulation may comprise a rapid release component combined with a conventional release component at a lower dose than would conventionally be necessary, and a delayed release component. Such a formulation is useful to a patient who expects an imminent sexual encounter irrespective of recent food intake, but who is uncertain of the exact timing, and who wishes to avoid distracting or harmful side-effects.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided with an initial delay of 0.15 to 2 hours, and with a duration of activity of approximately 12 hours. Such a formulation may comprise a conventional release component at a lower dose than would conventionally be necessary combined with either a prolonged release component or a pulsed release component. Such a formulation is useful to a patient who expects a sexual encounter at a time which is not less than 2 hours in the future, but is very uncertain of the timing and who does not wish to be restricted by recent or imminent food intake, and who wishes to avoid distracting or harmful side-effects. A b.i.d. presentation of this formulation may be employed for the purposes of continuous treatment.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided both rapidly and with a duration of activity of approximately 12 hours. Such a formulation may comprise a rapid release component combined with a conventional release component at a lower dose than would conventionally be necessary, and a prolonged release component. Such a formulation is useful to a patient who expects an imminent sexual encounter irrespective of recent food intake, and who wishes to be prepared for sexual activity for an extended period of time, and who wishes to avoid distracting or harmful side-effects.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided with an initial delay of 0.15 to 2 hours, and with duration of activity of approximately 16-24 hours. Such a formulation may comprise a conventional release component at a lower dose than would conventionally be necessary

combined with either a prolonged release component. Such a formulation is useful to a patient who expects a sexual encounter at a time which is not less than 2 hours in the future, but is very uncertain of the timing and who wishes to be prepared for sexual activity for an extended period of time, and who does not wish to be restricted by recent or imminent food intake, and who wishes to avoid distracting or harmful side-effects.

Another preferred embodiment of this invention is a formulation in which a dose of sildenafil within the therapeutic window is provided both rapidly and with a duration of activity of approximately 16-24 hours. Such a formulation may comprise a rapid release component combined with a conventional release component at a lower dose than would conventionally be necessary, and a prolonged release component. Such a formulation is useful to a patient who expects an imminent sexual encounter irrespective of recent food intake, and who wishes to be prepared for sexual activity for a much extended period of time, and who wishes to avoid distracting or harmful side-effects. It should be appreciated that this approach to providing a variety of specially designed formulations to address specific circumstances is especially useful for over-the-counter products where the patient is able to self-diagnose and choose the most appropriate product for his specific needs.

Moreover, it is also believed that these formulations may provide effective therapy for female patients suffering from sexual disorders including but not limited to lack of clitoral arousal. This is especially surprising since the innovator company have reported lack of efficacy for sildenafil in female patients.

It should be appreciated that the dose of sildenafil, calculated as the free base, will be adjusted in consideration of the amount of sildenafil in each component and the total amount so as to ensure that blood plasma levels remain within the therapeutic window whilst achieving the effect desired and described above.

The quantity of sildenafil required in each component of each formulation can be determined by the skilled worker from the information provided in this invention. Firstly the target pharmacokinetic profile for the formulation is selected in line with the objects of the present invention. Then, from knowledge of the therapeutic window as defined herein, the mean rate of elimination of sildenafil in the body, and the release profile of sildenafil from each component, it is a matter of routine experimentation to establish the necessary quantity of sildenafil in each component.

In view of the variability of individual patient response to sildenafil, it is envisaged that each of the formulations of this invention will be provided in a range of strengths to permit titration of dose for individual patients.

Preferably, the compositions are in unit dosage form. Unit dosage forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants, effervescent agents, and wetting agents.

5           Examples of binding agents include but are not limited to: acacia, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol,  
10 starch, syrup, tragacanth.

          Examples of fillers include but are not limited to: calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium  
15 oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, xylitol.

          Examples of lubricants include but are not limited to: calcium stearate, glyceryl  
20 monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, zinc stearate.

          Examples of glidants include but are not limited to: colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, talc.

25           Examples of disintegrants include but are not limited to: alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrillin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycolate.

30           Examples of effervescent agents are effervescent couples such as an organic acid and a metal carbonate or bicarbonate. Suitable organic acids include but are not limited: citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, succinic acid, and alginic acid, and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate and arginine carbonate. Alternatively,  
35 only the base component of the effervescent couple may be present.

The solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are conventional in the art. The tablets may be coated according to methods known in normal pharmaceutical practice. For example see Pharmaceutical dosage forms: tablets, Volume 1 second edition, H A Lieberman, L Lachman and J B Schwartz (eds) Marcel Dekker, 1989, New York and G C Cole & J Hogan in Pharmaceutical coating technology, Taylor & Francis, London, 1995 which are herein included by reference.

Formulations of the present invention may be used for the treatment of human male erectile dysfunction, which method comprises administering a formulation of the present invention comprising an effective amount of sildenafil and/or a pharmaceutically acceptable salt thereof to a sufferer in need thereof.

Formulations of the present invention may also be used for the treatment of human female sexual dysfunction, which method comprises administering a formulation of the present invention comprising an effective amount of sildenafil and/or a pharmaceutically acceptable salt thereof to a sufferer in need thereof.

Formulations of the present invention may also be used in the preparation of a medication for use in the treatment of human male erectile dysfunction.

Formulations of the present invention may also be used in the preparation of a medication for use in the treatment of human female sexual dysfunction.

The present invention also provides a pharmaceutical composition for use in the treatment of human male erectile dysfunction or human female sexual dysfunction in which the pharmaceutical composition is as defined in the present invention.

The following examples are merely illustrative of the present invention and should not be considered as limiting the scope of the invention in any way.

In Examples 52 to 65 hereinbelow it should be appreciated that the amount of active ingredient is not specified precisely but is readily calculated from a consideration of the target product profile required within the scope of the present invention without undue experimentation. The sildenafil citrate used in these examples may be replaced by other salts of sildenafil with compatible solubility properties.

The present invention also relates to novel compounds and to their use in medical therapy, in particular to their use in the treatment and/or prophylaxis of disorders associated with PDE5 inhibition.

The present invention also relates to processes for preparing these novel compounds. Sildenafil is generically described in US patent 5,250,534 as a selective cGMP PDE inhibitor useful in the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.

Sildenafil free base i.e. 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, is specifically described in US patent 6,204,383 B1 as an agent with pharmaceutical utility in the treatment of male sexual dysfunction.

5           Sildenafil citrate is the active ingredient in VIAGRA®, which is approved for use in the treatment of MED. The choice of a form of a pharmaceutical agent having a basic functional group is not a matter of routine. The fact that Pfizer (the originator company) markets the citrate salt could lead one skilled in the art to believe that other forms were less preferred since the citrate salt is an unusual choice of salt to market. The choice of salts of sildenafil  
10 other than the prior art citrate salt is not therefore *prima facie* obvious in view of this technical prejudice and other concerns about the formation and properties of such salts. There are problems and technical hurdles to be overcome when selecting a salt other than citrate such as whether a different salt can exist at all, whether the properties of such a salt would be satisfactory, comparable or better than the prior art citrate salt. Whether a suitable method exists for  
15 the preparation of a salt other than the prior art citrate salt is not a matter of routine experimentation.

          There is a need to find alternative forms of sildenafil other than the prior art citrate which are pharmaceutically acceptable. Such forms apart from finding use in medical therapy and as useful intermediates are also useful in providing new active ingredients containing the  
20 active moiety sildenafil which could form the basis for providing new value-added line extenders in the form of advantageous formulations or new uses.

          We have found that salts of sildenafil with certain long chain fatty acids can be prepared and have a pleasant and fully acceptable flavour which permits the use of formulations such as chewable tablets, chewing gum, and oral suspensions. The invention accordingly encompasses such chewable tablets, chewing gum, and oral suspensions, but also is of value in  
25 swallow tablets and other conventional formulations. Accordingly, the present invention provides sildenafil salts with long chain fatty acids.

          Whilst the compounds of the present invention are *prima facie* inventive, they also show unexpected advantages and /or overcome technical prejudice. When hereinafter mentioned, the issue of whether a particular novel form would have advantageous properties in  
30 this area over prior art forms would not be predictable. Therefore an advantage of the present novel forms over the prior art forms would be an unexpected advantage. Examples of unexpected advantages are selected from one or more of the following:

          Advantages during manufacture in terms of the timing and cost of production, availability of starting materials, reproducibility, and safety.  
35

          Advantages during manufacture in terms of improved yield and purity. The yield is established by comparison of the weights of cost-critical starting material and product making



allowance for molecular weights and purities. Purities are established by hplc, gc or other conventional analytical method by means of a validated procedure and comparison with a reference standard. See for example Remington: The Science and Practice of Pharmacy 20th edition, Alfonso R Gennaro editor, Lippincott, Williams, and Wilkins, Philadelphia USA, ISBN 0-683-306472, page 597.

Advantages during manufacture in terms of improved filterability, for example the avoidance of clogging or blinding of filter cloths, and the need for large or expensive or sophisticated filtration apparatus. Filterability testing procedures are based on the concept of  $V_{max}$ .  $V_{max}$  modelling is based on the theory that there is some maximum volume of a fluid which will pass a filter at a given pressure. At that point, the flow across the filter will be zero and therefore the resistance of the pad to flow infinite. On the basis of this model the rate of flow of filtrate is proportional to the driving force and the cross-sectional area of the filter bed. Measurements of flow rates and timing of standardised operations may be used to demonstrate advantage.

Advantages during manufacture in terms of improved washability result from the physical properties of the material and the size, shape and surface properties of any particles may be present, which are not *per se* predictable. Quantification is possible by measurement of, for example, the volume and cost of solvent, duration of agitation, and number of washes required to achieve a standardised reduction in adherent impurity levels. Another relevant factor which would constitute an advantage is a reduction in the loss of product resulting from washing procedures.

Advantages during manufacture in terms of improved ease of drying also result from the physical properties of the material and the size, shape and surface properties of the material, which are not *per se* predictable. Quantification is achievable by measurement of the length of time and temperature in a specific drying apparatus to achieve a standardised reduction in the solvent level in a standardised quantity of product. Other relevant factors which may give rise to an advantage include the need for agitation, and the need for or suitability for use in efficient apparatus such as filter driers.

Improvements in the colour of a product are linked in perception and often in reality with purity and quality, so may constitute a valuable advantage. Standard colour tests are described in the major pharmacopoeias, for example the European Pharmacopoeia 4<sup>th</sup> edition 2001, and United States Pharmacopoeia 24<sup>rd</sup> edition 1999-2003 and for example USP 2000 page 1926. Colour may be defined as the perception or subjective response of an observer to the objective stimulus of radiant energy in the visible spectrum extending over a range 400nm to 700nm in wavelength. Three attributes are commonly used to identify a colour: 1) hue, or the quality by which one colour family is distinguished from another, such as red, yellow, blue, green and intermediate terms; 2) value, or the quality that distinguishes a light colour

from a dark one; and 3) chroma, or the quality that distinguishes a strong colour from a weak one, or the extent to which a colour differs from a grey of the same value. The perception of colour and colour matches is dependent on conditions of viewing and illumination. Determinations should be made using diffuse, uniform illumination under conditions that reduce shadows and nonspectral reflectance to a minimum. The surfaces of powders should be smoothed under gentle pressure so that a planar surface free from irregularities is presented. Liquids should be compared in matched colour-comparison tubes, against a white background. If results are found to vary with illumination, those obtained in natural or artificial daylight are to be considered correct. Colours of standards should be as close as possible to those of the test specimens for quantifying colour differences. Instrumental methods for measurement of colour provide more objective data than the subjective viewing of colours by a small number of individuals.

The extent to which a product is associated with chemical impurities arising from earlier stages of synthesis is essentially unpredictable and depends both on the synthetic process, the nature of reagents used in the process, and on the physical, chemical, and surface properties of the product. For example a novel salt, polymorph, or pseudopolymorph will have a different and unpredictable profile of trace impurities than a comparator salt. Quantification may be achieved by measurement and characterisation of impurity profiles, for example by GC-MS or LC-MS analysis and comparison with a reference material. Identification of all impurities is not essential providing sufficient characterisation is obtained from the analytical methodology, though it is of course desirable.

From the point of view of manufacturing and formulation efficiency high bulk density in a product is generally regarded as an advantage, since it allows for smaller apparatus and more acceptable unit doses. Furthermore, the need for costly grinding and compaction procedures can be avoided or at least reduced. The European Pharmacopoeia describes definitions and methods by which bulk density of a powder may be measured. Apart from the inherent density of a material which depends on factors such as crystal structure which is unpredictable, there is also the contribution of interparticulate void volume which is equally unpredictable. The bulk density is determined by measuring the volume of a known mass of powder, which has been passed through a screen, into a graduated cylinder. The tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed.

The ability of a powder to flow efficiently through manufacturing apparatus is a significant factor affecting the economics of manufacture and will vary according to the form of material. For example different salts, polymorphs, and pseudopolymorphs will have different

inherent flow properties, though isolation procedures will also have an effect. Suitable definitions and methods of measurement are described in standard reference texts, for example European Pharmacopoeia 4<sup>th</sup> edition 2001, and United States Pharmacopoeia 24<sup>th</sup> edition 1999-2003 and Remington: The Science and Practice of Pharmacy 20th edition, Alfonso R Gennaro editor, Lippincott, Williams, and Wilkins, Philadelphia USA. Measurement may be for example in terms of the angle of repose, which may be determined experimentally by a number of methods with slightly differing results. A typical method is to pour the powder in a conical heap on a level, flat surface and measure the included angle with the horizontal.

One of the factors affecting the safety of a manufacturing process and hence the cost of the manufacturing facility is the flammability of a material. Typical measurement procedure include the "Burning Rate Test" or "Fire Train Test" as defined in United States Department of Transportation and United Nations regulations (49 CFR 173 Appendix E and UN Recommendations on the Transport of Dangerous Goods, also EEC Directive 79/831 Annex Part A: Methods for the Determination of Physico-Chemical Properties 3.10 Flammability of Solids. A typical test involves applying a source of ignition to a powder "train" measuring 250 mm x 20 mm x 10 mm and measuring the rate at which the powder burns.

Another unpredictable property of particulate pharmaceutical products which affects safety and hence cost of manufacture is the tendency to produce dusts or fines during processing, which dusts or fines vary in their hazardous nature. This property is associated with the static electrical properties of the material. Standard test methods and protocols exist to quantify these problems. For example BS 5958 part 1 - Code of practice for control of undesirable static electricity, British Standards Institute, 1991; VDI Fortschritt-Berichte 2263; ISO 6184/1; IEC 1241-2-1, Electrical apparatus for use in the presence of combustible dust Part 2: Test methods, Section 1: Methods for determining the minimum ignition temperatures of dust. International Electrotechnical Commission, first edition, 1994-12

Other advantages which differentiate unpredictably between alternative forms of a drug substance may be quantified in terms of improved chemical stability. Standard test methods are described in the major pharmacopoeias and are also referenced on the US Food and Drug Administration Web site. Typically accelerated storage tests are performed by storage for a period of 1 year or more at elevated temperature (e.g.40°C) and at standard humidity conditions (e.g. 75% RH), with samples being taken at regular intervals of approximately 1 month and assayed for overall purity, specific impurities, and a general impurity screen.

In addition, chemical interactions between drug substance and typical excipients used for formulation will differ for different forms of a drug substance, making one form advantageous in one formulation, though not necessarily advantageous in a different formulation. Examples include the interaction between amine drugs and lactose.

Stability to irradiation, especially visible and ultra-violet light is of increasing importance in pharmaceutical science and represents another area in which alternative forms of a drug substance may have significantly and unpredictably different properties. Testing details, such as light source, flux density, and duration are described in Federal Register Notices Volume 62, Number 95, pages 27115-27122, together with recommendations for analytical methodology and assessment of results.

Pharmaceutical materials with relatively high melting points are generally easier to formulate and are subject to less attrition and clumping during processing. Melting points and glass transition temperatures will differ greatly for different salts, polymorphs, pseudopolymorphs, or other forms of a drug and are in essence unpredictable. Methods for measuring melting points are well-described in the European Pharmacopoeia 4<sup>th</sup> edition 2001, and United States Pharmacopoeia 24<sup>rd</sup> edition 1999-2003. Various methods are acceptable but differ in detail, for example the melting point determined by the capillary method is the temperature at which the last solid particle of a compact column of a substance in a tube passes into the liquid phase. Suitable apparatus is described in the above mentioned publications and may be calibrated using melting point reference substances such as those of the World Health Organisation or other appropriate substances.

Some materials have a tendency to change their physical form during storage, which can be a disadvantage in pharmaceutical manufacture. For example materials can settle and compact and lose their ability to flow freely. One polymorphic form may wholly or partially convert to another over an uncertain time-frame, or solvates and hydrates may lose their solvent or water, and the resultant change in the physical properties of the drug substance can lead to a formulation with uncertain, unreliable, and unpredictable characteristics. Clearly a polymorphic conversion can only occur from a less stable to a more stable form, so there are advantages associated with thermodynamic stability, and the relative stability of a novel form is *a priori* unpredictable.

All substances absorb moisture when exposed to different relative humidity environments, but the extent and humidity response and temperature response varies very considerably. The term hygroscopicity describes both the rate and the extent of water uptake. It is well established that hygroscopic products are difficult to handle and hence more expensive to formulate. Hygroscopicity is not *a priori* predictable, and an alternative salt may well be advantageous in this respect. Apparatus for measurement of moisture contents of samples under controlled humidity conditions is available commercially, e.g. from I Holland Ltd., Nottingham, U.K. Simple measurements may be made by monitoring the appearance and weight of samples exposed to atmospheres of known constant humidity and temperature, as described in, for example, The Merck Index 12<sup>th</sup> edition, Merck and Co Inc.

An important property of a drug substance is its solubility in water and other solvents. There is a link between solubility and bioavailability in as much as very water-insoluble drugs can only be made bioavailable by very careful formulation. The need for high solubility in water or other parenteral media is self-evident, and in general both high, moderate, or low solubility's can be important for different formulations. Formulations designed for sustained release may benefit from very low aqueous solubility. Apparatus and procedures for the measurement of solubility are described in detail in both the European Pharmacopoeia 4<sup>th</sup> edition 2001, and United States Pharmacopeia 24<sup>rd</sup> edition 1999-2003.

Another property that influences the ability of a drug substance to go into solution and which varies among different solid forms of a drug substance is the degree of wetting, which affects the rate of dissolution. Wetting is the ability of liquids to form boundary surfaces with solid materials, and is determined by measuring the contact angle which a liquid forms in contact with a solid. The smaller the contact angle the larger the wetting tendency. Wetting phenomena are described in Remington: The Science and Practice of Pharmacy 20th edition, Alfonso R Gennaro editor, Lippincott, Williams, and Wilkins, Philadelphia USA on pages 278-9. In order for immersion of a solid to occur, the liquid must displace air and spread over the surface of the solid. When liquids cannot spread over a solid surface spontaneously, and therefore the spreading coefficient  $S$  is negative, it is said that the solid is not wetted. An important parameter reflecting the degree of wetting is the angle made by the liquid with the solid surface at the point of contact. By convention, when wetting is complete, the contact angle is 0°. In non-wetting situations it theoretically can increase to a value of 180°, where a spherical droplet makes contact with solid at only one point.

The ability of different forms of a drug to admix with specific common excipients across the formulation / delivery range of technologies is very important and will differ in a non-predictable manner depending on the specific properties of the drug form. Pharmaceutical excipients are substances, other than the active pharmaceutical ingredient, that are used in the finished dosage form. There are very many widely differing excipients each with particular characteristics which form the basis of many widely differing formulations. Excipients and their properties are described in detail in the pharmaceutical literature, for example in Remington: The Science and Practice of Pharmacy 20th edition, Alfonso R Gennaro editor, Lippincott, Williams, and Wilkins, Philadelphia USA. They serve many functions, for example they stabilise the drug substance by providing antioxidant, heavy-metal chelating, or light-protection properties. They also may be used to enhance bioavailability and to control the release from dosage forms. For solid dosage forms, they provide suitable properties for dispensing the drug substance in accurate dosage units that have reproducible release properties. Diluents provide a flowable bulk, binders hold powders together after wet granulation, lubricants provide punch-releasing properties, and disintegrants help to disperse dosage forms in

the GI tract. There is a risk, which may be avoided by careful selection of the form of the drug, of incompatibilities between drug substance and excipients. Screens to detect drug-ex-

5     cipient incompatibilities have been developed using elevated temperature and added water to accelerate potential interactions in ternary and more complex powder blends (Serajuddin ATM *et al* Pharm Res 1991 8(suppl): S103) and such methods have been shown to be capable of rapidly detecting chemical incompatibilities and giving good correlations with results using powder blends of drug and excipients at elevated temperatures and humidity.

The present invention provides amorphous, crystalline or liquid sildenafil salts with long chain fatty acids.

10     In the first aspect of this invention, the novel salts of sildenafil with long chain fatty acids may be in the form of an amorphous solid. Such amorphous sildenafil salts with long chain fatty acids may be used as an ingredient for inclusion in a range of formulations such as conventional tablets and capsules, in particular, a chewable tablet or formulated into a chew-

15     ing gum or suspension or liquid for oral administration, or may be prepared in a form in which the salt is absorbed in a carrier, for example an excipient or a mixture of excipients for tableting or other formulation, or as a solution in a wax or similar pharmaceutically acceptable polymer, such as PEG or PVA. In one preferred aspect of the invention, the salt is formulated as a component of a sweet or chocolate based confection.

Alternatively, sildenafil salts with long chain fatty acids may be in crystalline form.

20     More than one crystalline form may be possible and such polymorphs and pseudo polymorphs including hydrates and solvates also form an aspect of this invention.

Alternatively, sildenafil salts with long chain fatty acids may be in liquid form. Such liquids may be prepared by conventional methods such as dissolving a crystalline or amorphous material in a suitable solvent.

25     Sildenafil is the active moiety in sildenafil citrate which is the active ingredient in VI-AGRA®.

The term fatty acid is understood by one skilled in the art and comprises a monobasic carboxylic acid with a carbon and hydrogen containing substituent group. Long chain is to be understood as comprising a substituent group with six or more carbon atoms. Typically the

30     carbon and hydrogen containing substituent group is a C<sub>6</sub>-C<sub>24</sub> alkyl group or a C<sub>6</sub>-C<sub>24</sub> alkenyl group, i.e. the long chain fatty acid is of formula RC(O)OH wherein R is C<sub>6</sub>-C<sub>24</sub> alkyl or C<sub>6</sub>-C<sub>24</sub> alkenyl.

Examples of salted versions of sildenafil with long chain fatty acids include:

Amorphous sildenafil decanoic acid salt

35     Amorphous sildenafil docosanoic acid salt

Amorphous sildenafil eicosanoic acid salt

Amorphous sildenafil heneicosanoic acid salt

- Amorphous sildenafil heptadecanoic acid salt
- Amorphous sildenafil lauric acid salt
- Amorphous sildenafil myristic acid salt
- Amorphous sildenafil nonadecanoic acid salt
- 5 Amorphous sildenafil nonanoic acid salt
- Amorphous sildenafil octanoic acid salt
- Amorphous sildenafil palmitic acid salt
- Amorphous sildenafil pentadecanoic acid salt
- Amorphous sildenafil stearic acid salt
- 10 Amorphous sildenafil tetracosanoic acid salt
- Amorphous sildenafil tricosanoic acid salt
- Amorphous sildenafil tridecanoic acid salt
- Amorphous sildenafil undecanoic acid salt
- Amorphous sildenafil undecylenic acid salt
- 15 Crystalline sildenafil decanoic acid salt
- Crystalline sildenafil docosanoic acid salt
- Crystalline sildenafil eicosanoic acid salt
- Crystalline sildenafil heneicosanoic acid salt
- Crystalline sildenafil heptadecanoic acid salt
- 20 Crystalline sildenafil lauric acid salt
- Crystalline sildenafil myristic acid salt
- Crystalline sildenafil nonadecanoic acid salt
- Crystalline sildenafil nonanoic acid salt
- Crystalline sildenafil octanoic acid salt
- 25 Crystalline sildenafil palmitic acid salt
- Crystalline sildenafil pentadecanoic acid salt
- Crystalline sildenafil stearic acid salt
- Crystalline sildenafil tetracosanoic acid salt
- Crystalline sildenafil tricosanoic acid salt
- 30 Crystalline sildenafil tridecanoic acid salt
- Crystalline sildenafil undecanoic acid salt
- Crystalline sildenafil undecylenic acid salt

The preparation of solid sildenafil free base is described in US patent 6,204,383 B1.

- Alternatively, a solution of sildenafil free base may be prepared from the commercially available citrate salt by basifying a suspension of the citrate salt in a mixture of water and dichloromethane to a pH of between 8 and 10 and separating the organic phase. Sildenafil base is obtained by evaporation of the organic phase.
- 35

The long-chain fatty acids of this invention are available commercially from chemical suppliers such as Aldrich Chemical Company in the UK.

A solution of a salt of sildenafil with a long-chain fatty acid may be prepared by contacting stoichiometric quantities of the acid and base components of the salt, for example by heating an equivalent of sildenafil base and the long chain fatty acid in hot absolute ethanol or methanol at a concentration of 1% to 20% by weight. Alternatively a solution in dichloromethane may be prepared by heating an equivalent of sildenafil base and the long chain fatty acid in dichloromethane at a similar range of concentrations. Alternatively a mixture of these solvents or other solvents such as may be used. Optionally a miscible co-solvent may be used at a proportion of between 1:10 and 10:1. Suitable acids include decanoic acid, docosanoic acid, eicosanoic acid, heneicosanoic acid, heptadecanoic acid, lauric acid, myristic acid, nonadecanoic acid, nonanoic acid, octanoic acid, palmitic acid, pentadecanoic acid, stearic acid, tetracosanoic acid, tricosanoic acid, tridecanoic acid, undecanoic acid, undecylenic acid. Suitable co-solvents include n-propanol, propan-2-ol, acetone, 2-butanone, diethyl ether, toluene, and acetonitrile or a mixture thereof. Amorphous sildenafil long chain fatty acid salts are then isolated by either rapid vacuum evaporation, or spray drying.

If a vacuum evaporation technique is used, it should be carried out as rapidly as possible and under conditions which avoid the presence of seeds of the crystalline salt, to avoid crystallisation of the salt.

If a spray drying technique is used, a concentration of between 2% and 40% weight/volume salt in solution, optionally at elevated temperature, may be used though a concentration of between 10 and 25% is preferred. Aqueous mixtures containing organic solvents may be spray dried in a closed loop spray dryer. If a closed loop spray drier is used the organic solvent content may be raised further up to 100%. The apparatus parameters are adjusted to give an acceptable product by routine means, but control of outlet gas temperature and solvent content of the outlet gas is particularly important. Hence it is preferred that the outlet temperature is kept above 40°C but below 70°C, more preferably below 50°C, and the solvent content of the outlet gases is kept below 2 grammes per 100 grammes, more preferably below 1.2 grammes per 100 grammes. The technology of spray drying is described in the following publications which are incorporated herein by reference: Spray-drying handbook 5th edition by K Masters, Longman Scientific & Technical, 1991 ISBN 0582062667; Spray-drying of pharmaceuticals for controlled release pulmonary drug delivery by Noha Patel, University of Bath, 2000; Spray-drying of particles intended for inhalation by Kristina Mos'em, Department of Pharmaceutics, Copenhagen, Danish University of Pharmaceutical Sciences 2003, ISBN 8778345243.

In a variation of the spray drying procedure, the solution of sildenafil salt with a long chain fatty acid may be mixed with a suspension of one or more finely powdered excipients or



excipients in solution before spray drying, thus preparing in one step a platform formulation for tableting or other preparation of a drug product. Known techniques may be employed to coat the particles with enteric or other known coatings for control of drug release after administration.

5           Drying to the full extent that is desirable for a stable pharmaceutical product is not always practicable during efficient use of the isolation apparatus, particularly in the case of spray drying, so in all the above procedures, a final air or vacuum drying step may be necessary to reduce residual water and solvent to an acceptable level.

10           A solution of a salt of sildenafil may also be prepared by passing a solution of a strong acid salt of sildenafil or sildenafil in a solvent in which the fatty acid sildenafil salt is soluble through a strong base ion-exchange column in which the column material is in the desired fatty acid salt form. The properties and techniques for conditioning and use of ion exchange resins are generally described in the literature, for example: Ion Exchange Resins 2nd edition by Robert Kunin, John Wiley and Sons, Inc. New York, 1958; The use of ion-exchange resins as potential bioadhesive drug delivery systems, by Sarah J Jackson, University of Nottingham, UK 1999; Ion exchange resins by Robert Kunin, R.E. Krieger, Malabar, Fla 1990, ISBN 0894644289; BDH Chemicals Ltd: Ion exchange resins 6th edition, BDH Chemicals Ltd, Poole, UK 1981; Ion-exchange resins – properties and applications, Rohm & Haas, Philadelphia; Chromatography edited by E. Heftmann, Van Nostrand Reinhold Company, 15           New York (1975), and these publications are incorporated herein by reference. Suitable ion exchange resins include: AMBERJET™ 4200(Cl), Amberlite® IRA-400 (Cl), Amberlite® IRA-410, Amberlite® IRA-900, Amberlite® IRA-743, Dowex® 1X2-100, Dowex® 1X2-200, Dowex® 1X2-400, Dowex® 1X4-50, Dowex® 1X4-100, Dowex® 1X4-200, Dowex® 1X4-400, Dowex® 1X8-50, Dowex® 1X8-100, Dowex® 1X8-200, Dowex® 1X8-400, 20           Dowex® 21K Cl, Dowex® 2X8-100, Dowex® 2X8-200, Dowex® 2X8-400, Dowex® 22 Cl, Dowex® MARATHON® A, Dowex® MARATHON® A2, Dowex® MSA-1, Dowex® MSA-2, Dowex® 550A OH, Sephadex® QAE A-25, Sephadex® QAE A-50, DOW 25           XYS-40013.00®

30           Crystalline salts of sildenafil with long chain fatty acids are prepared by trituration of the amorphous salts with one of the solvents (or a mixture of solvents) preferably from the following list of preferred solvents, i.e., diethyl ether, di-isopropyl ether, *tert*-butylmethylether, di-*n*-butyl ether, butylvinylether, *tert*-butylvinylether, tetrahydrofuran, 1,4-dioxane, *n*-heptane, *n*-hexane, cyclohexane, cyclopentane, toluene, *o*-xylene, *m*-xylene, *p*-xylene, dichloromethane, chloroform, carbon tetrachloride, chlorodibromofluoromethane.

35           Alternatively, a solvent (or a mixture of solvents) from the following list may be used to triturate and crystallise amorphous sildenafil salts with long chain fatty acids: methyl ace-

tate, ethyl acetate, propyl acetate, ethyl formate, isobutyl acetate, isobutyl formate, acetonitrile, isobutyronitrile, acetone, butanone, isopropylmethylketone, isobutylmethylketone, *tert*-butylmethylketone, *sec*-butylmethylketone, *n*-butylmethylketone, cyclopentanone, cyclohexanone.

5 Other more polar solvents which also have utility for trituration are the following: water, methanol, ethanol, *n*-propanol, propan-2-ol, 1-butanol, isobutyl alcohol, cyclopentanol, 2-ethoxyethanol, 2-methyl-2-butanol, ethyleneglycol, *tert*-butanol, acetic acid, propionic acid. And, though less preferred, the solvents below may also be used for trituration: N,N-dimethylformamide, N,N'-dimethylacetamide, N-methylpyrrolidone, formamide, anisole, sul-  
10 folane, nitromethane, N,N'-dimethylpropyleneurea, dimethylsulfoxide, benzene, chlorobenzene, 1,2-dichlorobenzene, 4-methylmorpholine, N,N,N',N'-tetramethylethylenediamine, pyridine, diisopropylamine, triethylamine, aqueous ammonia.

Suitable trituration techniques include addition of a small amount of solvent to the amorphous salt, insufficient to cause complete solution, and scratching with a glass rod and/or  
15 ultrasonication. Scratching is carried out in a glass tube for periods of approximately 5-10 minutes at a time, then leaving the tube to stand for 1 to 2 hours. Preferably the suspension/paste is brought onto the sides of the vessel during scratching to allow partial evaporation of the solvent. The procedure is then repeated several times. Alternatively the process may be automated by agitating the suspension/paste very vigorously with a small magnetic stirrer  
20 in the presence of some quartz anti-bumping granules or other abrasive material such as carborundum. Alternatively the mixture may be subjected to thermal shock by repeated cyclic ultra-freezing with liquid nitrogen followed by heating. Combinations of these techniques may be used.

Another technique which may be employed is to raise the temperature of the amorphous salt above the glass point and to raise and lower the temperature in a cyclic manner.  
25 This technique may be used in combination with thermal shock treatment and scratching.

After trituration, the crystalline product is dried under moderate vacuum to remove excess solvent but not such vigorous conditions as to desolvate any solvate that may have been formed.

30 The existence of a crystalline salt may be demonstrated by a combination of techniques. Solution nmr and or elemental analysis is used to demonstrate that both acid and base components are present. The salt is characterised by one or more of the following techniques: infra-red spectroscopy, Raman spectroscopy, X-ray powder or single crystal diffraction, solid-state nmr, melting point, DSC, DTA, optical and electron microscopy. The salt may be pre-  
35 sent as a hydrate or a solvate.

Once a crystalline salt has been prepared on the small scale by one of the techniques described above so that seeds are available and a suitable solvent has been identified, other

methods may be employed which are more suitable for large scale synthesis. For example, direct crystallisation from a solvent or solvent mixture which has been prepared by mixing the acid and base components optionally at elevated temperature. The solution is made supersaturated by cooling, partial evaporation, or addition of an antisolvent. Alternatively, crystallisation from a supercritical fluid may be employed. Alternatively a salt may be prepared by adding a soluble conjugate salt to a soluble salt of sildenafil in a solvent in which the target salt is insoluble, i.e. the salt of sildenafil with X is prepared by mixing sildenafil/Y with Z/X (a soluble salt of X). For example a salt of sildenafil with a long chain fatty acid may be prepared by adding an ammonium salt of a long chain fatty acid to a solution of a salt of sildenafil with a weak acid such as acetic acid or similar, preferably in the presence of seeds of the crystalline target salt.

Repeated application of the above techniques for inducing crystallisation of amorphous sildenafil salts may give rise to more than one crystal form of each salt, including polymorphs and pseudopolymorphs such as hydrates and solvates. Even when products are the same crystal form as determined by spectroscopic methods, it is often the case that the product that crystallises from one set of solvent conditions will have superior properties from a product obtained from another set of conditions. This may be the result of an improved crystal shape (habit) or density. Additional ways of preparing polymorphs and pseudopolymorphs include repeated small-scale precipitation of salts from a range of solvents (for example the lists of solvents recommended for trituration procedures above) by heating to dissolution, then cooling or partly evaporating. In addition an antisolvent may be added (selected from those solvents which experimentally are found not to dissolve the salt, even with heating). Preferably non-crystalline sildenafil salts are used for these preparations since this minimises the presence of pre-existing crystal forms which may inhibit the production of alternative crystalline products. Alternatively, hydrates and solvates may be treated with solvents or subjected to a range of different humidities to give other solvates or hydrates. Alternatively, the solvates or hydrates may be subjected to vacuum or oven drying/desolvation, or plunged into an immiscible hot solvent (for example xylene).

Alternatively existing crystalline forms may be subjected to a combination of very high pressure and optionally high temperature, for example melts, or amorphous material maintained above the glass temperature can be induced to crystallise to give a new product. More stable polymorphs may be generated by means of a "polymorph amplifier". This procedure comprises the preparation of a stirred suspension of a crystalline salt in a selected solvent (approximately 5-10% in solution at the lower temperature) and raising the temperature until approximately 90-95% of the solid is dissolved, then allowing the suspension to cool slowly, with stirring, until most of the salt has crystallised. This procedure is repeated cyclically many times, and the product at each stage tested for any change in form.

Crystallisation of novel crystal forms may be brought about by crystallising (for example by evaporation) on quartz or other active surfaces.

Once a novel crystalline form has been produced by application of the above described techniques, improved direct crystallisation techniques can be established by routine experimentation, since seeds of the new form will now be available.

The existence of polymorphs and pseudopolymorphs may be demonstrated by various techniques in combination. Solution NMR and/or elemental analysis is used to demonstrate that both acid and base components are present. The salt is characterised by one or more of the following techniques: infra-red spectroscopy, Raman spectroscopy, X-ray powder or single crystal diffraction, solid-state NMR, melting point, DSC, DTA, optical and electron microscopy, measurements of density, wetting angle, solubility, stability, and flow properties.

The fatty acid salts of sildenafil of this invention may also be prepared as solid or liquid solutions or dispersions in a liquid or polymeric carrier or matrix.

Such matrix dispersions may be prepared in a variety of ways; the salt may be added to the matrix material either as a solid or in solution and the matrix material itself may also be either in the form of a solid (or liquid, as appropriate) or in solution. If both materials are solids then heating and stirring of a melt may be utilised to form a homogenous mixture before the product is cooled, and either ground to a powder, or left as a liquid or semi-liquid suitable for further formulation. Various techniques are known for the formation of suitable granules and platform products from melts, for example spray congealing techniques to produce pellets have been described by Kanig J.Pharm Sci 53, 188, 1964 and by Kreuschner et al. Acta Pharm. Tech. 23, 159, 1980. A liquid matrix may be used to dissolve the solid salt, or a solution of the matrix product may be formed by mixing a solution of the salt with a solution of the matrix material, and the solvent subsequently removed by evaporation or spray-drying. Suitable solvents for preparing solid or liquid solutions or dispersions include water, common alcohols, ketones, esters and, ethers. Particularly preferred solvents are water, methanol, ethanol, n-propanol, propan-2-ol, 1-butanol, isobutyl alcohol, cyclopentanol, 2-ethoxyethanol, 2-methyl-2-butanol, ethyleneglycol, *tert*-butanol, acetone, butanone, isopropylmethylketone, isobutylmethylketone, *tert*-butylmethylketone, *sec*-butylmethylketone, *n*-butylmethylketone, cyclopentanone, cyclohexanone, methyl acetate, ethyl acetate, propyl acetate, ethyl formate, isobutyl acetate, isobutyl formate, diethyl ether, di-isopropyl ether, *tert*-butylmethylether, di-*n*-butyl ether, butylvinylether, *tert*-butylvinylether, tetrahydrofuran, 1,4-dioxane, dichloromethane, acetonitrile, and isobutyronitrile.

In a variation on the procedures described above for the preparation of amorphous salts, the liquid or polymeric carrier or matrix material or solution thereof may form the solvent for the salt formation reaction. Hence the acid and base components may be added separately to the matrix material or solution thereof, optionally with heating to produce a melt or

otherwise ensure a homogenous mixture. The product may then be cooled or evaporated and further treated to produce a form suitable for further formulation.

Suitable ratios of the salt to liquid or polymeric carrier or matrix material may vary from 1:100 to 10:1, preferably from 1:20 to 3:1.

5 If a volatile solvent is used to form the matrix dispersion, it may be difficult to remove it all by evaporation. In the case of solvents such as water or ethanol this is not a problem and substantial residues may be tolerated, indeed may improve the stability and properties of the product. However residues which decrease the viscosity to the extent that crystallisation may occur on storage are undesirable. Less desirable solvents must be removed sufficiently by extended, optionally elevated temperature evaporation to ensure a pharmaceutically acceptable product.

Suitable liquid or polymeric carrier or matrix materials include the following: animal, vegetable or mineral oils, fats, waxes, chocolate, chewing gum base, maize oil, lecithin, groundnut oil, sunflower oil, cottonseed oil, lauroylmonoglyceride, lanolin, gelatin, isinglass, agar, carnauba wax, beeswax, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polyethylene glycol esters, ovalbumin, soybean proteins, gum arabic, starch, modified starch, crospovidone, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, ethyl cellulose, chicle, polypropylene, dextrans, including dextran 40, dextran 70 and dextran 75, dextrans, alpha-, beta-, gamma-cyclodextrins, hydroxypropyl-beta-cyclodextrins, alkylpolyglucosides, chitosan, polyvinylacetate, ethylene vinyl acetate, lectins, carbopols, silicon elastomers, polyacrylic polymers, maltodextrins, lactose, fructose, inositol, trehalose, maltose, raffinose, lauryl alcohol, polysorbate 80, and mixtures.

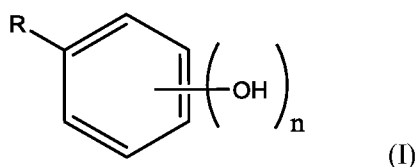
25 Preferred materials are PVP and PEG, which are available in various grades differing chiefly in their mean molecular weight. In the case of PVP this may be between 2,000 and 3,000,000, however material in the range 8,000 to 500,000 is more preferred e.g. PVP K-15, K-30, K-60, K-90. In the case of PEG products the mean molecular weight may be in the range 200 to 20,000, but 1,000 to 10,000 is more preferred e.g. PEG 2000, PEG 8000.

30 It should be appreciated that the salts of the present invention may be prepared on any suitable scale according to the procedures herein outlined and those procedures which are conventional to one skilled in the art of pharmaceutical chemistry, in particular in the preparation of salt forms. Techniques for scale-up are described in the literature for example Pharmaceutical Process Scale-Up by Michael Levin, Marcel Dekker, New York 2003, ISBN 35 0824706250, which publication is incorporated herein by reference.

Once prepared as described above, amorphous, crystalline and liquid solutions of sildenafil salts with long chain fatty acids may be formulated into pharmaceutical compositions, according to procedures well known in the art. Suitable procedures include those provided in Remington: The Science and Practice of Pharmacy 20th edition, Alfonso R Gennaro editor, Lippincott, Williams, and Wilkins, Philadelphia USA, ISBN 0-683-306472; The art, science, and technology of pharmaceutical compounding by Loyd V Allen, American Pharmaceutical Association, 2001, ISBN 1582120358 - incorporated herein by reference. Suitably, these compositions are adapted for oral use such as tablets, capsules, zydis, gums, candies, chocolates, sachet and oral liquids, or are adapted for topical use such as gels, lotions, patches, or ointments, or are adapted for parenteral use such as intravenous, intramuscular, or subcutaneous injection, or are adapted for use as suppositories, or finally are adapted for inhalation therapy such as bronchial or nasal inhalation therapy.

The invention also provides a co-crystal, which co-crystal comprises sildenafil and a co-crystal former, which co-crystal former is a compound which comprises a phenol moiety. Compounds which comprise a phenol moiety include phenol itself and phenol substituted with one or more (typically from one to three) ring substituents.

Typically, in the co-crystal of the invention, the co-crystal former is a compound of formula (I)



wherein

n is an integer of from 1 to 3; and

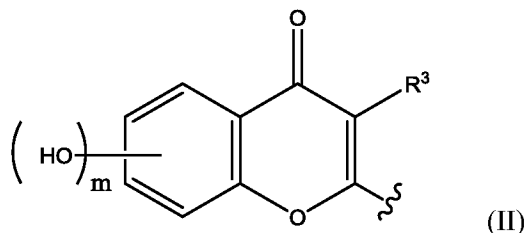
R is H, -C(O)OR<sup>2</sup>, -L-C(O)OR<sup>2</sup>, Ar or -L-Ar;

R<sup>2</sup> is H or unsubstituted C<sub>1-4</sub> alkyl;

L is -CH=CH-

Ar is phenyl or naphthyl, which phenyl or naphthyl is unsubstituted or substituted with from 1 to 3 groups selected from OH and C<sub>1-4</sub> alkyl; or

Ar is a group of formula (II)



wherein

R<sup>3</sup> is H or OH, and

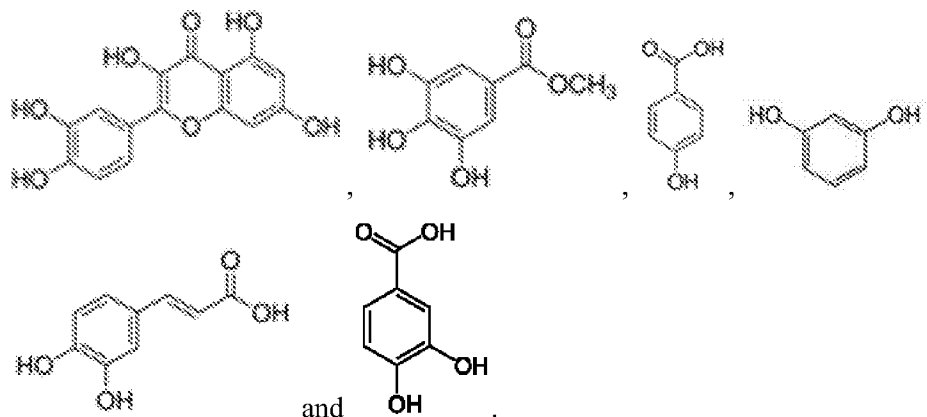
m is 0, 1 or 2.

Usually, when R is H, n is 2 or 3.

Often, R<sup>2</sup> is H or methyl. Typically, Ar is phenyl, which phenyl is unsubstituted or substituted with from 1 to 3 OH groups; or Ar is typically said group of formula (II) wherein

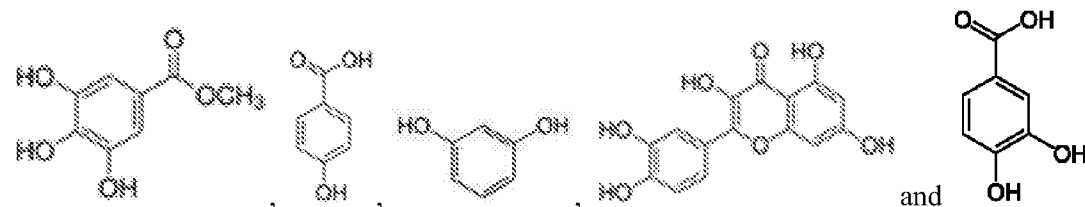
5 R<sup>3</sup> is OH.

The co-crystal former may for instance be selected from compounds having the following structures:



10

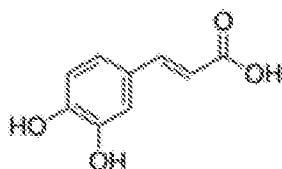
In one embodiment, the co-crystal former is selected from compounds having the following structures:



and the molar ratio of the sildenafil to the co-crystal former in the co-crystal is 1:1.

15

In another embodiment, the co-crystal former is a compound having the following structure:



and the molar ratio of the sildenafil to the co-crystal former in the co-crystal is 3:2.

20

The sildenafil in the co-crystal is generally sildenafil base as opposed to a salt of sildenafil, i.e. it is generally 5-{2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

The co-crystal of the invention may for instance be any of the co-crystals exemplified herein below. It may be any one of the co-crystals P42-I-A, P42-I-B, P42-III, P42-VI-B, P42-

VI-C, P42-VI-D, P42-VI-E, P42-VII, P42-VIII or P42-IX. It may have the characterisation data of any one of these exemplified co-crystals.

The invention also provides a pharmaceutical composition comprising: (i) a co-crystal of the invention as defined herein, and (ii) a pharmaceutically acceptable carrier.

5 The following examples are merely illustrative of the present invention and are not intended to limit it in any way:

### **EXAMPLES**

#### 10 **EXAMPLE 1**

##### Preparation of amorphous sildenafil decanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of decanoic acid (0.182 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil decanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.68 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material.

15  
20 Analysis: C, 59.4%; H, 7.8%; N, 13.0%

#### **EXAMPLE 2**

##### Preparation of amorphous sildenafil decanoic acid salt

A solution of sildenafil decanoate is prepared by heating and ultrasonating a suspension of sildenafil free base (5.0 grammes) and decanoic acid (1.82 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

25

Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
30 Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material, Analysis: C, 59.4%; H, 7.8%; N, 13.0%

35



**EXAMPLE 3**Preparation of crystalline sildenafil decanoic acid salt

Amorphous sildenafil decanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 59.4%; H, 7.8%; N, 13.0%

**EXAMPLE 4**10 Preparation of amorphous sildenafil docosanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of docosanoic acid (0.36 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil decanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.8%; H, 9.2%; N, 10.3%

20

**EXAMPLE 5**Preparation of amorphous sildenafil docosanoic acid salt

A solution of sildenafil docosanoate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and docosanoic acid (3.6 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	42-46°C
Nozzle diameter	2 mm
30 Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.8%; H, 9.2%; N, 10.3%

35

**EXAMPLE 6**Preparation of crystalline sildenafil docosanoic acid salt

Amorphous sildenafil docosanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder dif-  
5 fraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta.  
Analysis: C, 64.8%; H, 9.2%; N, 10.3%

**EXAMPLE 7**Preparation of amorphous sildenafil eicosanoic acid salt

10 Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of eicosanoic acid (0.33 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil eicosanoate is isolated as a glass. After evaporation in the rotary  
15 evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.1%; H, 9.0%; N, 10.7%

**EXAMPLE 8**Preparation of amorphous sildenafil eicosanoic acid salt

A solution of sildenafil eicosanoate is prepared by heating and ultrasonating a suspension of sildenafil free base (5.0 grammes) and eicosanoic acid (3.3 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial  
25 closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	43-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
30 Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below  
35 0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.1%; H, 9.0%; N, 10.7%

**EXAMPLE 9**

Preparation of crystalline sildenafil eicosanoic acid salt

Amorphous sildenafil eicosanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 64.1%; H, 9.0%; N, 10.7%

**EXAMPLE 10**Preparation of amorphous sildenafil heneicosanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of heneicosanoic acid (0.34 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil heneicosanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.5%; H, 9.1%; N, 10.5%

**EXAMPLE 11**Preparation of amorphous sildenafil heneicosanoic acid salt

A solution of sildenafil heneicosanoate is prepared by heating and ultrasonically suspending a suspension of sildenafil free base (5.0 grammes) and heneicosanoic acid (3.4 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	44-49°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 64.5%; H, 9.1%; N, 10.5%

**EXAMPLE 12**

Preparation of crystalline sildenafil heneicosanoic acid salt

Amorphous sildenafil heneicosanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta.

5 Analysis: C, 64.5%; H, 9.1%; N, 10.5%

**EXAMPLE 13**Preparation of amorphous sildenafil heptadecanoic acid salt

10 Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of heptadecanoic acid (0.29 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil heptadecanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide  
15 drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.79 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material,

Analysis: C, 62.9%; H, 8.7%; N, 11.3%

**EXAMPLE 14**Preparation of amorphous sildenafil heptadecanoic acid salt

A solution of sildenafil heptadecanoate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and heptadecanoic acid (2.9 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a  
25 commercial closed-loop spray-drying apparatus, Fielder Mobile Minor<sup>®</sup> manufactured by Niro.

Inlet temperature setting: 90°C

Outlet temperature: 44-48°C

Nozzle diameter 2 mm

30 Pump speed (peristaltic): 26-28 rpm

Feed rate 2 kg/hour

Nitrogen flow 87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below  
35 0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 62.9%; H, 8.7%; N, 11.3%

**EXAMPLE 15**Preparation of crystalline sildenafil heptadecanoic acid salt

Amorphous sildenafil heptadecanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder dif-  
5 fraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis:  
C, 62.9%; H, 8.7%; N, 11.3%

**EXAMPLE 16**Preparation of amorphous sildenafil lauric acid salt

10 Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of lauric acid (0.21 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil laurate is isolated as a glass. After evaporation in the rotary evaporator,  
15 the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.71 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 60.5%; H, 8.1%; N, 12.5%

**EXAMPLE 17**Preparation of amorphous sildenafil lauric acid salt

A solution of sildenafil laurate is prepared by heating and ultrasonating a suspension of sildenafil free base (5.0 grammes) and lauric acid (2.1 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial  
25 closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
30 Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below  
0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typi-  
35 cal of non-crystalline material. Analysis: C, 60.5%; H, 8.1%; N, 12.5%

**EXAMPLE 18**

Preparation of crystalline sildenafil lauric acid salt

Amorphous sildenafil laurate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 60.5%;  
5 H, 8.1%; N, 12.5%

**EXAMPLE 19**Preparation of amorphous sildenafil myristic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of myristic acid (0.24 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil myristate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and  
10 dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.74 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 61.5%; H, 8.3%; N, 12.0%

**EXAMPLE 20**Preparation of amorphous sildenafil myristic acid salt

A solution of sildenafil myristate is prepared by heating and ultrasonically suspending a suspension of sildenafil free base (5.0 grammes) and myristic acid (2.4 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

25 Inlet temperature setting: 90°C  
Outlet temperature: 42-48°C  
Nozzle diameter 2 mm  
Pump speed (peristaltic): 26-28 rpm  
Feed rate 2 kg/hour  
30 Nitrogen flow 87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.5 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 61.5%; H, 8.3%; N, 12.0%

35

**EXAMPLE 21**Preparation of crystalline sildenafil myristic acid salt

Amorphous sildenafil myristate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 61.5%; H, 8.3%; N, 12.0%

5

**EXAMPLE 22**Preparation of amorphous sildenafil nonadecanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of nonadecanoic acid (0.32 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil nonadecanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.82 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 63.7%; H, 8.9%; N, 10.9%

**EXAMPLE 23**Preparation of amorphous sildenafil nonadecanoic acid salt

A solution of sildenafil nonadecanoate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and nonadecanoic acid (3.2 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor<sup>®</sup> manufactured by Niro.

25	Inlet temperature setting:	90°C
	Outlet temperature:	45-49°C
	Nozzle diameter	2 mm
	Pump speed (peristaltic):	26-28 rpm
	Feed rate	2 kg/hour
30	Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.5 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 63.7%; H, 8.9%; N, 10.9%

35

**EXAMPLE 24**Preparation of crystalline sildenafil nonadecanoic acid salt

Amorphous sildenafil nonadecanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 63.7%; H, 8.9%; N, 10.9%

5

**EXAMPLE 25**Preparation of amorphous sildenafil nonanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of nonanoic acid (0.17 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil nonanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.67 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 58.8%; H, 7.7%; N, 13.3%

**EXAMPLE 26**Preparation of amorphous sildenafil nonanoic acid salt

A solution of sildenafil nonanoate is prepared by heating and ultrasonating a suspension of sildenafil free base (5.0 grammes) and nonanoic acid (1.7 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.5 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 58.8%; H, 7.7%; N, 13.3%

**EXAMPLE 27**Preparation of crystalline sildenafil nonanoic acid salt



Amorphous sildenafil nonanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 58.8%; H, 7.7%; N, 13.3%

5

**EXAMPLE 28**Preparation of amorphous sildenafil octanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of octanoic acid (0.152 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil octanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.65 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 58.2%; H, 7.5%; N, 13.6%

10

15

**EXAMPLE 29**Preparation of amorphous sildenafil octanoic acid salt

A solution of sildenafil octanoate is prepared by heating and ultrasonicing a suspension of sildenafil free base (5.0 grammes) and octanoic acid (1.52 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

20

Inlet temperature setting:	90°C
Outlet temperature:	42-46°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

25

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.5 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 58.2%; H, 7.5%; N, 13.6%

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**EXAMPLE 30**Preparation of crystalline sildenafil octanoic acid salt

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Amorphous sildenafil octanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 58.2%; H, 7.5%; N, 13.6%

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**EXAMPLE 31**Preparation of amorphous sildenafil palmitic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of palmitic acid (0.27 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil palmitate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.77 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 62.4%; H, 8.6%; N, 11.5%

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**EXAMPLE 32**Preparation of amorphous sildenafil palmitic acid salt

A solution of sildenafil palmitate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and palmitic acid (2.7 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

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Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

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After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.0 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 62.4%; H, 8.6%; N, 11.5%

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**EXAMPLE 33**Preparation of crystalline sildenafil palmitic acid salt

Amorphous sildenafil palmitate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 62.4%; H, 8.6%; N, 11.5%

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**EXAMPLE 34**Preparation of amorphous sildenafil pentadecanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of pentadecanoic acid (0.26 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil pentadecanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.76 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 62.0%; H, 8.4%; N, 11.7%

**EXAMPLE 35**Preparation of amorphous sildenafil pentadecanoic acid salt

A solution of sildenafil pentadecanoate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and pentadecanoic acid (2.6 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

25	Inlet temperature setting:	90°C
	Outlet temperature:	45-49°C
	Nozzle diameter	2 mm
	Pump speed (peristaltic):	26-28 rpm
	Feed rate	2 kg/hour
30	Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 62.0%; H, 8.4%; N, 11.7%

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**EXAMPLE 36**Preparation of crystalline sildenafil pentadecanoic acid salt

Amorphous sildenafil pentadecanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 62.0%; H, 8.4%; N, 11.7%

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**EXAMPLE 37**Preparation of amorphous sildenafil stearic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of stearic acid (0.3 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil stearate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 63.3%; H, 8.8%; N, 11.1%

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**EXAMPLE 38**Preparation of amorphous sildenafil stearic acid salt

A solution of sildenafil stearate is prepared by heating and ultrasonically a suspension of sildenafil free base (5.0 grammes) and stearic acid (3.0 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

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Inlet temperature setting:	90°C
Outlet temperature:	44-47°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

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After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.6 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 63.3%; H, 8.8%; N, 11.1%

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**EXAMPLE 39**Preparation of crystalline sildenafil stearic acid salt

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Amorphous sildenafil stearate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 63.3%; H, 8.8%; N, 11.1%

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**EXAMPLE 40**Preparation of amorphous sildenafil tetracosanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of tetracosanoic acid (0.39 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil tetracosanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.89 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 65.5%; H, 9.3%; N, 10.0%

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**EXAMPLE 41**Preparation of amorphous sildenafil tetracosanoic acid salt

A solution of sildenafil tetracosanoate is prepared by heating and ultrasonically suspending sildenafil free base (5.0 grammes) and tetracosanoic acid (3.9 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.6 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 65.5%; H, 9.3%; N, 10.0%

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**EXAMPLE 42**Preparation of crystalline sildenafil tetracosanoic acid salt

Amorphous sildenafil tetracosanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 65.5%; H, 9.3%; N, 10.0%

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**EXAMPLE 43**Preparation of amorphous sildenafil tricosanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of tricosanoic acid (0.374 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil tricosanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.87 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 65.2%; H, 9.2%; N, 10.1%

**EXAMPLE 44**Preparation of amorphous sildenafil tricosanoic acid salt

A solution of sildenafil tricosanoate is prepared by heating and ultrasonically suspending a suspension of sildenafil free base (5.0 grammes) and tricosanoic acid (3.74 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	45-49°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 3.5 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 65.2%; H, 9.2%; N, 10.1%

**EXAMPLE 45**Preparation of crystalline sildenafil tricosanoic acid salt

Amorphous sildenafil tricosanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 65.2%; H, 9.2%; N, 10.1%

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**EXAMPLE 46**Preparation of amorphous sildenafil tridecanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of tridecanoic acid (0.226 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil tridecanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.72 g.

X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 61.0%; H, 8.2%; N, 12.2%

**EXAMPLE 47**Preparation of amorphous sildenafil tridecanoic acid salt

A solution of sildenafil tridecanoate is prepared by heating and ultrasonically a suspension of sildenafil free base (5.0 grammes) and tridecanoic acid (2.26 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	45-49°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.8 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 61.0%; H, 8.2%; N, 12.2%

**EXAMPLE 48**Preparation of crystalline sildenafil tridecanoic acid salt

Amorphous sildenafil tridecanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta. Analysis: C, 61.0%; H, 8.2%; N, 12.2%

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**EXAMPLE 49**Preparation of amorphous sildenafil undecanoic acid salt

Solid sildenafil free base (0.5 grammes) is dissolved in a mixture of dichloromethane/methanol (5 ml, 9:1) with gentle warming and ultrasonication. A solution of undecanoic acid (0.2 g) in absolute ethanol is mixed very rapidly in a rotary evaporator flask. High vacuum is applied and the flask is maintained at an external temperature of 40°C and rotated rapidly. The solid amorphous sildenafil undecanoate is isolated as a glass. After evaporation in the rotary evaporator, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 0.7 g.

X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 60.0%; H, 7.9%; N, 12.7%

**EXAMPLE 50**Preparation of amorphous sildenafil undecanoic acid salt

A solution of sildenafil undecanoate is prepared by heating and ultrasonically suspending a suspension of sildenafil free base (5.0 grammes) and undecanoic acid (2.0 g) in absolute ethanol (100 ml). The solution is kept hot by means of a jacketed feeder system and spray dried in a commercial closed-loop spray-drying apparatus, Fielder Mobile Minor ® manufactured by Niro.

Inlet temperature setting:	90°C
Outlet temperature:	44-48°C
Nozzle diameter	2 mm
Pump speed (peristaltic):	26-28 rpm
Feed rate	2 kg/hour
Nitrogen flow	87 kg/hour

After completion of spray-drying, the flask is placed in a desiccator containing a dish of phosphoric oxide drying agent, and dried under high vacuum to a residual solvent level of below 0.2%. Yield 2.4 g. X-ray powder diffraction shows a single very broad diffraction peak typical of non-crystalline material. Analysis: C, 60.0%; H, 7.9%; N, 12.7%

**EXAMPLE 51**Preparation of crystalline sildenafil undecanoic acid salt



Amorphous sildenafil undecanoate (approx. 0.02 g) is triturated (as described in the main specification) until the form of the solid is observed to change. Analysis by x-ray powder diffraction shows characteristic sharp reflections in the range 5 to 30 degrees 2 theta.

Analysis: C, 60.0%; H, 7.9%; N, 12.7%

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**EXAMPLE 52: osmotic pump core containing sildenafil citrate**

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 (50/50)	10 mg

All the sildenafil citrate, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogenously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator. After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

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**EXAMPLE 53: osmotic pump core containing sildenafil free base**

Material	Ingredient	Amount
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Active	sildenafil	50 mg
Osmagent/Fillers	citric acid	50 mg
	sodium chloride	60 mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 (50/50)	10 mg

All the sildenafil, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator. After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

#### 20 EXAMPLE 54: osmotic pump core containing amorphous sildenafil

Material	Ingredient	Amount
Active	sildenafil base adsorbed on to Amberlite ® XAD-7	50 mg
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

All the sildenafil, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator. After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

20 **EXAMPLE 55: osmotic pump core containing a soluble salt of sildenafil**

Material	Ingredient	Amount
Active	sildenafil mesylate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

All the sildenafil, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator. After drying,

the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

**EXAMPLE 56: osmotic pump core containing ultrafine sildenafil**

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

Pass all the excipients and the active agent separately through a 60 mesh screen. Sildenafil citrate drug substance is loaded into a specially constructed 0.5 metre stainless steel ball milling chamber in which the inner surface has been treated with a Teflon coating. To the chamber is added a selection of Zirconium Oxide (Zircoa Inc.) grinding beads with diameters ranging from 1 mm up to 50 mm to fill approximately 50% of the chamber volume. The mill chamber is then rotated at a speed to allow cascading of mill contents to occur, usually a full rotation every 2 seconds. This milling process is continued for 4 days. After day 4, half of the mannitol is added to chamber and the milling process is continued for a further day. The purpose of the mannitol is to act as a carrier substrate for the cohesive ultrafine particles. The ultrafine sildenafil, sodium chloride, the remaining mannitol, polyvinylpyrrolidone, and part of the sodium lauryl sulphate are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously

blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator. After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

15 **EXAMPLE 57: rapid release layer containing sildenafil mesylate compressed around an osmotic pump core containing sildenafil citrate**

Osmotic pump inner core formula

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

Rapid release outer layer formula

Ingredient /rapid layer	Amount (mg per tablet)	Material
Active	25 mg (pfb)	sildenafil mesylate
Filler	30 mg	microcrystalline cellulose
Filler	15 mg	dibasic calcium phosphate dihydrate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate

20 All the sildenafil, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate for the core are passed through a 60 mesh screen and mixed in a V-blender for

30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator.

5 After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an

10 approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical

15 aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

The rapid release layer is prepared by blending the ingredients from the rapid release formula table. Sildenafil mesylate, half of the microcrystalline cellulose, half of the dibasic calcium

20 phosphate and half of the sodium croscarmellose are blended in a Fielder granulator for 30 minutes. The mixture is then removed and blended for a further 30 minutes with the remaining dibasic calcium phosphate, sodium croscarmellose, and microcrystalline cellulose using a twin shell V-blender. The magnesium stearate is then added to the mixture and mixed together for 5 minutes.

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This material is then compressed around the osmotic pump cores by means of a Kilian RUD press-coating tableting machine to form a rapid release layer around the cores.

**EXAMPLE 58: rapid release layer containing ultrafine sildenafil compressed around an osmotic pump core containing sildenafil citrate**

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Osmotic pump inner core formula

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg

Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

## Rapid release outer layer formula

<b>Ingredient /rapid layer</b>	<b>Amount (mg per tablet)</b>	<b>Material</b>
Active	25 mg (pfb)	Ultrafine sildenafil citrate
Filler	30 mg	microcrystalline cellulose
Filler	15 mg	dibasic calcium phosphate dihydrate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate

All the sildenafil, sodium chloride, mannitol, polyvinylpyrrolidone, and half of the sodium lauryl sulphate for the core are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is agitated for 20 minutes or until satisfactory granulation has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, and dried in a warm fluidised bed granulator.

After drying, the granules are milled and passed through a 20 mesh screen, then the remainder of the sodium lauryl sulphate is added and mixed together for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture until an approximate 10% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 2 mm depending upon drug release requirements.

The sildenafil mixture for the rapid release layer is prepared by loading sildenafil citrate drug substance into a specially constructed 0.5 metre stainless steel ball milling chamber in which the inner surface has been treated with a Teflon coating. To the chamber is added a selection of Zirconium Oxide (Zircoa Inc.) grinding beads with diameters ranging from 1 mm up to 50

mm to fill approximately 50% of the chamber volume. The mill chamber is then rotated at a speed to allow cascading of mill contents to occur, usually a full rotation every 2 seconds. This milling process is continued for 4 days. After day 4, half of the microcrystalline cellulose is added to chamber and the milling process is continued for a further day. The purpose of the microcrystalline cellulose is to act as a carrier substrate for the cohesive ultrafine particles. The milled active is then blended with the remaining microcrystalline cellulose, half of the dibasic calcium phosphate and half of the sodium croscarmellose in a Fielder a granulator for 30 minutes. The mixture is then removed and blended with the remaining dibasic calcium phosphate, sodium croscarmellose in a V-blender for a further 30 minutes. The magnesium stearate is then added to the mixture and mixed together for 5 minutes. The product is then compressed around the osmotic pump cores by means of a Kilian RUD press-coating tabletting machine to form the rapid release layer for the drug dosage form.

**EXAMPLE 59: rapid release layer containing an effervescent couple of sildenafil citrate compressed around an osmotic pump core containing sildenafil citrate**

Osmotic pump inner core formula

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

Rapid release outer layer formula

Ingredient /rapid layer	Amount (mg per tablet)	Material
Active	25 mg (pfb)	sildenafil citrate
Filler	10 mg	microcrystalline cellulose
Effervescent Couple	15 mg	citric acid
	25 mg	sodium bicarbonate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate

Pass all the excipients and the active agent separately through a 60 mesh screen. The osmotic pump cores are prepared by the procedures detailed in the preceding Examples 52 onwards.



The sildenafil mixture for the rapid release layer is prepared by blending the ingredients from the rapid release outer layer formula table. The active, half of the microcrystalline cellulose, half of the dibasic calcium phosphate and half of the sodium croscarmellose are blended in a Fielder granulator for 30 minutes. The mixture is then removed and blended with the remaining dibasic calcium phosphate, sodium croscarmellose, microcrystalline cellulose in a twin shell V-blender for a further 30 minutes. The magnesium stearate is then added to the mixture and mixed together for 5 minutes. The product is then compressed around the osmotic pump cores by means of a Kilian RUD press-coating tableting machine to form the rapid release layer for the drug dosage form.

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**EXAMPLE 60: rapid release layer of sildenafil citrate sprayed around an osmotic pump core containing sildenafil citrate**

Osmotic inner core formula

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	Cellulose Acetate/PEG 400 ( 50/50)	10 mg

15 Rapid release outer layer formula

Ingredient	Amount % w/w
Sildenafil citrate	12.5
Opadry Clear	3.0
Polysorbate 80	1.0
Purified water	qs

Pass all the excipients and the active agent separately through a 60 mesh screen. The osmotic pump cores are prepared by the procedures detailed in the preceding Examples 52 onwards.

The rapid release layer of sildenafil is prepared by loading the osmotic pump cores into a Manesty Accela-Cota rotating coating pan and directly film coating the inner cores with a layer of sildenafil citrate mixture until the desired weight gain is achieved. Coating is performed using an inlet temperature between 60-66°C, an exhaust temperature between 39-40°C, a bed temperature fixed between 43-46°C, an atomising air-pressure of 1.5 to 2.5 bar, an airflow of 1400-1500 m<sup>3</sup>/hr (800-900cfm), and a spray rate of 200-300 g/min.

In alternative embodiments of the invention, the sildenafil citrate in the rapid release layer may be replaced by amorphous or ultrafine sildenafil citrate or other salts of sildenafil, for example sildenafil mesylate.

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**EXAMPLE 61: capsule containing a rapid release tablet of sildenafil mesylate and an osmotic pump tablet containing sildenafil citrate**

Osmotic pump tablet

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

15 Rapid release tablet

Ingredient	Amount (mg per tablet)	Material
Active	25 mg (pfb)	sildenafil mesylate
Filler	30 mg	microcrystalline cellulose
Filler	15 mg	dibasic calcium phosphate dihydrate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate

The osmotic core tablet is prepared from the ingredients in the table by the procedures described in the preceding Examples 52 onwards.

The rapid release tablet is prepared by first blending the ingredients in the rapid release tablet table. Thus, the sildenafil mesylate, half of the microcrystalline cellulose, half of the dibasic calcium phosphate and half of the sodium croscarmellose are blended in a Fielder granulator

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for 30 minutes. The mixture is then removed and blended with the remaining dibasic calcium phosphate, sodium croscarmellose, microcrystalline cellulose in a twin shell V-blender for a further 30 minutes. The magnesium stearate is then added to the mixture and mixed together for 5 minutes. The resulting mixture is then compressed using a Korsch tablet press. The osmotic tablet and the rapid release tablet are encapsulated together into a hard gelation DB capsule Size AA (Capsugel) using a Zanassi 70 capsule filling machine (IMA).

**EXAMPLE 62: osmotic pump containing sildenafil citrate with a time delay**

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	Cellulose Acetate/PEG 400 ( 80/20)	10 mg

10 Lubricated granules for proton pump cores are prepared from the ingredients in the table by the procedures described in the preceding Examples 52 onwards. The lubricated granules are transferred to a conventional tablet press (Manesty, Fette, Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (80:20) mixture is sprayed on to the cores from a acetone/water mixture until an approximately 20% increase in weight gain has been achieved. The coated cores are then allowed to cure to ensure that a well-defined coat with full integrity has been achieved. Next a passage way is created through the semipermeable membrane either by mechanical means or using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes are between 0.05 mm up to 20 2 mm depending upon drug release requirements.

The result of a thicker coat (~20% by weight) and a higher level of cellulose acetate (80%) than in previous Examples is that a delay will occur before the osmotic pump is activated due to the slower ingress of aqueous fluids through the semi-permeable membrane. Modification of the coat thickness and permeability enables control of delay times and rate of release. Typically delay times may be adjusted from as little as 0.5 hrs to about 8 hours.

**EXAMPLE 63: osmotic pump core containing sildenafil citrate with a pH dependent delay**

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-permeable membrane	cellulose acetate/PEG 400 ( 50/50)	10 mg

The osmotic pump core is prepared from the ingredients in the table by the procedures described in the preceding Examples 52 onwards.

A delay is induced onto the normal operation of the osmotic pump core by the application of a pH dependant coating, for example a coating that will dissolve at pH greater than 5.0. Hence, application of an enteric coat confers protection to the tablet core until it reaches the small or large intestine. A suitable enteric coat may consist of Eudragit L30 D-55 (30% aqueous dispersion) 76.8% w/w, triethyl citrate 7.7 % w/w, talc 15.5 % w/w, or alternatively the enteric coat could consist of Eudragit S100/S12.5.

**EXAMPLE 64: osmotic pump core containing sildenafil citrate with delayed activation, surrounded by a rapid release layer of sildenafil mesylate**

Osmotic pump core with delayed activation

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride	55 mg
	mannitol	55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Semi-Permeable Membrane	cellulose acetate/PEG 400 ( 80/20)	10 mg

Rapid release outer layer

Ingredient /rapid layer	Amount (mg per tablet)	Material
Active	25 mg (pfb)	sildenafil mesylate

Filler	30 mg	microcrystalline cellulose
Filler	15 mg	dibasic calcium phosphate dihydrate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate

The delayed activation osmotic pump core is prepared from the ingredients of the table by the procedures described in Example 62.

- 5 The rapid release layer is prepared by first blending the ingredients in the rapid release outer layer table. All the sildenafil mesylate, half the microcrystalline cellulose, half the dibasic calcium phosphate, and half the sodium croscarmellose are blended in a Fielder granulator for 30 minutes. The mixture is then removed and blended with the remaining dibasic calcium phosphate, sodium croscarmellose, and microcrystalline cellulose using a twin shell V-blender for
- 10 a further 30 minutes. The magnesium stearate is then added to the mixture and mixed together for 5 minutes. This rapid releasing layer is then compressed around the duly formed osmotic pump cores by the employment of a Kilian RUD press-coating tableting machine.

**EXAMPLE 65: osmotic core with an enteric coat containing sildenafil citrate, surrounded by a rapid release layer of sildenafil mesylate**

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Inner osmotic core with an enteric coat

Material	Ingredient	Amount
Active	sildenafil citrate	50 mg (pfb)
Osmagent/Fillers	sodium chloride mannitol	55 mg 55mg
Binder	polyvinylpyrrolidone K30	9 mg
Solubiliser/Lubricant	sodium lauryl sulphate	6 mg
Core Weight		175 mg
Semi-Permeable Membrane	Cellulose Acetate/PEG 400 ( 50/50)	10 mg
Final Coat Weight		185 mg

Rapid release outer layer formula

Ingredient /rapid layer	Amount (mg per tablet)	Material
Active	25 mg (pfb)	sildenafil mesylate

Filler	30 mg	microcrystalline cellulose
Filler	15 mg	dibasic calcium phosphate dihydrate
Disintegrant	4.25 mg	sodium croscarmellose
Lubricant	0.75 mg	magnesium stearate
Final weight of IR layer	75 mg	

Pass all the excipients and the active agent separately through a 60 mesh screen. Sildenafil, sodium chloride, mannitol, part of the sodium lauryl sulphate and polyvinylpyrrolidone are passed through a 60 mesh screen and mixed in a V-blender for 30 minutes. The dry blended material is then transferred to a large granulator and a granulating fluid consisting of water is sprayed onto the mixture. The mixture is then agitated for 20 minutes at an appropriate blending speed to ensure an adequate endpoint has been achieved. The homogeneously blended material is then passed through a 30 mesh screen, prior to drying in a warm fluidised bed granulator. After drying, the granules are milled and passed through a 20 mesh screen prior to the remainder of the sodium lauryl sulphate being added to the granules and mixed for a further 10 minutes. The lubricated granules are then transferred to a conventional tablet press (Korsch) and compressed into 175 mg, 8 mm round biconvex tablet cores. These cores are then transferred into a Manesty Accela-Cota rotating coating pan and a film coat of cellulose acetate/polyethylene glycol (50:50) mixture is sprayed on to the cores from a acetone/water mixture to approximately 10% increase in weight gain has been achieved. The coated cores are then allowed to cure for an appropriate period time and temperature to ensure that a well-defined coat with full integrity has been achieved (0.1 mm to 0.3 mm thick). Next a passage way is created through the semipermeable membrane either through mechanical means or more likely by using a laser drilling machine (Coherent, Convergent Prima). Typical aperture sizes can lie between 0.05 mm up to 2 mm depending upon therapeutic rate requirements.

A lag time can be induced on to the osmotic pump by the application of a pH dependant coatings i.e. dissolve at pH's greater than 5.0. In this example, the application of an enteric coat guarantees that the coat dissolves either in the small or large intestine where the pH lies between pH 5.0 to 7.0 as oppose to dissolving in the stomach where the pH lies below 5.0.

The enteric coat consists of Eudragit L30 D-55 (30% aqueous dispersion) 76.8%w/w, Triethyl Citrate 7.7 %w/w, Talc 15.5 % w/w or alternatively the enteric coat could consist of Eudragit S100/S12.5.

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The rapid releasing layer is prepared by first blending the ingredients in the above table. Sildenafil mesylate, half of the microcrystalline cellulose, half of the dibasic calcium phosphate and half of the sodium croscarmellose are blended in fielder granulator for 30 minutes. The mixture is then removed and blended with the remaining dibasic calcium phosphate, sodium croscarmellose, microcrystalline cellulose using a twin shell V-blender for a further 30 minutes. The magnesium stearate is then added to the mixture and then mixed for 5 minutes. The resulting product is then compressed around the osmotic pump cores by means of a Kilian RUD press-coating tableting machine to form the rapid release layer for the drug dosage form.

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The principles described in the above Examples can be applied to the production of sildenafil dosage forms with any combination of rapid, conventional, delayed and prolonged release characteristics to deliver the blood plasma profiles required for the improved formulations of this invention, and to deliver sildenafil within the therapeutic window either more rapidly than the currently marketed swallow tablets containing sildenafil, or continuously for a long period of time compared to the currently marketed swallow tablets containing sildenafil, or more rapidly and continuously for a long period of time when compared to currently marketed swallow tablets containing sildenafil.

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#### **Pharmacological Data**

In the prescribing information for VIAGRA™, published as reference 69-5485-00-9, under the heading of clinical pharmacology, in particular under the sub-heading of "pharmacokinetics and metabolism", mean sildenafil plasma concentrations in healthy male volunteers after administration of a single dose of 100 mg of sildenafil are provided in figure 1. Under the sub-heading "pharmacodynamics" it is stated that "The time course of effect in one study, showing an effect for up to 4 hours but the response was diminished compared to 2 hours." This information is herein incorporated by reference.

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The formulations of the present invention are tested in the animal and human models described in the patents and references herein mentioned and found to be PDE5 inhibitors. The formulations of the present invention can therefore be used in the treatment and/or prophylaxis of the disorders described in the above mentioned patents and are incorporated herein by reference. Guidance is to place the tablet under the tongue for 60 seconds (see caffeine summary where we tested how much caffeine dissolved by doing this as substitute for Viagra) then swallow the tablet. Described herein is our model of how the tablet dissolves based on

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different pH levels by our estimates we will deliver the equivalent sildenafil in plasma somewhere around to a normal dose of 100 mg with about 112% to 116% of AUC (so within 505b2 guidelines). We will model and/or test in human next to confirm.

## 5 EXAMPLE 66: Sildenafil Cocrystal Screening

This Example describes the results of the project entitled “Cocrystal screening of P42” conducted at the Scientific and Technological Centers of the University of Barcelona (CCiT-UB). The study has been performed by the technicians of the Polymorphism and Calorimetry Unit (CCiT-UB) in collaboration with the X-ray diffraction Unit (CCiT-UB). The main aim of the study was the search of new cocrystals of Sildenafil (referenced as P42) by performing a cocrystal screening.

### 1. Bibliographic precedents

- 15 - Patent EP0463756A1 (1991): it claims preparation methods for synthesis of Sildenafil base and other pyrazolopyrimidinethione derivatives. PXRD diffractogram and DSC/TGA thermograms are not reported.
- Mustafa M. E I-Abadelah, Salim S. Sabria, Monther A. Khanfar, Wolfgang Voelte and Căcilia Maichle-Mössmer. *Zeitschrift für Naturforschung B.*, (1999) Volume 54b, Pages 1323–1326. A crystal structure is reported: iso-Sildenafil base (CCDC: CAXZEG).
- 20 - Patent WO02102802A (2002): it claims preparation methods for the synthesis of Sildenafil base and other pyrazolopyrimidinethione derivatives. PXRD diffractogram and DSC/TGA thermograms are not reported.
- Hemmige S. Yathirajan, Basavegowda Nagaraj, Padmarajaiah Nagarajaa and Michael Bolteb. *Acta Crystallographica*, (2005), 61, Pages 489-491. A crystal structure is reported: Sildenafil citrate monohydrate (CCDC: FEDTEO).
- Iwona Wawer, Maciej Pisklak and Zdzisław Chilmonczyk, *Journal of Pharmaceutical and Biomedical Analysis*, (2005), 38, Pages 865–870. Sildenafil base and its citrate  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{15}\text{N}$  NMR spectra.
- 30 - Rahul Banerjee, Prashant M. Bhatt and Gautam R. Desijaru, *Crystal Growth & Design*, (2006), 6(6), Pages 1468-1478. The following crystal structures are reported: Sildenafil saccharinate hemikis (ethanol) clathrate (CCDC: QEKVEI), Sildenafil saccharinate methanol clathrate (CCDC: QEKVIM), Sildenafil saccharinate hemikis (dimethylsulfoxide) clathrate (CCDC: QEKVOS), Sildenafil saccharinate nitromethane clathrate (CCDC: QEKVUY), Sildenafil saccharinate hemikis (pyrrolidinone) clathrate (CCDC: QEKWAF), Sildenafil saccharinate (CCDC: QEKVEJ), Sildenafil
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- saccharinate formamide clathrate (CCDC: QEKWIN), Sildenafil saccharinate hemikis (1,4-dioxane) clathrate (CCDC: QEKWOT), Sildenafil saccharinate hemikis (ethylene glycol) clathrate (CCDC: QEKWUZ), Sildenafil saccharinate hemikis (dimethylformamide) clathrate (CCDC: QEMLEA), Sildenafil saccharinate acetonitrile clathrate (CCDC: QEMLIE) and Sildenafil saccharinate hemikis dehydrate clathrate (CCDC: QEMLOK).
- 5
- Mahmoud M. Al Omari, Mohammad B. Zughul, J. Eric D. Davies and Adnan A. Badwan, *J. Incl. Phenom. Macrocycl. Chem* (2007) 57 Pages: 379–384. Sildenafil:  $\beta$ -cyclodextrin complex. PXRD diffractogram and DSC/TGA thermograms are not reported.
  - 10 - Patent WO2007080362A1 (2007): it claims Sildenafil Acetylsalicylic acid cocrystals. A PXRD diffractogram, crystal data and DSC/TGA thermograms are reported.
  - Patent WO2007110559A1 (2007): it claims: Sildenafil hydrochloride (polymorphs I, II and III); Sildenafil hydrogensulfate (polymorphs I, II and III); Sildenafil hemisulfate (polymorph I); Sildenafil hemitartrate (polymorphs I and II); Sildenafil esylate (polymorphs I, II, III and IV) and Sildenafil fumarate (polymorph I). PXRD diffractograms, crystal data (sildenafil esylate polymorph I) and a DSC thermogram are reported.
  - 15 - Patent PT16633364E (2008): preparation methods for the synthesis of Sildenafil base and Sildenafil citrate. PXRD diffractogram and DSC/TGA thermograms are not reported.
  - 20 - Patent WO2010146407A: it claims nanoparticles of Sildenafil citrate. A PXRD diffractogram (Figure 6) is reported.
  - Patent RU2012101818A: PXRD diffractogram and DSC/TGA thermograms are not reported.
  - 25 - Dmitrijs Stepanovs and Anatoly Mishnev, *Zeitschrift für Naturforschung B.*, (2012) Volume 67, Issue 10, Pages 491–494. Crystal structure is reported: Sildenafil base (form I) (CCDC: QEGTUT).
  - Palash Sanphui, Sridu Tothadi, Sommath Ganguly and Gautam R. Desijaru, *Molecular Pharmaceutics*, (2013), 10, Pages 4687-4697. The following crystal structures are reported: Sildenafil hemikis (oxalate) (CCDC: YIWWIM), Sildenafil hydrogenfumarate trihydrate (CCDC: YIWWOS), Sildenafil hemikis (succinate) monohydrate (CCDC: YIWWUY), Sildenafil hemikis (glutarate) (CCDC: YIWXAF), Sildenafil adipic acid cocrystal (CCDC: YIWXEJ), Sildenafil pimelic acid cocrystal (CCDC: YIWXIN), Sildenafil suberic acid cocrystal (CCDC: YIWXOT) and Sildenafil sebacic acid cocrystal (CCDC: YIWXUZ).
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- Miroslav Žegarac, Edislav Lekšić, PrimožŠket, Janez Plavec, Maja Devčić Bogdanović, Dejan-Krešimir Bučar, Miljenko Dumić and Ernest Meštrović, *CrystEngComm* (2014), 16, 32-35. A Sildenafil base: Acetylsalicylic acid cocrystal is reported: Crystal data: triclinic, P1,  $a = 9.6707(7) \text{ \AA}$ ,  $b = 12.3070(7) \text{ \AA}$ ,  $c = 14.5432(12) \text{ \AA}$ ,  $\alpha = 85.266(2)^\circ$ ,  $\beta = 74.549(5)^\circ$ ,  $\gamma = 82.829(6)^\circ$ ,  $V = 1653.1(2) \text{ \AA}^3$ ,  $T = 298(2) \text{ K}$  and  $Z = 2$ .
  - Somchai Sawatdee, Chaveng Pakawatchai, Kwanjai Nitichai, Teerapol Srichana and Hirihattaya Phetmung. *Saudi Pharmaceutical Journal*. (2015), 23, Pages 504-514. Crystallographic data of Sildenafil base (CCDC: QEGTUT) and Sildenafil citrate monohydrate (CCDC: FEDTEO) are reported.
  - Avani P. Khristi, Dr. Tejal Soni and Dr. B.N. Suhagia. *Indo American Journal of Pharmaceutical Research*, (2015), 5(7), Pages 2700-2708. Sildenafil citrate: Aspirin cocrystal. A PXRD diffractogram and a DSC thermogram are reported.
  - Dmitrijs Stepanovs, Mara Jureb and Anatoly Mishneva. *Mendeleev Commun.*, (2015), 25, Pages 49–50. Sildenafil salicylate: Crystal data: triclinic, P-1,  $a = 9.5030(3)$ ,  $b = 11.6242(4)$  and  $c = 14.2074(6) \text{ \AA}$ ,  $\alpha = 99.167(1)^\circ$ ,  $\beta = 108.370(1)^\circ$ ,  $\gamma = 92.229(2)^\circ$ ,  $V = 1463.75(9) \text{ \AA}^3$ ,  $T = 173(2) \text{ K}$  and  $Z = 2$ . The compound melts between 179–182 °C.
- 20 The calculated PXRD diagram from the crystal structure (CCDC) of the published P42 form in comparison to the initial batch of P42 (sildenafil base) as received is shown in figure 1.

## 2. Results and Discussion

### 2.1. Characterization of the initial batch

25 Initially, the sample supplied with reference Sildenafil base, batch: 101071417 (P42) (EXT-15-108) has been characterized by means of PXRD, DSC, TGA and <sup>1</sup>H-NMR. This sample corresponds to the same crystal structure reported in literature (CCDC ref. code: QEGTUT), according to their PXRD diffractograms (Figure 1). The original sample has been analyzed by PXRD after grinding and it remains unchanged (Figure 2). A melting point of 189°C is observed in the DSC analysis and no weight loss is observed in the TGA analysis from room temperature to 300°C.

### 2.2 Solubility study of P42

35 Initially, a solubility study of P42 in 30 solvents has been conducted at r.t. and at high temperature. P42 is soluble at r.t. in the following solvents: MeOH, EtOH, formic acid, MEK, acetone, MiBK, DMF, DMSO, AcOEt, THF, DME, dioxane, DCM, chloroform, acetic acid, benzyl alcohol and diethylamine; it is soluble at 50°C in IPA, butanol, ACN, toluene, xylene and

NH<sub>3</sub> (32%) in water. It is insoluble in ethylene glycol, H<sub>2</sub>O, pentane, heptane, cyclohexane, Et<sub>2</sub>O and DIE.

5 The solutions obtained from solubility experiments were kept sealed at room temperature for 24 hours and the solids which precipitated were isolated and analysed. In cases where no solid precipitated after 24 hours, the solutions were kept air-opened at room temperature until a solid crystallized. Anhydrous form I of sildenafil base has been obtained in some cases. Moreover, the following new forms have been isolated and characterized by means of DSC, TGA, PXRD and <sup>1</sup>H-NMR in some cases:

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- **Form II:** is obtained in most of the screening methodologies applied using ACN as solvent. According to its DSC, TGA and <sup>1</sup>H-NMR this form could be assigned to a new anhydrous form. DSC analysis shows in some batches an exothermic transitions and in others a melting and crystallization process. Its PXRD diagram has been indexed (a=35.82 Å, b=17.14 Å, c=8.14 Å, V=2483 Å<sup>3</sup>).

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- **Form P42-A:** is obtained in most of the screening methodologies applied using toluene as solvent. According to its TGA and <sup>1</sup>H-NMR this form could be assigned to a hemitoluene solvate. Its PXRD diagram has been indexed (a=15.07 Å, b=14.52 Å, c=12.85 Å, β=106.54°, V=2691 Å<sup>3</sup>).

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- **Form P42-B:** is obtained in the solubility study by using formic acid. According to its TGA and <sup>1</sup>H-NMR this form could be assigned to a formic acid salt. It could be attributed to two molecules of formic acid per molecule of P42. Its PXRD could not be indexed.

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- **Form P42-C:** is obtained in the solubility study by using dioxane. According to its TGA and <sup>1</sup>H-NMR this form could be assigned to a dioxane solvate. It could be attributed to one molecule of dioxane per molecule of P42. Its PXRD diagram has been indexed (a=37.44 Å, b=45.95 Å, c=11.33 Å, α=153.87°, β=40.94°, γ=146.89° V=4658 Å<sup>3</sup>).

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- **Form P42-D:** is obtained in the solubility study by using acetic acid. According to its TGA and <sup>1</sup>H-NMR this form could be assigned to an acetic acid cocrystal. Its PXRD diagram has been indexed (a=19.20 Å, b=14.76 Å, c=9.76 Å, β=97.90°, V=2737 Å<sup>3</sup>).

35

- **Form P42-E:** is obtained through slurry experiments by using chloroform as solvent. According to its TGA and <sup>1</sup>H-NMR this form could be assigned to an hydrate. Its PXRD diagram has been indexed (a=15.07 Å, b=14.52 Å, c=12.85 Å, β=106.54°, V=2691 Å<sup>3</sup>).

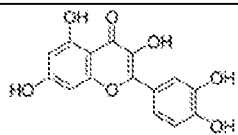
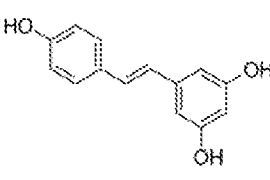
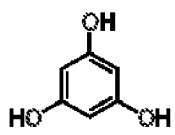
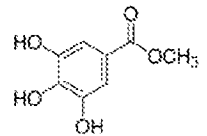
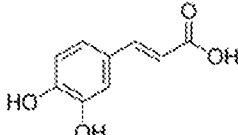
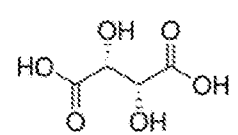
A comparison of the PXRD diagrams of these new forms of P42 is shown in Figures 3 and 4. The diagram in Figure 5 summarizes the different behaviour of forms I and II of P42.

### 2.3. Cocrystal screening

#### 5 2.3.1. Coformers

The following 13 coformers have been used after considering the virtual cocrystal prediction conducted with P42 (table 1).

**Table 1. Coformers used in P42 cocrystal screening**

Coformers	Description <sup>1</sup>
<b>Quercetin</b> (2) 	Linear formula: C <sub>15</sub> H <sub>10</sub> O <sub>7</sub> MW: 302.24 g/mol Melting point: 316°C
<b>Resveratrol</b> (3) 	Linear formula: C <sub>14</sub> H <sub>12</sub> O <sub>3</sub> MW: 228.24 g/mol Melting point: 253-255°C Melting point: 261-263°C
<b>Phloroglucinol</b> (4) 	Linear formula: C <sub>6</sub> H <sub>6</sub> O <sub>3</sub> MW: 126.11 g/mol Melting point: 215-220°C
<b>Methyl 3,4,5-trihydroxybenzoate</b> (Methyl gallate) (5) 	Linear formula: C <sub>8</sub> H <sub>8</sub> O <sub>5</sub> MW: 184.15 g/mol Melting point: 201-203°C
<b>Caffeic Acid</b> (6) 	Linear formula: C <sub>9</sub> H <sub>8</sub> O <sub>4</sub> MW: 180.16 g/mol Melting point: 211-213°C, des pka: 4.62
<b>Tartaric Acid</b> (7) 	Linear formula: C <sub>4</sub> H <sub>6</sub> O <sub>6</sub> MW: 150.09 g/mol Melting point: 170-172°C pKa1: 2.99 and pKa2: 4.40

<sup>1</sup> According to Sigma Aldrich description.

<b>3hydroxy benzoic acid</b> (8)		Linear formula: C <sub>7</sub> H <sub>6</sub> O <sub>3</sub> MW: 138.12 g/mol Melting point: 200-203°C pKa1: 4.06 and pKa2: 9.92
<b>4-Hydroxybenzoic Acid</b> (9)		Linear formula: C <sub>7</sub> H <sub>6</sub> O <sub>3</sub> MW: 138.12 g/mol Melting point: 213-217°C pKa1: 4.48 and pKa2: 9.32
<b>2-tert-butylbenzene-1,4-diol</b> ( <i>tert</i> -Butylhydroquinone) (10)		Linear formula: C <sub>10</sub> H <sub>14</sub> O <sub>2</sub> MW: 166.22 g/mol Melting point: 127-129°C
<b>Resorcinol</b> (11)		Linear formula: C <sub>6</sub> H <sub>6</sub> O <sub>2</sub> MW: 110.11 g/mol Melting point: 109-112°C
<b>3 4 5 trichyeroxy propoxy ester</b> (12)		Linear formula: C <sub>10</sub> H <sub>12</sub> O <sub>5</sub> MW: 212.20 g/mol Melting point: 146-149°C
<b>3,4 – Dihydroxybenzoic Acid</b> (13)		Linear formula: C <sub>7</sub> H <sub>6</sub> O <sub>4</sub> MW: 154.12 g/mol Melting point: 197-200°C pKa1: 4.48 and pKa2: 8.83
<b>Sorbic acid</b> (14)		Linear formula: C <sub>6</sub> H <sub>8</sub> O <sub>2</sub> MW: 112.13 g/mol Melting point: 132-135°C pKa: 4.8

### 2.3.2. Drop-Grinding (DG) experiments

Drop grinding experiments were undertaken with 20-50 mg of the total mixture (API:coformer, 1:1) and one drop of four different solvents. 32 experimental combinations of P42 with 8 solid coformers in 4 solvents were performed (table 2).

**Table 2. Drop-grinding experiments with P42<sup>2</sup>**

Coformer	Solvent
----------	---------

<sup>2</sup> Results: (0) negative result, (1) positive result: P42 + coformer + new peaks observed by PXRD

#		IPA	ACN	Toluene	THF
2	Quercetin	1	1	1	1
3	Resveratrol	0	1	0	0
4	Phloroglucinol	1	1	0	0
5	Methyl gallate	1	1	0	1
7	Tartaric Acid	1	1	1	1
8	3-Hydroxybenzoic Acid	1	1	1	1
9	4-Hydroxybenzoic Acid	1	1	1	1
10	<i>tert</i> -Butylhydroquinone	0	0	0	0

### 2.3.3. Reaction Crystallization (RC) and Slurry (SY) experiments

Reaction crystallization or slurry experiments have been performed with different solvents. Thirteen coformers have been selected according to the results obtained from DG experiments.

#### 5 Reaction Crystallization (RC)

Depending on the solubility, a saturated solution of the most soluble component (P42 or the coformer) in different solvents was prepared in a sealed vial under stirring. A small quantity of the less soluble component was added until it did not dissolve anymore. The suspension was kept under stirring for one day and the resulting solids were filtered and analyzed by PXRD.

#### 10 Slurries (SY)

Suspensions of P42 and different coformers in a 1:1 molar ratio (40-80 mg of the final mixture) in selected solvents were prepared. The sealed tubes were kept under stirring for one day and the resulting solids were filtered and analyzed by PXRD (table 3).

#### 15 Table 3. RC or SY of P42 with 13 coformers in different solvents<sup>3</sup>

Coformer	Solvent		
	IPA	ACN	THF
Quercetin	RC/2	SY/1	SY/2
Resveratrol	RC/0	RC/0	SY/1
Phloroglucinol	SY/0	SY/0	SY/0
Methyl gallate	RC/1	RC/2	SY/1
Caffeic Acid	RC/0	SY/2	SY/1

<sup>3</sup> Results: (0) negative, (1) positive: P42 + coformer + new peaks observed in PXRD, (2) positive: cocrystal or salt.

Tartaric Acid	RC/1	RC/1	RC/2
3-Hydroxybenzoic Acid	RC/1	RC/2	RC/1
4-Hydroxybenzoic Acid	RC/2	RC/2	SY/2
<i>tert</i> -Butylhydroquinone	SY/0	SY/0	SY/0
Resorcinol	SY/0	SY/2	SY/0
Propyl gallate	RC/0	SY/0	SY/0
3,4-Dihydroxybenzoic Acid	SY/2	RC/1	SY/1
Sorbic Acid	RC/0	RC/0	SY/0

#### 2.3.4. Identification and characterization of the new forms

From the cocrystal screening, some new multicomponent phases have been isolated and characterized by means of DSC, TGA, PXRD and <sup>1</sup>H-NMR. A brief description of the new forms is described as follows:

- **P42-I: P42: Quercetin.**

○ **P42-I-A:** It has been obtained by reaction crystallization in IPA. According to its TGA and <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of quercetin and 1 molecule of IPA per molecule of P42. Its PXRD diagram has been indexed ( $a=22.43 \text{ \AA}$ ,  $b=15.79 \text{ \AA}$ ,  $c=11.24 \text{ \AA}$ ,  $\beta=92.21^\circ$ ,  $V=3975 \text{ \AA}^3$ ) with a number of impurities equal to zero.

○ **P42-I-B:** It has been obtained by slurry in THF. According to its TGA and <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of quercetin and  $\frac{2}{3}$  molecules of THF per molecule of P42. Its PXRD diagram has been indexed ( $a=22.52 \text{ \AA}$ ,  $b=13.53 \text{ \AA}$ ,  $c=8.01 \text{ \AA}$ ,  $\alpha=57.96^\circ$ ,  $\beta=95.99^\circ$ ,  $\gamma=95.95^\circ$ ,  $V=2047 \text{ \AA}^3$ ) with a number of impurities equal to zero.

- **P42-III: P42:Methyl gallate.** It has been obtained by reaction crystallization in ACN. According to its <sup>1</sup>H-NMR, it could be attributed to 1 molecule of methyl gallate per molecule of P42. Its PXRD diagram has been indexed ( $a=12.98 \text{ \AA}$ ,  $b=13.45 \text{ \AA}$ ,  $c=11.99 \text{ \AA}$ ,  $\alpha=116.63^\circ$ ,  $\beta=82.45^\circ$ ,  $\gamma=118.59^\circ$ ,  $V=1628 \text{ \AA}^3$ ) with a number of impurities equal to zero.

- **P42-IV: P42:Tartaric acid.**

- 5
- **P42-IV-A:** It has been obtained by drop grinding in IPA. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of tartaric acid per molecule of P42. Its PXRD diagram has been indexed ( $a=18.07 \text{ \AA}$ ,  $b=13.61 \text{ \AA}$ ,  $c=7.59 \text{ \AA}$ ,  $\alpha=85.98^\circ$ ,  $\beta=92.34^\circ$ ,  $\gamma=110.08^\circ$   $V=1741 \text{ \AA}^3$ ) with a number of impurities equal to zero.
  - **P42-IV-B:** It has been obtained by slurry in THF. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of tartaric acid per 2 molecules of P42. Its PXRD diagram has been indexed ( $a=33.57 \text{ \AA}$ ,  $b=14.05 \text{ \AA}$ ,  $c=11.55 \text{ \AA}$ ,  $V=2483 \text{ \AA}^3$ ) with a number of impurities equal to zero.
- 10
- **P42-V-A: P42:3-Hydroxybenzoic acid.** It has been obtained by reaction crystallization in ACN. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 3-hydroxybenzoic acid and  $\frac{1}{4}$  molecule of ACN per molecule of P42. The PXRD diagram could not be indexed.
  - **P42-VI: P42:4-Hydroxybenzoic acid.**
- 15
- **P42-VI-B:** It has been obtained by drop grinding in ACN. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 4-hydroxybenzoic acid per molecule of P42. The PXRD diagram could not be indexed.
  - **P42-VI-C:** It has been obtained by reaction crystallization in IPA. According to its TGA and <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 4-hydroxybenzoic acid and  $\frac{1}{2}$  molecule of IPA per molecule of P42. The cell could not be indexed.
- 20
- **P42-VI-D:** It has been obtained by reaction crystallization in ACN. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 4-hydroxybenzoic acid per molecule of P42. The PXRD diagram could not be indexed.
- 25
- **P42-VI-E:** It has been obtained by slurry in IPA. According to its TGA and <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 4-hydroxybenzoic acid and  $\frac{1}{4}$  molecule of IPA per molecule of P42. The cell could not be indexed.
- 30
- **P42-VII: P42:Resorcinol.** It has been obtained by slurry in IPA. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of resorcinol per molecule of P42. The PXRD diagram has been indexed: ( $a=11.27 \text{ \AA}$ ,  $b=14.83 \text{ \AA}$ ,  $c=14.18 \text{ \AA}$ ,  $\alpha=38.10^\circ$ ,  $\beta=94.79^\circ$ ,  $\gamma=96.08^\circ$   $V=1453 \text{ \AA}^3$ ) with a number of impurities equal to zero.



- 5
- **P42-VIII: P42:3,4-dihydroxybenzoic acid.** It has been obtained by slurry in IPA. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 1 molecule of 3,4-dihydroxybenzoic acid and 1 molecule of IPA per molecule of P42. The PXRD diagram has been indexed: (a=12.76 Å, b=13.46 Å, c=12.11 Å α=112.03°, β=84.09°, γ=114.28° V=1750 Å<sup>3</sup>) with a number of impurities equal to zero.
  - 10 - **P42-IX: P42:Caffeic acid.** It has been obtained by slurry in IPA. According to its <sup>1</sup>H-NMR analysis, it could be attributed to 2 molecules of caffeic acid and 1 molecule of water per 3 molecules of P42. Its PXRD diagram has been indexed (a=25.84 Å, b=8.36 Å, c=20.31 Å, β=121.19°, V=3744 Å<sup>3</sup>) with a number of impurities equal to zero.

The PXRD of these new multicomponent forms of P42 are shown in figures 6 and 7.

15 The following table 4 summarizes the pKa values of the different cofomers which are interacting with P42 (form I (CCDC: QEGTUT), pKa: 8.4<sup>4</sup>) as a cocrystal or as a salt. The interaction has been studied according to the crystal structures published in CCDC. The acid cofomers used in the present screening are included.

**Table 4.** pKa values of different cofomers

<b>Cofomer</b>	<b>pKa values</b>	<b>CCDC code</b>	<b>Salt or Cocrystal</b>
Citric Acid	pKa1: 3.1 / pKa2: 4.8	FEDTEO	Salt monohydrate
Saccharin	pKa: 1.6	QEMLOK	Salt dihydrate
Oxalic Acid	pKa1: 1.2 / pKa2: 4.2	YIWWIM	Salt
Fumaric Acid	pKa1: 3.0 / pKa2: 4.4	YIWWOS	Salt trihydrate
Succinic Acid	pKa1: 4.2 / pKa2: 5.6	YIWWUY	Salt monohydrate
Glutaric Acid	pKa1: 4.3 / pKa2: 5.4	YIWXAF	Salt
Adipic Acid	pKa1: 4.4 / pKa2: 5.4	YIWXEJ	Cocrystal

<sup>4</sup> J. Chem. Eng. Data **2009**, 54, 2914–2917.

Pimelic Acid	pKa1: 4.5 / pKa2: 5.4	YIWXIN	Cocrystal
Suberic Acid	pKa1: 4.5 / pKa2: 5.4	YIWXOT	Cocrystal
Sebacic Acid	pKa1: 4.6 / pKa2: 5.6	YIWXUZ	Cocrystal
Salicylic Acid	pKa: 3.5	-	-
Caffeic Acid	pKa: 4.6	-	P42-IX
Tartaric Acid	pKa1: 3.0 / pKa2: 4.5	-	P42-IV
3-Hydroxybenzoic Acid	pKa1: 4.1 / pKa2: 9.9	-	P42-V
4-Hydroxybenzoic Acid	pKa1: 4.5 / pKa2: 9.3	-	P42-VI
3,4-Dihydroxyben- zoic Acid	pKa1: 4.5 / pKa2: 8.8	-	P42-VIII
Sorbic Acid	pKa: 4.8	-	-

According to these data we can assess the formation of salt or cocrystal depending on the coformer pKa values. Thus, coformers with pKa values higher than 4.5 will probably form a cocrystal, coformers with pKa values lower than 4.2 will probably form a salt, coformers with pKa values between 4.3 and 4.5 will require the crystal structure to confirm/discard the proton transfer. However, the confirmation of salt/cocrystal formation will always need the determination of the crystal structure by means of SXR. In this sense, we have prepared a battery of crystallizations of all the new forms discovered during this study.

### 10 3. Conclusions

- A new anhydrous form of P42 has been obtained through a slurry experiment in ACN and it has been characterized.
- Five new forms of P42 have been isolated from the solubility study and they have been characterized: P42-A (toluene solvate), P42-B (formic acid salt), P42-C (dioxane solvate), P42-D (acetic acid salt or cocrystal) and P42-E (hydrate).
- Several multicomponent forms of P42 have been obtained through a cocrystal screening with nine of the 13 coformers used: quercetin, phoroglucinol, methyl gallate, caffeic

acid, tartaric acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, resorcinol and 3,4-hydroxybenzoic acid.

- The new multicomponent form of P42 with Quercetin (1:1 stoichiometry) has been obtained in two different forms: one IPA solvate form and one THF solvate form, which have been isolated and characterized.
- The new multicomponent form of P42 with Phloroglucinol has not been isolated and characterized in pure form.
- The new multicomponent form of P42 with Methyl gallate (1:1 stoichiometry) has been isolated and characterized.
- The new multicomponent form of P42 with Tartaric acid has been obtained in two different forms: (1:1 stoichiometry) and (2:1 stoichiometry), which have been isolated and characterized. According to the pKa values these forms are expected to be salts.
- The new multicomponent form of P42 with 3-Hydroxybenzoic acid (1:1 stoichiometry) has been obtained in ACN solvate form, which have been isolated and characterized. According to the pKa values this form is expected to be a salt.
- The new multicomponent form of P42 with 4-Hydroxybenzoic acid (1:1 stoichiometry) has been obtained in two different polymorphic forms, one IPA solvate form and one THF solvate form, which have been isolated and characterized. One of these forms has not been isolated and characterized in pure form. According to the pKa values these forms are expected to be cocrystals.
- The new multicomponent form of P42 with Resorcinol (1:1 stoichiometry) has been isolated and characterized.
- The new multicomponent form of P42 with 3,4-Dihydroxybenzoic acid (1:1 stoichiometry) has been obtained in IPA solvate form, which have been isolated and characterized. According to the pKa values this form is expected to be a cocrystal.
- The new multicomponent form of P42 with Caffeic acid (2:3 stoichiometry) has been obtained as a hydrated form, which have been isolated and characterized. According to the pKa values this form is expected to be a cocrystal.

#### **EXAMPLE 67**

30

#### **Sildenafil Citrate Compression Coating**

<b>Sustained Release</b>		
<b>Component</b>	<b>(mg/tab)</b>	<b>(% w/w)</b>
Sildenafil Citrate	112.389	37.463
SuperTab 24AN (Anhydrous lactose)	123.111	41.037

Methocel K100 LV DC2	60.000	20.000
Aerosil 200 (Hydrophilic fumed silica)	1.500	0.500
Magnesium Stearate	3.000	1.000
<b>Total</b>	<b>300.000</b>	<b>100.000</b>

### Sustained Release Core

Contains 112.389mg of Sildenafil Citrate. This amount is the equivalent of 80mg Sildenafil base per tablet.

### 5 Method of manufacture

- All components are dispensed (except the lubricant) into a Pestle and Mortar
- Mix for 4 minutes
- Dispense the Magnesium Stearate (Lubricant)
- Mix for 1 minute

10 Compressed on a Manesty F3 compression machine using 9mm Round Normal Convex tooling

- Target weight: 300mg
- Target Hardness: 10kp

### Proposed Immediate Release Layers

15 Two different sizes have been trialled with the aim of deciding the most appropriate size to be carried forward; the outer layer contains 28.097mg of Sildenafil Citrate per tablet. This is equivalent to 20mg of Sildenafil base.

<b>Immediate Release 250mg</b>		
<b>Component</b>	<b>(mg/tab)</b>	<b>(% w/w)</b>
Sildenafil Citrate	28.097	11.239
Isomalt 721	205.153	82.061
Sodium Starch Glycolate	10.000	4.000
Peppermint Flavour 501500 TP0504	2.500	1.000
Stevia	0.500	0.200
Sucralose	2.500	1.000
Magnesium Stearate	1.250	0.500
<b>Total</b>	<b>250.000</b>	<b>100.000</b>

<b>Immediate Release 900mg</b>		
<b>Component</b>	<b>(mg/tab)</b>	<b>(% w/w)</b>

Sildenafil Citrate	28.097	3.122
Isomalt 721	811.603	90.178
Sodium Starch Glycolate	36.000	4.000
Peppermint Flavour 501500 TP0504	9.000	1.000
Stevia	1.800	0.200
Sucralose	9.000	1.000
Magnesium Stearate	4.500	0.500
<b>Total</b>	<b>900.000</b>	<b>100.000</b>

### Method of Manufacture

- Sildenafil Citrate dispensed and mixed in a Pestle and Mortar using a Geometric dilution method with Isomalt 721
- 5
- All other components (except lubricant) dispensed and added to the Pestle and Mortar
  - Mix for 2 minutes
  - Dispense the Magnesium Stearate (Lubricant)
  - Mix for 1 minute

10 250mg - Compressed on a Manesty F3 compression machine using 9mm Round Normal Convex tooling

- Target weight: 250mg
- Target Hardness: 5kp

900mg - Compressed on a Manesty F3 compression machine using 14mm Round Normal Convex tooling

- 15
- Target weight: 900mg
  - Target Hardness: 5kp

### Final proposed manufacture combing the two formulations

- The Sustained release core will be made as described previously (but with flat tooling)
- 20
- Depending on the final size required the tooling will be changed to 10 – 20mm Flat tooling
  - The tablet die will be filled with approximately 50% of the Immediate release blend
  - The Sustained Release core will be placed centrally into the pre-filled die.
  - The remaining Immediate release blend will be added
- 25
- Tablet will be compressed to a suitable hardness

### Dissolution Summary

Aim: To produce dissolution profiles at the following conditions for immediate release/sustained release development formulations and the comparator product (Pfizer Viagra tablets).

- 0.01M hydrochloric acid (pH 2.0)
- 5 • pH 4.5 phosphate buffer
- pH 6.8 phosphate buffer with CTAB

### **Analytical Testing**

Tablets were tested using dissolution with UV endpoint to obtain drug release profiles.

#### 10 Dissolution conditions (0.01M hydrochloric acid, pH 2.0)

Apparatus	USP I (basket)
Dissolution media	0.01 M hydrochloric acid
Volume dissolution media	900ml
Temperature	37°C
Speed	100rpm
Sampling points	As detailed in data for specific sample
Detection	UV at 267nm

#### Dissolution conditions (pH 4.5 buffer)

Apparatus	USP I (basket)
Dissolution media	0.13 M potassium monophosphate (KH <sub>2</sub> PO <sub>4</sub> ) adjusted to pH 4.5 with sodium hydroxide
Volume dissolution media	900ml
Temperature	37°C
Speed	100rpm
Sampling points	As detailed in data for specific sample
Detection	UV at 267nm

#### Dissolution conditions (pH 6.8 buffer with surfactant)

Apparatus	USP I (basket)
Dissolution media	50 mM sodium phosphate buffer (NaH <sub>2</sub> PO <sub>4</sub> ), 0.125% CTAB, adjusted to pH 6.8
Volume dissolution media	900ml
Temperature	37°C
Speed	100rpm

Sampling points As detailed in data for specific sample  
 Detection UV at 267nm

**Tablet details:****Sildenafil (Pfizer) Dose**

25mg (as 35.1mg sildenafil citrate)

50mg (as 70.2mg sildenafil citrate)

100mg (as 140.5mg sildenafil citrate)

**Sustained Release Development Product****16CF25/026**

112.39mg sildenafil citrate (equivalent to 80mg  
 sildenafil base)

**Immediate Release Development Product****16CF25/027**

28.097mg sildenafil citrate (equivalent to 20mg  
 sildenafil base)

**1. Results for dissolution performed in 0.01M hydrochloric acid**

5

**1.1 Viagra 25mg**

Time-point (mins)	25mg Viagra tablets		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	106	105	101
10	106	105	102
15	107	106	102
20	107	106	102
30	107	106	103
45	108	106	103
60	108	107	105

**1.2 Viagra 50mg**

Time-point (mins)	50mg Viagra Tablets		
	% dissolved		
	Vessel 4	Vessel 5	Vessel 6
0	0	0	0
5	101	98	105
10	101	98	105
15	101	99	106
20	102	99	106
30	102	100	106
45	103	100	107
60	103	100	106

### 1.3 Viagra 100mg

Time-point (mins)	100mg Viagra Tablets		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	93	100	98
10	100	101	99
15	101	102	100
20	101	102	100
30	101	98	101
45	100	102	100
60	101	103	101

### 5 1.4 Sustained-release development formulation – 16CF25/026

Time-point (hours)	16CF25/026		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
0.5	23	21	16
1	38	35	29
1.5	53	50	43
2	67	63	57



2.5	80	75	70
3	90	87	82
3.5	97	97	92
4	98	101	97
4.5	98	101	97

**1.5 Immediate-release development formulation – 16CF25/027**

16CF25/027 - 0.01 M HCl			
Time-point (minutes)	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	89	86	83
10	103	104	102
15	103	105	102

**2. Results for dissolution performed in pH 4.5 phosphate buffer**

5

**2.1 Viagra 25mg**

100mg Viagra Tablets		
Time-point (mins)	% dissolved	
	Vessel 1	Vessel 2
0	0	0
5	99	96
10	100	108
15	100	100
20	101	97
30	99	99
45	100	99
60	100	99

**2.2 Viagra 50mg tablets**

100mg Viagra Tablets		
Time-point (mins)	% dissolved	
	Vessel 1	Vessel 2

0	0	0
5	101	102
10	103	105
15	104	106
20	103	105
30	100	104
45	104	106
60	106	108

### 2.3 Viagra 100mg tablets

Time-point (mins)	100mg Viagra Tablets	
	% dissolved	
	Vessel 1	Vessel 2
0	0	0
5	94	91
10	99	100
15	97	97
20	99	97
30	99	95
45	100	99
60	99	98

### 5 2.4 Sustained-release development formulation – 16CF25/026

Time-point (hours)	16CF25/026 - pH 4.5 buffer		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
0.5	16	17	15
1	26	26	24
1.5	35	35	33
2	44	44	42
2.5	53	52	51
3.5	71	71	69
4.5	89	88	87
5.5	99	98	98

### 2.5 Immediate-release development formulation – 16CF25/027

16CF25/027 - pH 4.5 buffer			
Time-point (minutes)	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	93	86	88
10	101	100	102
15	101	100	102

**Results for dissolution performed in pH 6.8 phosphate buffer with 0.125% CTAB**

**3.1 Viagra 25mg tablets**

25mg Viagra Tablets			
Time-point (mins)	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	59	59	58
10	67	69	69
15	72	74	74
20	74	79	78
30	80	85	84
45	87	90	90
60	91	93	93
90	91	95	95
120	91	96	95
150	90	97	94

5

**3.2 Viagra 50mg tablets**

50mg Viagra Tablets			
Time-point (mins)	% dissolved		
	Vessel 4	Vessel 5	Vessel 6
0	0	0	0
5	66	65	69
10	71	73	77

15	75	77	80
20	83	81	82
30	83	86	86
45	88	90	90
60	90	92	92
90	93	95	93
120	94	97	95
150	97	98	96

### 3.3 Viagra 100mg tablets

Time-point (mins)	100mg Viagra Tablets		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	65	58	59
10	68	64	64
15	73	66	66
20	73	68	67
30	77	71	70
45	78	74	72
60	82	76	75

Note – Dissolution was only run for 60 minutes, not fully dissolved

5

### 3.4 Sustained-release development formulation – 16CF25/026

Time-point (hours)	16CF25/026 – pH 6.8 + CTAB		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
1	19	17	18
2	36	33	35
3	54	49	49
4	71	68	63
5	86	82	74
6	98	95	91

8	100	96	98
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### 3.5 Immediate-release development formulation – 16CF25/027

Time-point (mins)	16CF25/027 – pH 6.8 + CTAB		
	% dissolved		
	Vessel 1	Vessel 2	Vessel 3
0	0	0	0
5	64	76	73
10	87	90	88
15	91	91	90
20	93	93	91
30	93	94	93
45	95	95	94
60	95	95	94

### EXAMPLE 68

5

#### Sildenafil Citrate Compression Coating

Sustained Release		
Component	(mg/tab)	(% w/w)
Sildenafil Citrate	112.389	37.463
SuperTab 24AN (Anhydrous lactose)	123.111	41.037
Methocel K100 LV DC2	60.000	20.000
Aerosil 200 (Hydrophilic fumed silica)	1.500	0.500
Magnesium Stearate	3.000	1.000
<b>Total</b>	<b>300.000</b>	<b>100.000</b>

#### Sustained Release Core

Contains 112.389mg of Sildenafil Citrate. This is the equivalent of 80mg Sildenafil per tablet.

#### 10 Method of manufacture

- All components are dispensed (except the lubricant) into a Pestle and Mortar
- Mix for 4 minutes
- Dispense the Magnesium Stearate (Lubricant)
- Mix for 1 minute

Compressed on a Manesty F3 compression machine using 9mm Round Normal Convex tooling

- Target weight: 300mg
- Target Hardness: 10kp

## 5 **Immediate Release Layer**

### **Formulation Details**

An immediate release tablet was formulated with API Sildenafil base (250 mg tablet containing 20mg sildenafil base) with composition shown in the following table.

<b>Batch No:</b>	<b>Formulation details</b>
16CF25/033	API: 8% w/w Sildenafil base (20 mg) 85.3% w/w Isomalt 721 (213.25 mg) 4% Sodium starch glycolate (10 mg) 1% Peppermint flavour 501500 TP0504 (2.5 mg) 0.2% Stevia tasteva (0.5 mg) 1% Sucralose (2.5 mg) 0.5% Magnesium stearate (1.25 mg)

## 10 **Method of Manufacture**

- Sildenafil base dispensed and mixed in a Pestle and Mortar using a Geometric dilution method with Isomalt 721
- All other components (except lubricant) dispensed and added to the Pestle and Mortar
- Mix for 2 minutes

- 15
- Dispense the Magnesium Stearate (Lubricant)
  - Mix for 1 minute

250mg - Compressed on a Manesty F3 compression machine using 9mm Round Normal Convex tooling

- Target weight: 250mg
- Target Hardness: 5kp

20

### **Final proposed manufacture combining the immediate release formulation of sildenafil base 16CF25/033 with the sustained-release core formulation 16CF25/026 of sildenafil citrate described in Example 67**

- 25
- The Sustained release core will be made as described previously in Example 67 (with flat tooling)
  - Depending on the final size required the tooling will be 10 – 20mm Flat tooling
  - The tablet die will be filled with approximately 50% of the Immediate release blend

- The Sustained Release core will be placed centrally into the pre-filled die.
- The remaining Immediate release blend will be added

Tablet will be compressed to a suitable hardness

#### 5 **Analytical Testing of Immediate Release Sildenafil Base Formulation 16CF25/033**

Tablets of Immediate release formulation 16CF25/033 were tested using a dissolution system with UV endpoint to obtain drug release profiles in pH 4.5 phosphate buffer and 0.01M hydrochloric acid media.

10

Dissolution conditions:

USP I (basket)	
Dissolution media	pH 4.5 phosphate buffer or 0.01M hydrochloric acid
Volume dissolution media	900ml
Temperature	37°C
Speed	100rpm
Sampling points	5, 10, 15, 20, 30, 45 and 60 minutes
Filtration	0.45 µm PTFE filter units
Detection	UV at 267nm

#### **16CF25/033 in 0.01M HCl**

Time-point (min)	16CF25/033 0.01M HCl		
	Vessel 1	Vessel 2	Mean
0	0	0	0
5	79	81	80
10	98	97	98
15	99	97	98
20	99	99	99
30	98	98	98
45	99	98	98
60	99	98	98

15

#### **16CF25/033 in pH 4.5 phosphate buffer**

Time-point (min)	16CF25/033 - pH 4.5		
	Vessel 3	Vessel 4	Mean
0	0	0	0
5	41	34	38
10	70	70	70
15	83	80	82
20	87	86	86
30	90	86	88
45	91	88	90
60	93	89	91



CLAIMS

1. A pharmaceutical composition comprising sildenafil or a pharmaceutically acceptable salt or co-crystal thereof admixed with excipients in a multicomponent pharmaceutical composition, wherein a first component is adapted to deliver sildenafil rapidly to promote fast onset of action, and a further component is adapted to deliver the sildenafil from dose to dose, wherein the sildenafil is delivered from dose to dose within the therapeutic window.
2. A pharmaceutical composition according to claim 1 comprising said first component which is adapted to deliver sildenafil rapidly to promote fast onset of action, a second component which is adapted to deliver the sildenafil from dose to dose, and a third component wherein the sildenafil is delivered from dose to dose within the therapeutic window.
3. A pharmaceutical composition according to claim 1 or claim 2 wherein the pharmaceutical composition is a dosage form.
4. A pharmaceutical composition according to any one of claims 1 to 3, comprising:  
a first component which is adapted to deliver the sildenafil rapidly to promote a fast onset of action, and  
a second component which is adapted to deliver the sildenafil from dose to dose, and which is further adapted to also deliver the sildenafil from dose to dose within the therapeutic window.
5. A pharmaceutical composition according to any one of the preceding claims wherein the pharmaceutical composition is in the form of a swallow tablet.
6. A pharmaceutical composition according to claim 5, wherein the tablet comprises:  
a first component which is adapted to deliver the sildenafil rapidly to promote a fast onset of action, and  
a second component which is adapted to deliver the sildenafil from dose to dose, and which is further adapted to also deliver the active ingredient from dose to dose within the therapeutic window.
7. A pharmaceutical composition according to any one of claims 4 to 6, wherein the first component comprises sildenafil admixed with one or more excipients which promote rapid release.

8. A pharmaceutical composition according to any one of claims 4 to 7, wherein the first component comprises sildenafil admixed with one or more excipients which promote immediate release.
- 5 9. A pharmaceutical composition according to claim 7 or claim 8 wherein the first component comprises from 10% to 30% by weight of the total amount of sildenafil in the first and second components, optionally wherein the first component comprises 20% by weight of the total amount of sildenafil in the first and second components.
- 10 10. A pharmaceutical composition according to any one of claims 7 to 9, wherein the first component comprises from 10mg to 30mg of sildenafil admixed with said excipients, optionally wherein the first component comprises 20mg of sildenafil admixed with said excipients.
11. A pharmaceutical composition according to any one of claims 7 to 9, wherein the first  
15 component comprises from 5mg to 15mg of sildenafil admixed with said excipients, optionally wherein the first component comprises 10mg of sildenafil admixed with said excipients.
12. A pharmaceutical composition according to any one of claims 7 to 9, wherein the first  
20 component comprises from 2.5 to 7.5 mg of sildenafil admixed with said excipients, optionally wherein the first component comprises 5mg of sildenafil admixed with said excipients.
13. A pharmaceutical composition according to any one of the preceding claims wherein the first component is a rapidly disintegrating component comprising: said sildenafil, a disintegrating agent and optionally a swelling agent.
- 25 14. A pharmaceutical composition according to claim 13 wherein the first component comprises: said sildenafil; a disintegrant which is a disaccharide alcohol, carboxymethylcellulose or sodium croscarmellose; and optionally a modified starch.
- 30 15. A pharmaceutical composition according to claim 13 or claim 14 wherein the first component comprises said sildenafil, isomalt and sodium starch glycolate.
16. A pharmaceutical composition according to any one of claims 1 to 12 wherein the first component is a rapidly disintegrating component comprising: said sildenafil in a matrix  
35 of a buccal fluid-dispersible polymer, and a polysaccharide.

17. A pharmaceutical composition according to claim 16 wherein the buccal fluid-dispersible polymer comprises gelatine, or wherein the polysaccharide comprises mannitol, or wherein the buccal fluid-dispersible polymer comprises gelatine and the polysaccharide comprises mannitol.
- 5
18. A pharmaceutical composition according to any one of claims 1 to 12 wherein the first component is a rapidly disintegrating component comprising: (i) said sildenafil, (ii) an effervescence agent, and (iii) a disintegrating agent or a water soluble excipient.
- 10
19. A pharmaceutical composition according to claim 18 wherein the effervescence agent comprises an alkali metal carbonate or bicarbonate and optionally an organic acid.
20. A pharmaceutical composition according to claim 18 or claim 19 wherein the water soluble excipient is a sugar, optionally wherein the sugar is mannitol.
- 15
21. A pharmaceutical composition according to any one of claims 1 to 12 wherein the first component is a rapidly disintegrating component comprising: said sildenafil and a melt-spun sugar which comprises filaments of the sugar.
- 20
22. A pharmaceutical composition according to claim 21 wherein the sugar is sucrose.
23. A pharmaceutical composition according to any one of claims 1 to 12 wherein the first component is a rapidly disintegrating component comprising: said sildenafil, a low mould ability saccharide and a high mould ability saccharide, wherein the low mould ability saccharide is granulated using the high mould ability saccharide as a binder.
- 25
24. A pharmaceutical composition according to claim 23 wherein the low mould ability saccharide is lactose or mannitol and/or the high mould ability saccharide is maltose or maltitol.
- 30
25. A pharmaceutical composition according to any one of claims 1 to 12 wherein the first component is a rapidly disintegrating component comprising: said sildenafil which is dispersed or adsorbed over a high surface area inert substrate.
- 35
26. A pharmaceutical composition according to claim 25 wherein the substrate is an ion exchange resin, a polymeric absorbent, activated carbon, or silica gel.

27. A pharmaceutical composition according to claim 25 or claim 26 wherein the substrate is selected from: Amberlite® XAD-4, Amberlite® XAD-7, Amberlite® XAD-16, AMBERSORB® 348F, AMBERSORB® 563, AMBERSORB® 572, Activated carbon, Activated carbon Darco®, Activated carbon Darco® G-60, Activated carbon Darco® KB, Activated carbon Darco® KB-B, Activated carbon Norit®, and silica gel.
28. A pharmaceutical composition according to any one of the preceding claims wherein the sildenafil in the first component is a pharmaceutically acceptable salt of sildenafil.
29. A pharmaceutical composition according to any one of the preceding claims wherein the sildenafil in the first component is sildenafil citrate.
30. A pharmaceutical composition according to claim 29 wherein the first component further comprises a taste masking agent or a flavouring agent.
31. A pharmaceutical composition according to any one of claims 1 to 27 wherein the sildenafil in the first component is sildenafil free base.
32. A pharmaceutical composition according to any one of claims 1 to 27 wherein the sildenafil in the first component is in the form of a co-crystal of sildenafil.
33. A pharmaceutical composition according to claim 32 wherein the co-crystal is as defined in any one of claims 95 to 103.
34. A pharmaceutical composition according to any one of claims 1 to 27 wherein the sildenafil in the first component is a salt of sildenafil with a fatty acid.
35. A pharmaceutical composition according to claim 34 wherein the salt of sildenafil with a fatty acid is as defined in any one of claims 105 to 108.
36. A pharmaceutical composition according to any one of claims 4 to 35 wherein the second component comprises sildenafil and one or more excipients which promote modified release.
37. A pharmaceutical composition according to claim 36 wherein the second component comprises from 70% to 90% by weight of the total amount of sildenafil in the first and second

components, optionally wherein the second component comprises 80% by weight of the total amount of sildenafil in the first and second components.

5 38. A pharmaceutical composition according to any one of claims 4 to 37 wherein the second component comprises from 70mg to 90mg of sildenafil, and one or more excipients which promote modified release, optionally wherein the second component comprises 80mg of sildenafil, and one or more excipients which promote modified release.

10 39. A pharmaceutical composition according to any one of claims 4 to 37 wherein the second component comprises from 35mg to 45mg of sildenafil, and one or more excipients which promote modified release, optionally wherein the second component comprises 40mg of sildenafil, and one or more excipients which promote modified release.

15 40. A pharmaceutical composition according to any one of claims 4 to 37 wherein the second component comprises from 17.5mg to 22.5 mg sildenafil, and one or more excipients which promote modified release, optionally wherein the second component comprises 20mg of sildenafil, and one or more excipients which promote modified release.

20 41. A pharmaceutical composition according to any one of claims 4 to 40 wherein the sildenafil in the second component is sildenafil citrate.

42. A pharmaceutical composition according to any one of claims 4 to 40 wherein the sildenafil in the second component is sildenafil free base.

25 43. A pharmaceutical composition according to any one of claims 4 to 40 wherein the sildenafil in the second component is a salt of sildenafil with a fatty acid, optionally wherein the salt of sildenafil with a fatty acid is as defined in any one of claims 105 to 108, or the sildenafil in the second component is in the form of a co-crystal of sildenafil, optionally wherein the co-crystal is as defined in any one of claims 95 to 103.

30 44. A pharmaceutical composition according to any one of claims 36 to 43, wherein the excipients which promote modified release in the second component comprise one or more polymers.

35 45. A pharmaceutical composition according to any one of claims 36 to 44 wherein the second component comprises: said sildenafil and a hydrophilic matrix suitable for promoting prolonged release of the sildenafil.

46. A pharmaceutical composition according to claim 45 wherein the hydrophilic matrix comprises a polymer which is a cellulose ether or xanthan gum.
- 5 47. A pharmaceutical composition according to claim 46 wherein the cellulose ether is selected from carboxymethylcellulose (CMC), methylcellulose (MC) and derivatives thereof, hydroxyethylcellulose (HEC) and derivatives thereof, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose, and ethylcellulose (EC).
- 10 48. A pharmaceutical composition according to any one of claims 45 to 47 wherein the second component further comprises a filler, optionally wherein the filler is lactose.
49. A pharmaceutical composition according to any one of claims 45 to 48 wherein the second component further comprises hydrophilic silica.
- 15 50. A pharmaceutical composition according to any one of claims 36 to 44 wherein the second component comprises: said sildenafil and a dissolvable or erodible polymer suitable for promoting prolonged release of the sildenafil.
- 20 51. A pharmaceutical composition according to claim 50 wherein the polymer is selected from glyceryl monostearate, acrylic resins, ethylcellulose, stearyl alcohol, hydroxypropylcellulose, carboxymethyl-cellulose, hypromellose, methylcellulose, hydroxyethyl-methylcellulose, sodium carboxymethylcellulose.
- 25 52. A pharmaceutical composition according to any one of claims 36 to 44 wherein the second component comprises: a composition comprising sildenafil, which composition is coated with a porous or semipermeable membrane suitable for promoting prolonged release of the sildenafil.
- 30 53. A pharmaceutical composition according to claim 52 wherein the semi-permeable membrane comprises a polymer.
54. A pharmaceutical composition according to claim 52 or claim 53 wherein the semi-permeable membrane comprises a methacrylate polymer, ethylcellulose, cellulose acetate,
- 35 poly(ethylene glycol), or a mixture of two or more thereof.

55. A pharmaceutical composition according to claim 54 wherein the semi-permeable membrane comprises cellulose acetate and poly(ethylene glycol).
56. A pharmaceutical composition according to any one of claims 52 to 55 wherein the composition comprising sildenafil which is coated with the membrane further comprises an osmagent.
57. A pharmaceutical composition according to claim 56 wherein the osmagent is selected from sodium chloride, potassium chloride, lithium chloride, magnesium chloride, magnesium sulphate, lithium sulphate, sodium sulphate, potassium sulphate, citric acid, mannitol, ribose, arabinose, galactose, leucine, glycine, fructose, sucrose, and sodium and other bicarbonates, or a mixture of two or more thereof.
58. A pharmaceutical composition according to any one of claims 36 to 44 wherein the second component comprises: said sildenafil and a coating for delaying exposure of the sildenafil to buccal, gastric, or intestinal fluids.
59. A pharmaceutical composition according to claim 58 which comprises beadlets, pellets, spheroids, minitablets and/or granules comprising the sildenafil which are coated with said coating.
60. A pharmaceutical composition according to claim 58 or claim 59 wherein the coating comprises an enteric coating which dissolves at a pH greater than 5.0.
61. A pharmaceutical composition according to claim 60 wherein the enteric coating comprises a methacrylic acid-methyl methacrylate co-polymer.
62. A pharmaceutical composition according to claim 58 or claim 59 wherein the coating comprises a pH-dependent polymer.
63. A pharmaceutical composition according to claim 62 wherein the pH-dependent polymer is selected from cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate 50, hydroxypropylmethylcellulose phthalate 55, polyvinylacetate phthalate, methacrylic acid-methyl methacrylate copolymer (1:1), methacrylic acid-methyl methacrylate copolymer (2:1), methacrylic acid-ethyl acrylate copolymer (2:1), hydroxypropylmethylcellulose acetate succinate, poly(methylvinylether/maleic acid) monoethylester, poly(methylvinylether/maleic acid)n-butyl ester, and shellac.

64. A pharmaceutical composition according to claim 58 or claim 59 wherein the coating is a non-pH-dependant degradable coating.

5 65. A pharmaceutical composition according to claim 64 wherein the coating comprises a non-pH-dependent polymer, optionally wherein the polymer is selected from: acacia, alginate, amylase, beeswax, carboxymethylcellulose, carnuba wax, cellulose acetate, cholesterol, ethyl-  
10 cellulose, fatty acids, gelatine, glyceryl behenate, glyceryl monostearate, glyceryl mono-distearate, glyceryl tripalmitate, hypromellose, hydroxypropylcellulose, hydrogenated vegetable oil, lecithin, methylcellulose, paraffin wax, pectin, polyethylene glycol, polycaprolactone, polyglycolic acid, polylactic acid, polyglyclide-co-lactide co-polymers, polyvinylprrolydone, starch, stearic acid, stearyl alcohol, partially hydrogenated cottonseed oil/soyabean oil, partially hydrogenated palm oil, partially hydrogenated cottonseed oil, partially hydrogenated soyabean oil, partially hydrogenated castor oil, and polyethylene glycol 3350.

15

66. A pharmaceutical composition according to any one of the preceding claims, wherein the first component is adapted to deliver sildenafil rapidly to promote fast onset of action wherein the sildenafil is adapted in a way to increase its solubility, optionally wherein the sildenafil comprises a co-crystal of sildenafil, optionally wherein the co-crystal of sildenafil  
20 is a co-crystal as defined in any one of claims 95 to 103.

67. A pharmaceutical composition according to any one of the preceding claims, wherein a second component is adapted to deliver the sildenafil from dose to dose by providing the sildenafil in a modified release form.

25

68. A pharmaceutical composition according to any one of the preceding claims, wherein a second component is adapted to deliver the sildenafil from dose to dose by providing the sildenafil in a modified release form by admixing it with a polymer.

30 69. A pharmaceutical composition according to claim 2 wherein the third component is adapted to deliver the sildenafil from dose to dose within the therapeutic window.

70. A pharmaceutical composition according to claim 69, wherein in the third component, the sildenafil is adapted to release rapidly and over a long period of time so that the  
35 sildenafil is released from dose to dose within the therapeutic window.

71. A pharmaceutical composition according to any one of claims 2, 69 and 70 wherein:



the first component is as defined in any one of claims 7 to 35 and 66; and  
the second component is as defined in any one of claims 36 to 65, 67 and 68.

72. A pharmaceutical composition according to any one of claims 2 and 69 to 71 wherein  
5 the third component comprises a pharmaceutically acceptable salt of sildenafil, sildenafil free  
base, a sildenafil co-crystal, or a mixture of two or more thereof.

73. A pharmaceutical composition according to any one of claims 2 and 69 to 72 wherein  
10 the third component comprises sildenafil citrate, a sildenafil fatty acid salt as defined in any  
one of claims 105 to 108, sildenafil free base, a sildenafil co-crystal which is optionally as de-  
fined in any one of claims 95 to 103, or a mixture of two or more thereof.

74. A pharmaceutical composition according to any one of claims 2 and 69 to 73 wherein  
15 the sildenafil in the third component is sildenafil citrate.

75. A pharmaceutical composition according to any one of claims 72 to 74 wherein the  
third component further comprises one or more excipients as defined in any one of claims 45  
to 65.

20 76. A pharmaceutical composition according to any one of claims 4 to 6, wherein the  
pharmaceutical composition comprises two components: said first component and said second  
component, wherein

the first component comprises sildenafil admixed with one or more excipients that fa-  
cilitate immediate release; and

25 the second component comprises sildenafil admixed with one or more excipients that  
facilitate a delayed release,

wherein the first component comprises from 10% to 30% by weight of the total  
amount of sildenafil in the first and second components and the second component comprises  
30 from 90% to 70% by weight of the total amount of sildenafil in the first and second compo-  
nents.

77. A pharmaceutical composition according to any one of claims 4 to 6, wherein the  
pharmaceutical composition comprises two components: said first component and said second  
component, wherein

35 the first component comprises from 10mg to 30mg sildenafil, optionally 20mg  
sildenafil, admixed with one or more excipients that facilitate immediate release; and

the second component comprises from 90mg to 70mg of sildenafil, optionally 80mg of sildenafil, admixed with one or more excipients that facilitate a delayed release.

78. A pharmaceutical composition according to any one of claims 4 to 6, wherein the  
5 pharmaceutical composition comprises two components: said first component and said second component, wherein:

(A) the first component comprises from 5mg to 15mg sildenafil, optionally 10mg sildenafil, admixed with one or more excipients that facilitate immediate release; and

10 the second component comprises from 45mg to 35mg sildenafil, optionally 40mg sildenafil, admixed with one or more excipients that facilitate a delayed release; or

(B) the first component comprises from 2.5mg to 7.5mg sildenafil, optionally 5mg sildenafil, admixed with one or more excipients that facilitate immediate release; and

15 the second component comprises from 17.5mg to 22.5mg of sildenafil, optionally 20mg sildenafil, admixed with one or more excipients that facilitate a delayed release.

79. A pharmaceutical composition according to any one of claims 76 to 78 wherein:  
the first component is as further defined in any one of claims 13 to 35; and  
the second component is as further defined in any one of claims 41 to 65.

20 80. A pharmaceutical composition according to any one of claims 76 to 78, wherein the first component comprises said sildenafil in the form of sildenafil citrate which is adapted to be released rapidly by being admixed with excipients which facilitate an immediate release which excipients are conventional excipients.

25 81. A pharmaceutical composition according to any one of claims 76 to 78 and 80, wherein the second component comprises said sildenafil citrate admixed with a polymer to facilitate a delayed release which polymer is a conventional polymer used in delayed release formulations.

30 82. A pharmaceutical composition according to any one of claims 76 to 78 wherein the sildenafil in the first component is a co-crystal of sildenafil, optionally wherein the co-crystal is as defined in any one of claims 95 to 103.

35 83. A pharmaceutical composition according to any one of claims 76 to 78 wherein the sildenafil in the first component is sildenafil free base.

84. A pharmaceutical composition according to any one of claims 76 to 78 wherein the sildenafil in the first component is a sildenafil fatty acid salt as defined in any one of claims 105 to 108.

5 85. A pharmaceutical composition according to any one of claims 76 to 84 which is a solid dosage form.

86. A pharmaceutical composition according to any one of claims 76 to 85 which is a swallow tablet.

10

87. A pharmaceutical composition according to any one of claims 4 to 86 wherein the first component is disposed on a surface of the second component.

15 88. A pharmaceutical composition according to any one of claims 4 to 87 which has a core-shell structure wherein the second component defines a core and the first component is disposed on the surface of the second component to form a shell which surrounds the core.

20 89. A multi-component dosage form comprising sildenafil, said dosage form being adapted in a first way to provide rapid release of sildenafil into the bloodstream, said dosage form being adapted in a second way to further provide a maintenance dose of sildenafil within the therapeutic window, and the dosage form being adapted in a third way to provide a modified or delayed release format of the sildenafil product which lasts from dose to dose.

25 90. A multi-component dosage form according to claim 89 which is a swallow tablet.

91. A multi-component dosage form according to claim 89 or claim 90 which comprises a first component and a second component as defined in any one of claims 4 to 88, and optionally comprises a third component as defined in any one of claims 2, 69, 70 and 72 to 75.

30 92. A multi-component dosage form according to any one of claims 89 to 91 which comprises:

sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as defined in any one of claims 95 to 103;

35 a fatty acid salt of sildenafil as defined in any one of claims 105 to 108, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and

said delayed release component, comprising a bolus dose of sildenafil, optionally wherein the sildenafil in the bolus dose is in the form of sildenafil citrate.

93. A multi-component dosage form according to any one of claims 89 to 91 which comprises:

from 2.5mg to 25mg sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as defined in any one of claims 95 to 103;

from 2.5mg to 25mg sildenafil in the form of a fatty acid salt of sildenafil as defined in any one of claims 105 to 108, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and

said delayed release component, comprising a bolus dose of sildenafil, optionally wherein the bolus dose of sildenafil is from 20mg to 95mg sildenafil, and optionally wherein the sildenafil in the bolus dose is in the form of sildenafil citrate.

94. A multi-component dosage form according to any one of claims 89 to 91 which comprises:

from 2.5 to 5mg sildenafil in the form of a co-crystal suitable for rapid release of sildenafil, which co-crystal is optionally as defined in any one of claims 95 to 103;

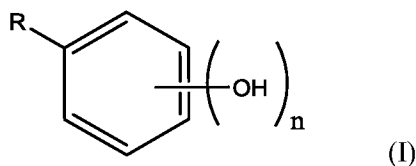
from 2.5 to 15mg sildenafil in the form of a fatty acid salt of sildenafil as defined in any one of claims 105 to 108, suitable for delivering sildenafil between onset of action from said rapid release and onset of a bolus amount of a delayed release component; and

said delayed release component, comprising a bolus dose of sildenafil, optionally wherein the sildenafil in the bolus dose is in the form of sildenafil citrate and optionally wherein the bolus dose is from 10mg to 80mg sildenafil, for instance 20mg sildenafil.

25

95. A co-crystal, which co-crystal comprises sildenafil and a co-crystal former, which co-crystal former is a compound which comprises a phenol moiety.

96. A co-crystal according to claim 95 wherein the co-crystal former is a compound of formula (I)



wherein

n is an integer of from 1 to 3; and

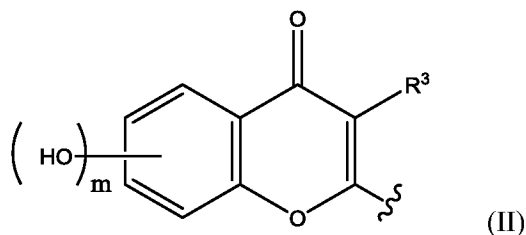
R is H, -C(O)OR<sup>2</sup>, -L-C(O)OR<sup>2</sup>, Ar or -L-Ar;

R<sup>2</sup> is H or unsubstituted C<sub>1-4</sub> alkyl;

L is -CH=CH-

Ar is phenyl or naphthyl, which phenyl or naphthyl is unsubstituted or substituted with from 1 to 3 groups selected from OH and C<sub>1-4</sub> alkyl; or

5 Ar is a group of formula (II)



wherein

R<sup>3</sup> is H or OH, and

m is 0, 1 or 2.

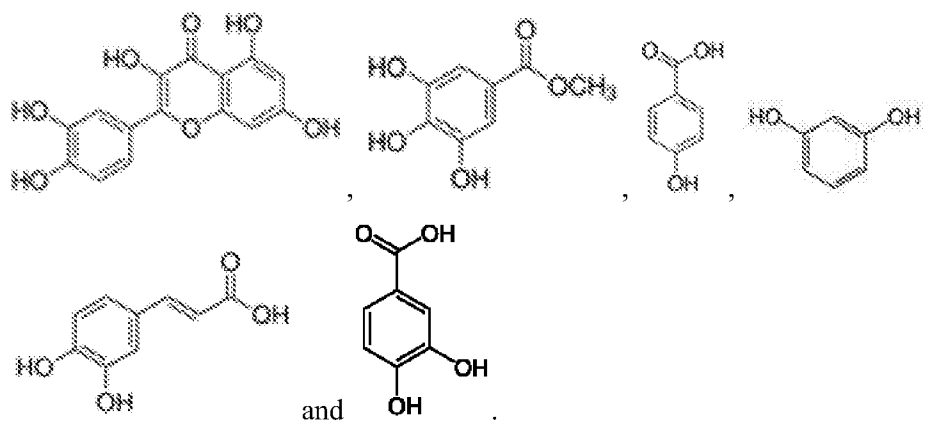
10

97. A co-crystal according to claim 96 wherein, when R is H, n is 2 or 3.

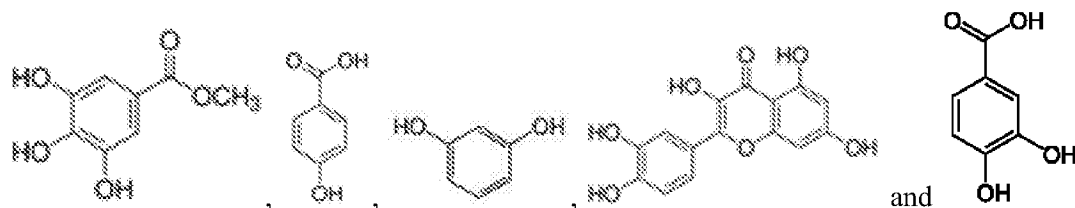
98. A co-crystal according to claim 96 or claim 97 wherein R<sup>2</sup> is H or methyl; Ar is phenyl, which phenyl is unsubstituted or substituted with from 1 to 3 OH groups; or Ar is said

15 group of formula (II) wherein R<sup>3</sup> is OH.

99. A co-crystal according to any one of claims 95 to 98 wherein the co-crystal former is selected from compounds having the following structures:

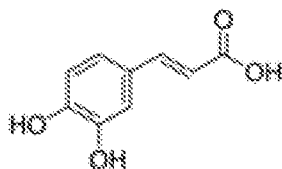


100. A co-crystal according to any one of claims 95 to 98 wherein the co-crystal former is selected from compounds having the following structures:



wherein the molar ratio of the sildenafil to the co-crystal former in the co-crystal is 1:1.

101. A co-crystal according to any one of claims 95 to 98 wherein the co-crystal former is a compound having the following structure:



wherein the molar ratio of the sildenafil to the co-crystal former in the co-crystal is 3:2.

102. A co-crystal according to any one of claims 95 to 101 wherein the sildenafil in the co-crystal is sildenafil base, i.e. 5-{2-ethoxy-5-[(4-methylpiperazin-1-yl)sulfonyl]phenyl}-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one.

103. A co-crystal according to any one of claims 95 to 102 which is co-crystal P42-I-A, P42-I-B, P42-III, P42-VI-B, P42-VI-C, P42-VI-D, P42-VI-E, P42-VII, P42-VIII or P42-IX as described herein.

104. A pharmaceutical composition comprising: (i) a co-crystal as defined in any one of claims 95 to 103, and (ii) a pharmaceutically acceptable carrier.

105. A salt of sildenafil with a long chain fatty acid.

106. A salt according to claim 105 which is amorphous or crystalline.

107. A salt according to claim 105 or claim 106 wherein the long chain fatty acid has formula R-C(O)OH wherein R is C<sub>6-24</sub> alkyl or C<sub>6-24</sub> alkenyl.

108. A salt according to any one of claims 105 to 107 wherein the long chain fatty acid is selected from decanoic acid, docosanoic acid, eicosanoic acid, heneicosanoic acid, heptadecanoic acid, lauric acid, myristic acid, nonadecanoic acid, nonanoic acid, octanoic acid, palmitic

acid, pentadecanoic acid, stearic acid, tetracosanoic acid, tricosanoic acid, tridecanoic acid, undecanoic acid, and undecylenic acid.

109. A pharmaceutical composition comprising: (i) a salt of sildenafil with a long chain  
5 fatty acid as defined in any one of claims 105 to 108, and (ii) a pharmaceutically acceptable carrier.

110. A pharmaceutical composition according to claim 109 which comprises (i) said salt of  
10 sildenafil and (ii) a polymeric carrier or matrix material.

111. A pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and  
110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as  
defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108,  
for use in a method of treatment of the human or animal body by therapy.

112. A pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and  
110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as  
defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108,  
for use in the treatment or prophylaxis of a disorder associated with PDE5 inhibition.

113. Use of a pharmaceutical composition as defined in any one of claims 1 to 88, 104,  
109 and 110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-  
crystal as defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105  
to 108, in the manufacture of a medicament for use in the treatment or prophylaxis of a disorder  
25 associated with PDE5 inhibition.

114. A method for the treatment or prophylaxis of a disorder associated with PDE5 inhibi-  
tion, which method comprises administering an effective amount of a pharmaceutical compo-  
sition as defined in any one of claims 1 to 88, 104, 109 and 110, a multi-component dosage  
30 form as defined in any one of claims 89 to 94, a co-crystal as defined in any one of claims 95  
to 103, or a salt as defined in any one of claims 105 to 108, to a sufferer in need thereof.

115. A pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and  
110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as  
35 defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108,  
for use in the treatment of human male erectile dysfunction.

116. Use of a pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and 110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108, in the manufacture of a medicament for use in the treatment of human male erectile  
5 dysfunction.

117. A method for the treatment of human male erectile dysfunction, which method comprises administering an effective amount of a pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and 110, a multi-component dosage form as defined in any  
10 one of claims 89 to 94, a co-crystal as defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108, to a human male in need thereof.

118. A pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and 110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as  
15 defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108, for use in the treatment of human female sexual dysfunction.

119. Use of a pharmaceutical composition as defined in any one of claims 1 to 88, 104, 109 and 110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-  
20 crystal as defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108, in the manufacture of a medicament for use in the treatment of human female sexual dysfunction.

120. A method for the treatment of human female sexual dysfunction, which method comprises administering an effective amount of a pharmaceutical composition as defined in any  
25 one of claims 1 to 88, 104, 109 and 110, a multi-component dosage form as defined in any one of claims 89 to 94, a co-crystal as defined in any one of claims 95 to 103, or a salt as defined in any one of claims 105 to 108, to a human female in need thereof.

30 121. A pharmaceutical composition, a multi-component dosage form, co-crystal or salt according to claim 115 or claim 118 for use as defined in said claim, the use according to claim 116 or claim 119, or a method according to claim 117 or claim 120, wherein:

said treatment comprises delivering sildenafil rapidly to promote fast onset of action, and delivering sildenafil from dose to dose within the therapeutic window.

35



122. A pharmaceutical composition, a multi-component dosage form, co-crystal or salt according to claim 115, 118 or 121 for use as defined in said claim, the use according to claim 116, 119 or 121, or a method according to claim 117, 120 or 121, wherein:

5 said treatment comprises providing rapid release of sildenafil into the bloodstream, providing a maintenance dose of sildenafil within the therapeutic window, and providing modified or delayed release of sildenafil to last from dose to dose.

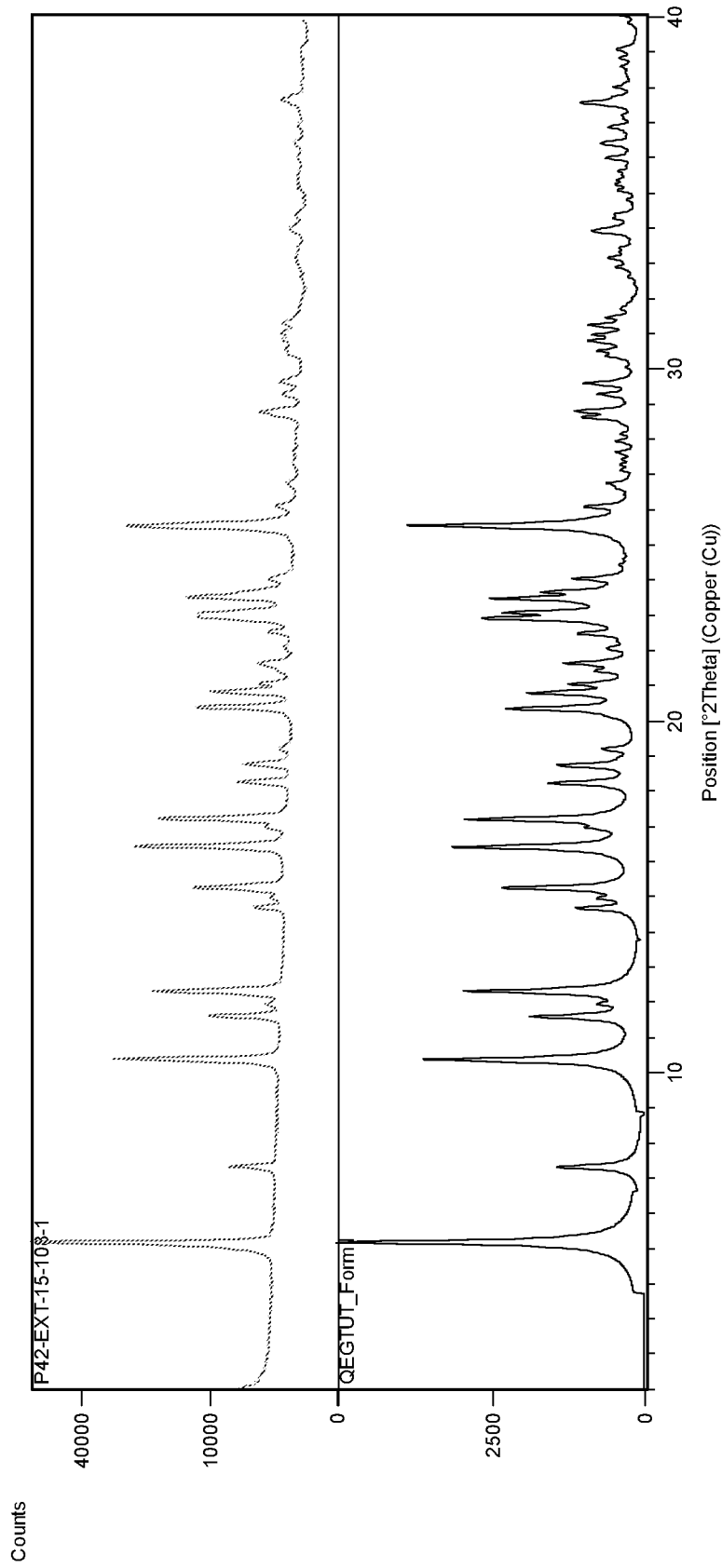


Fig. 1

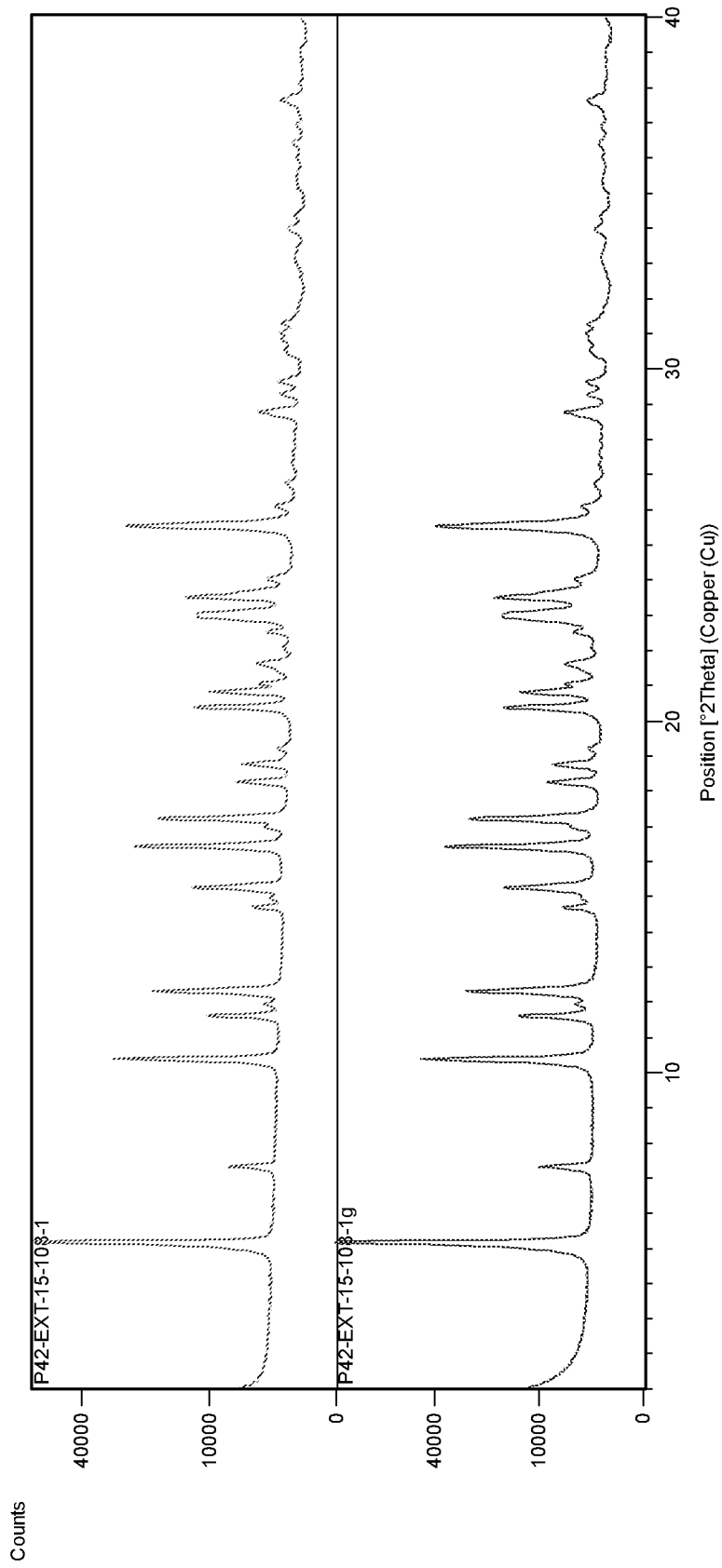


Fig. 2

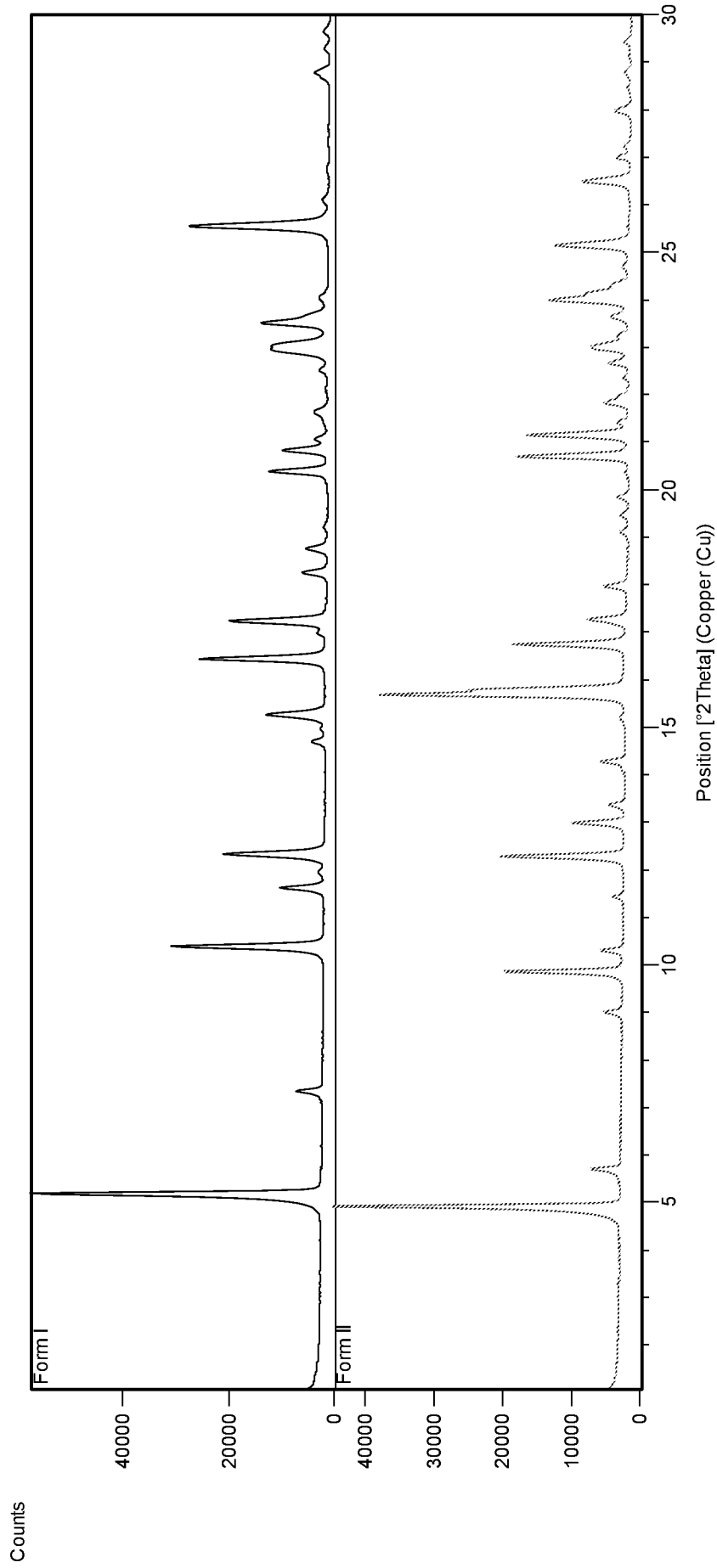


Fig. 3

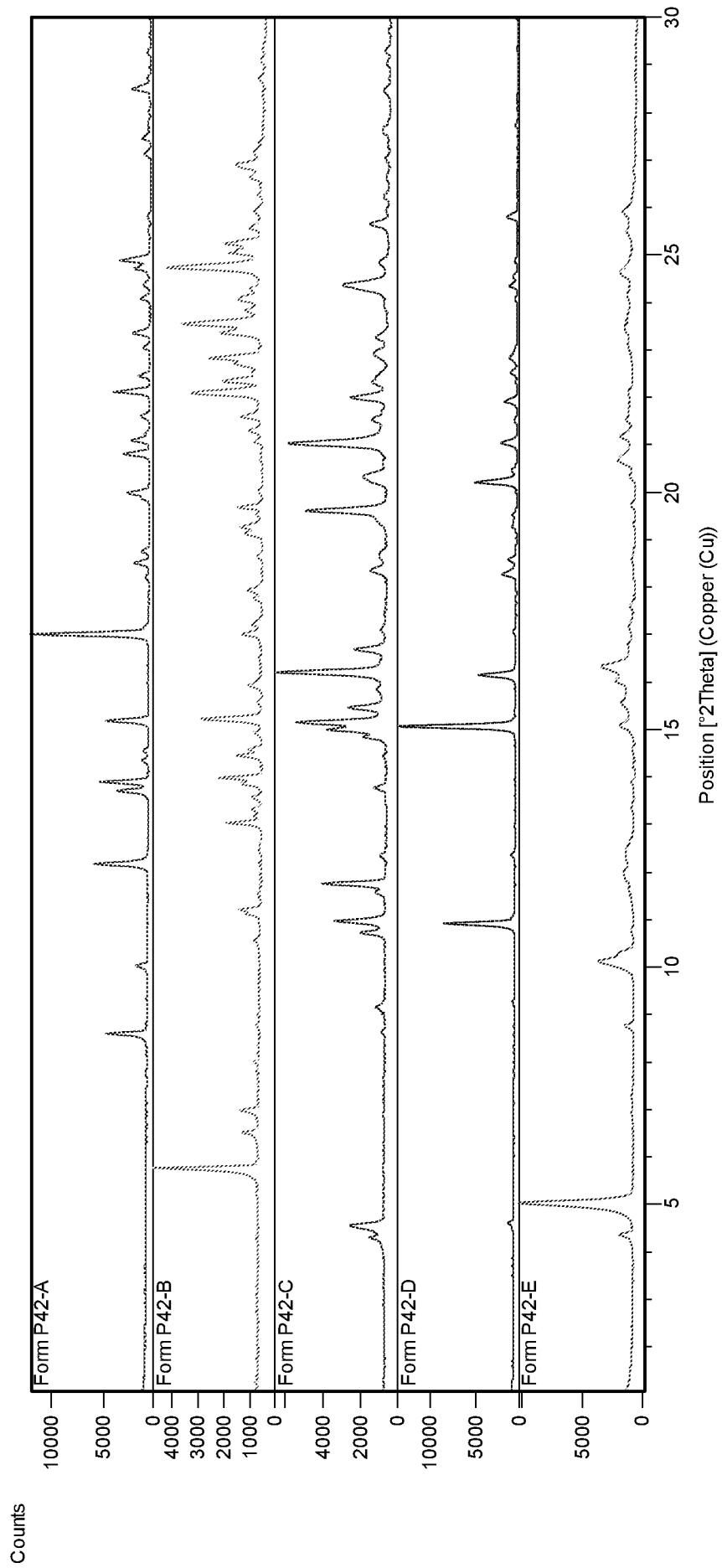


Fig. 4

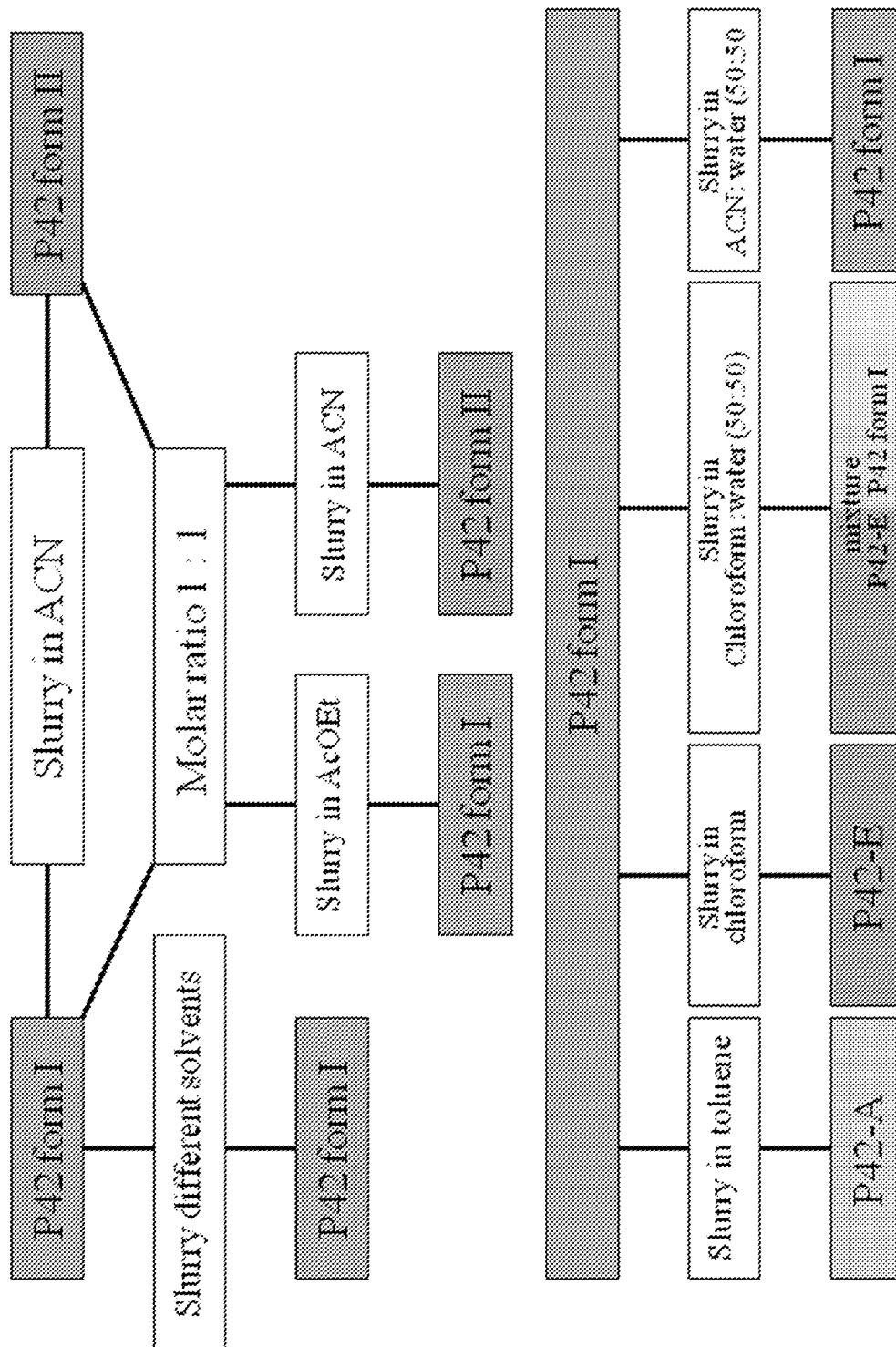


Fig. 5

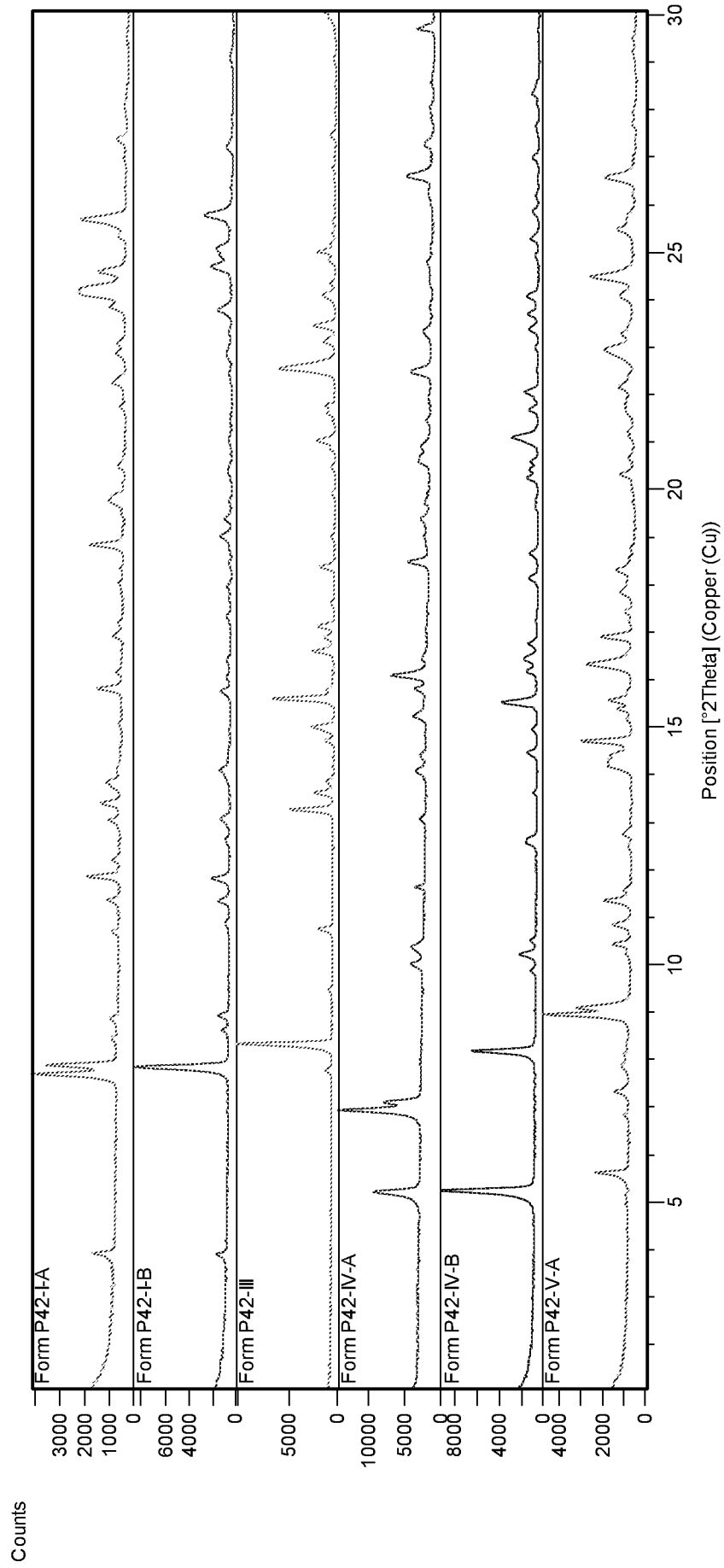


Fig. 6

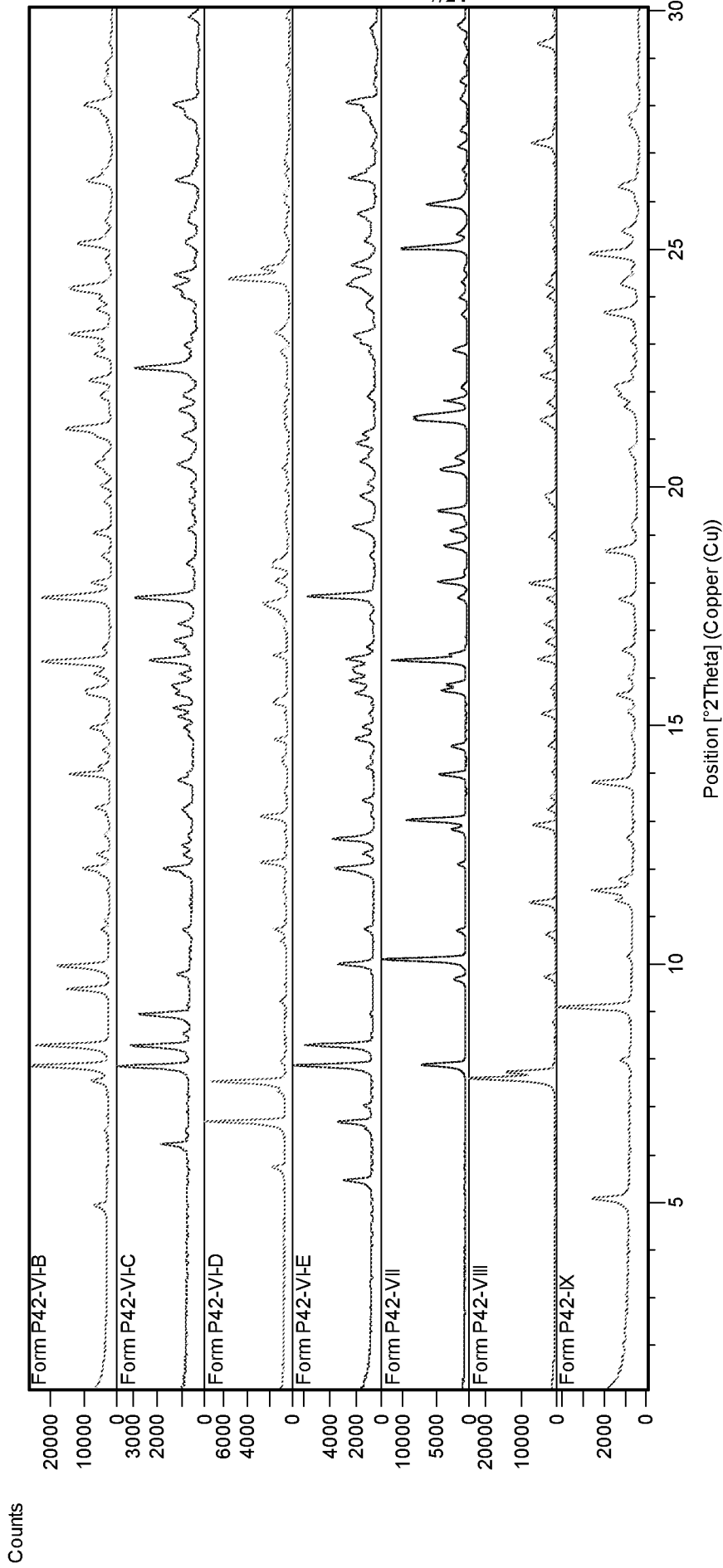
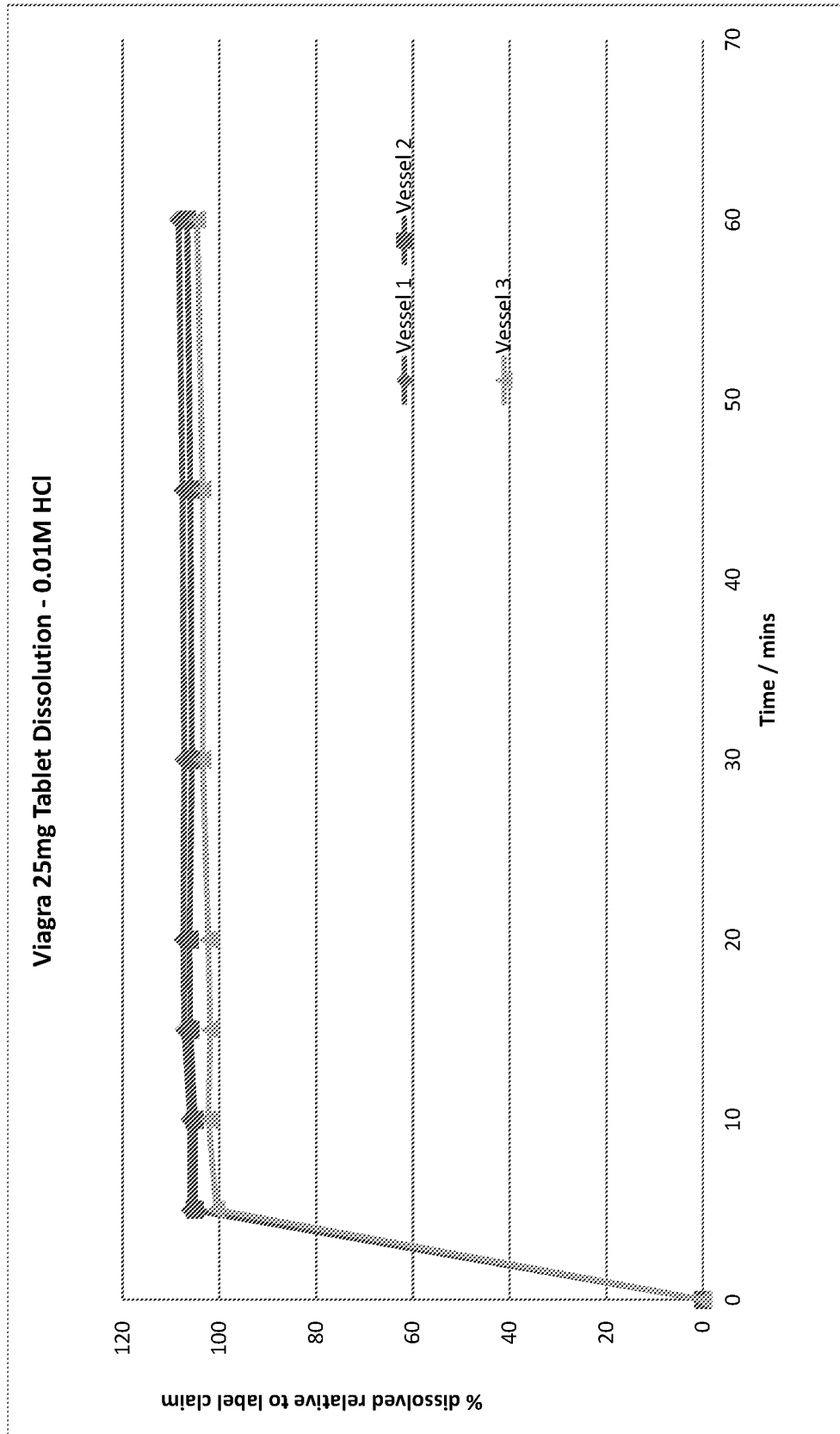


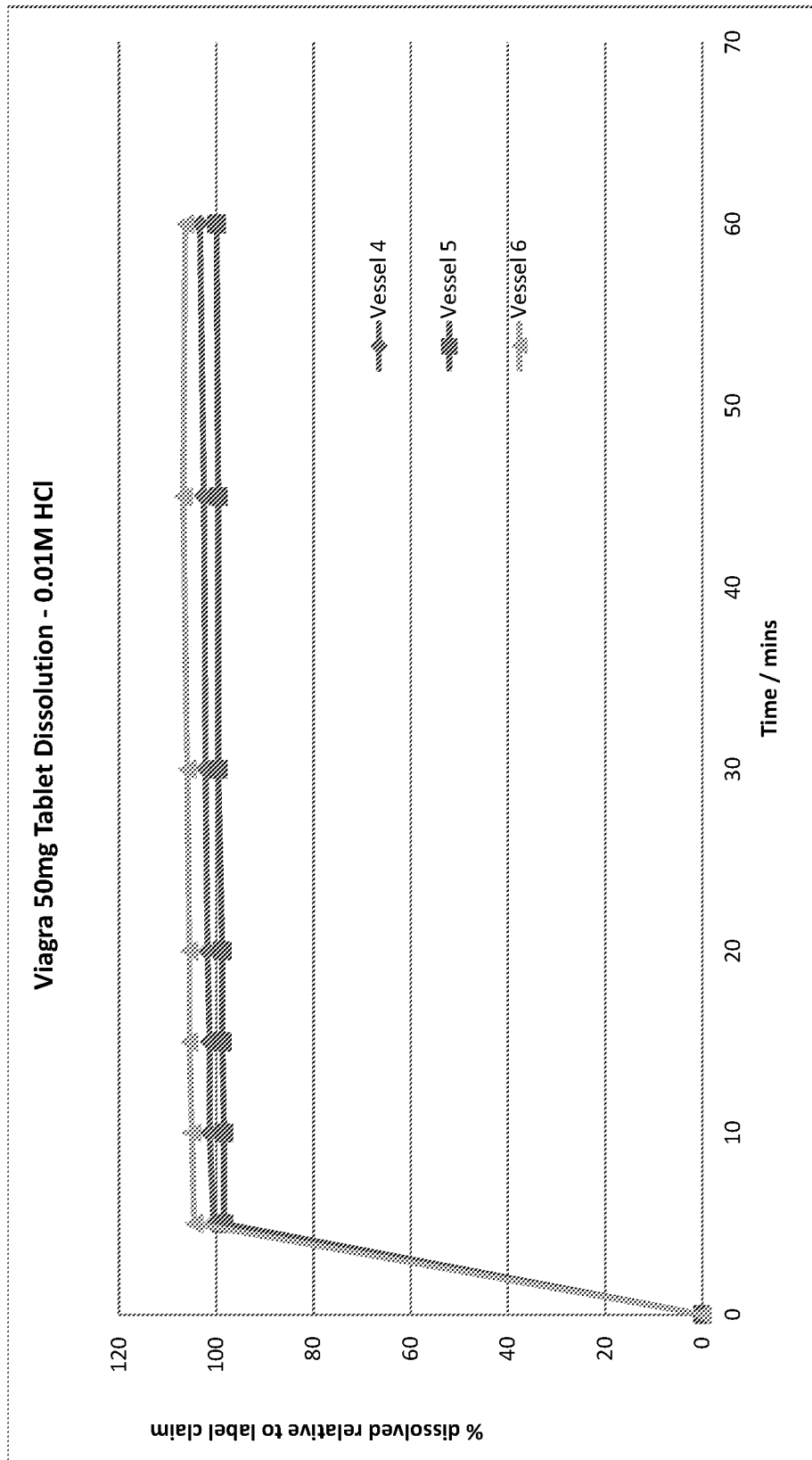
Fig. 7





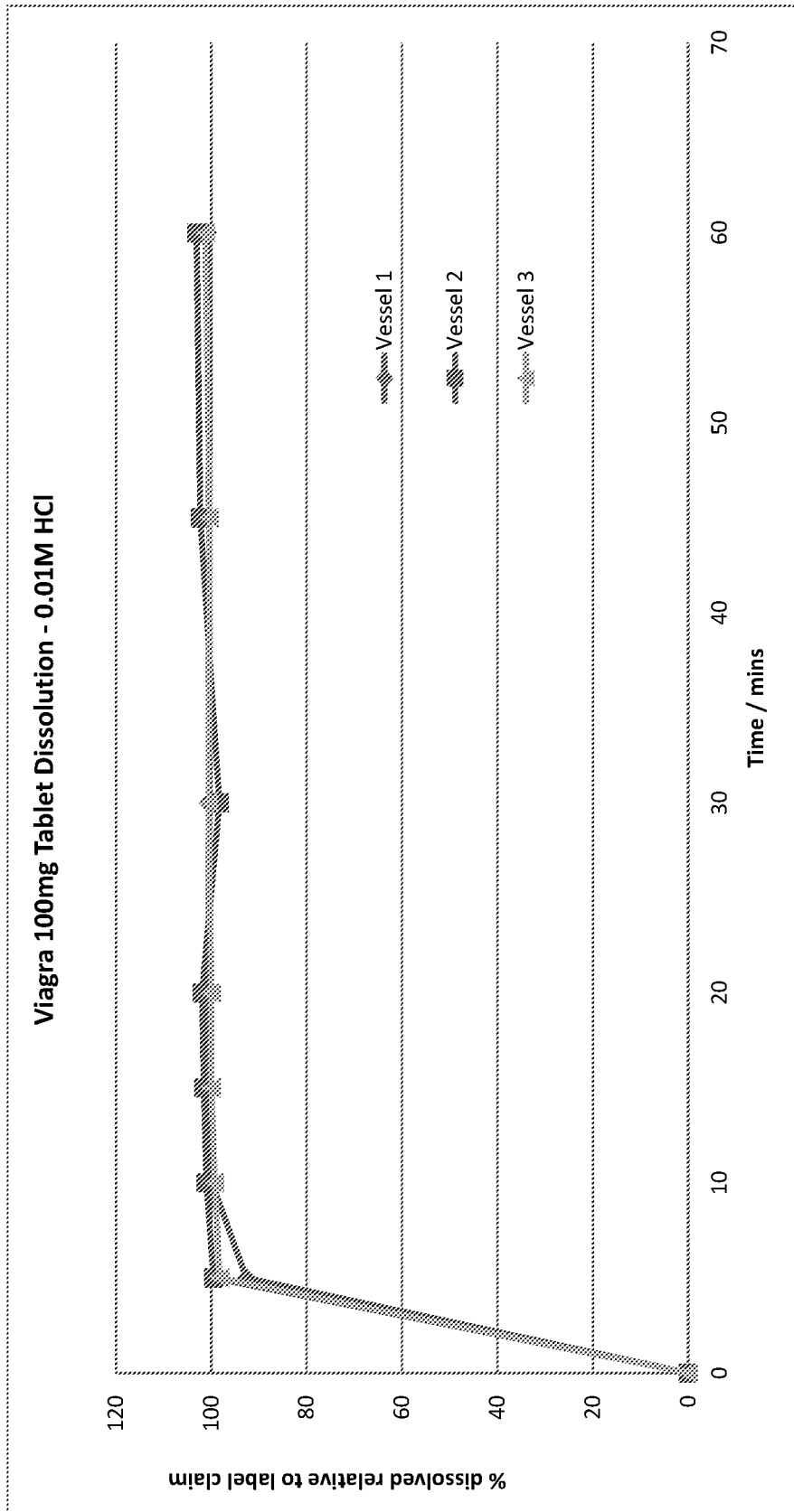
100 % release at 5 minutes

Fig. 8



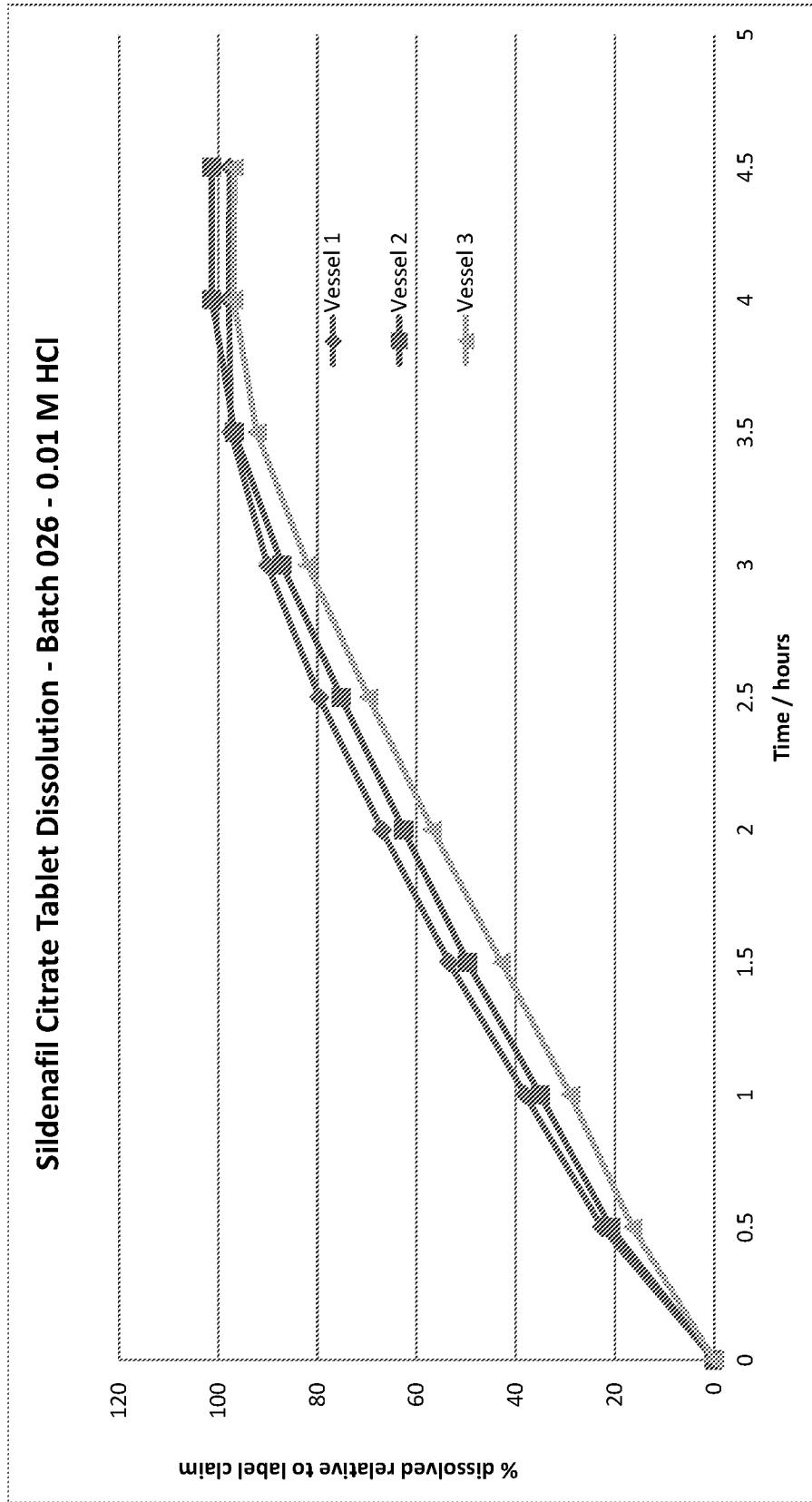
100 % release at 5 minutes

Fig. 9

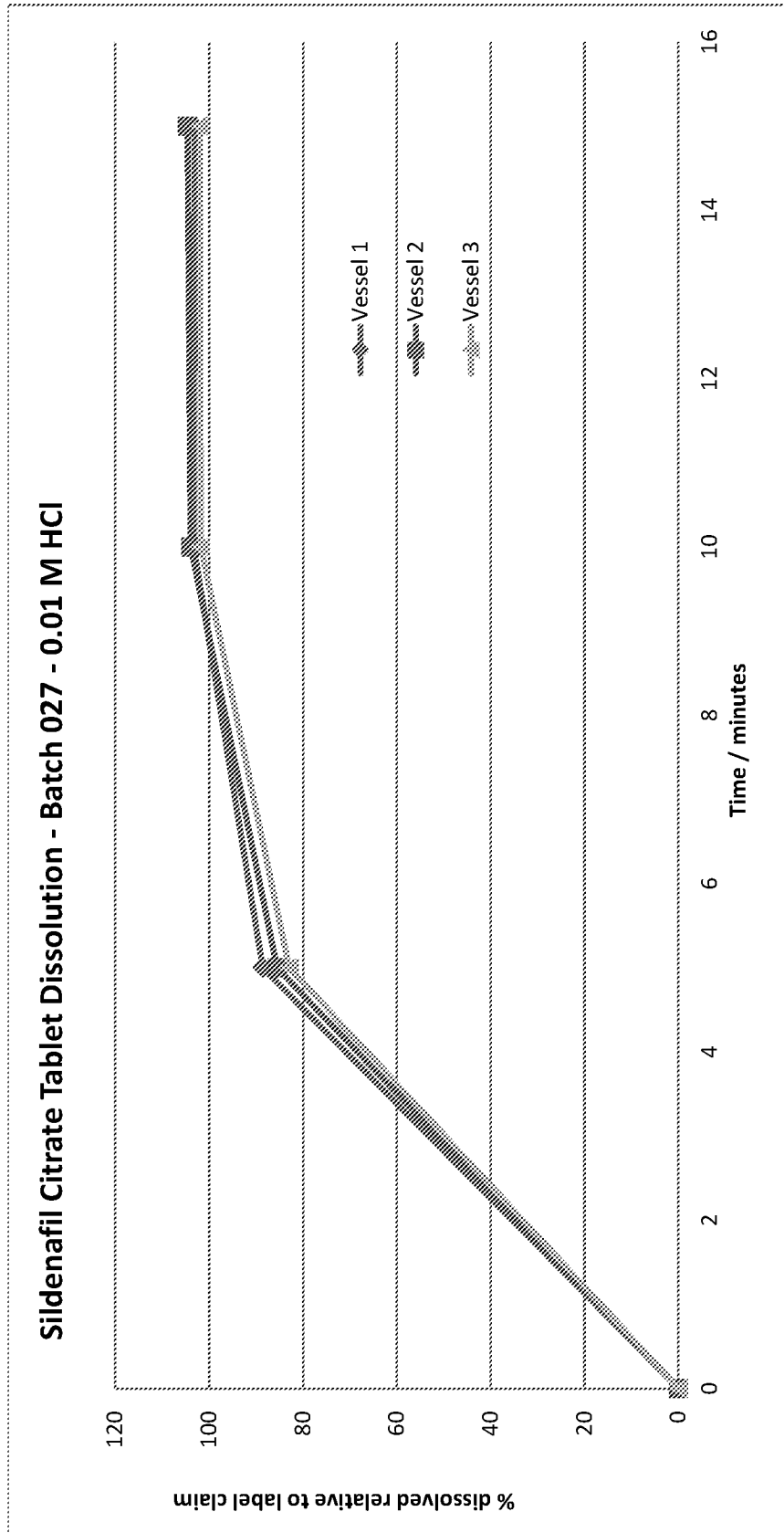


**100 % release at 5 minutes**

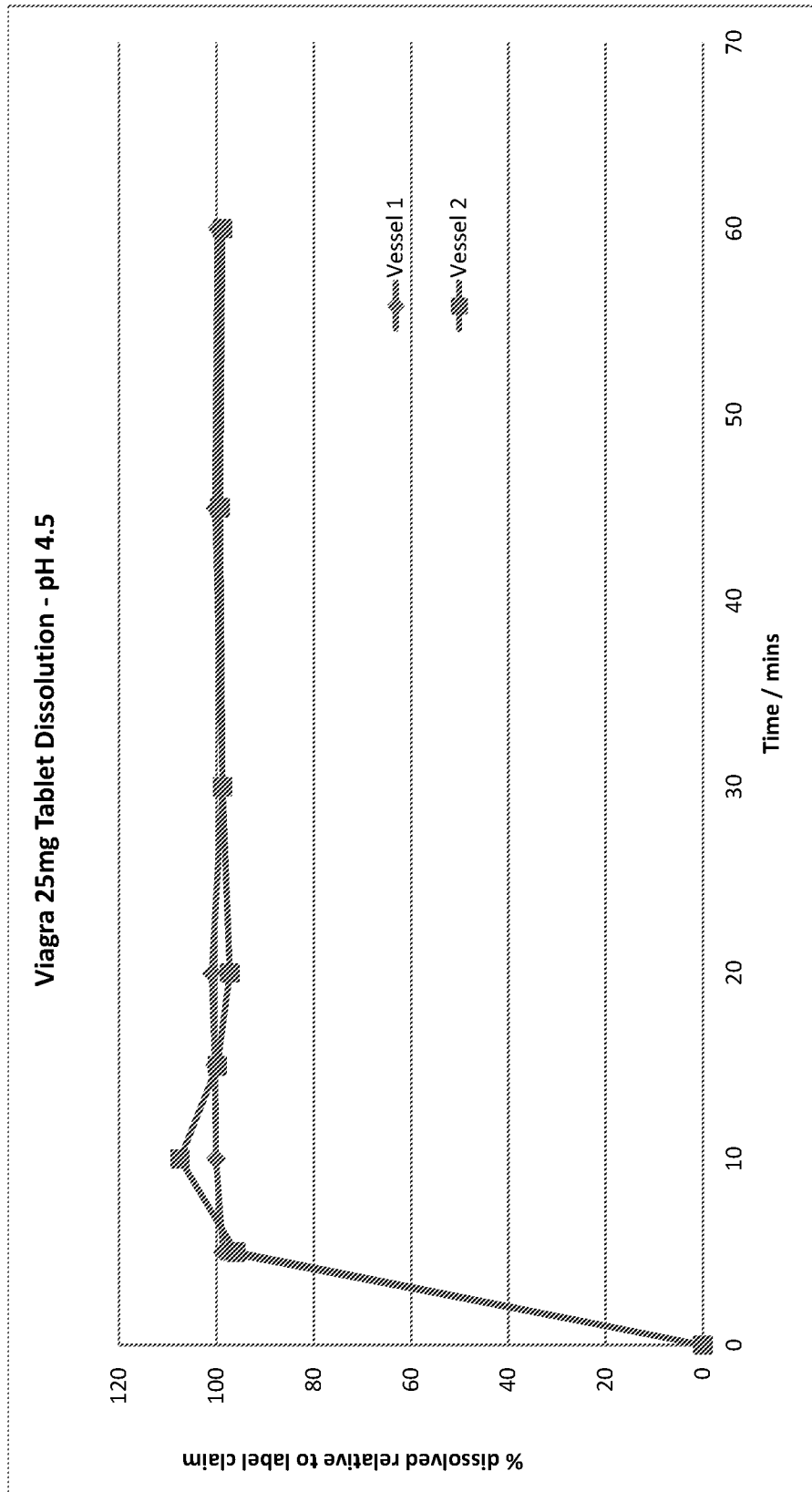
**Fig. 10**



**Fig. 11**

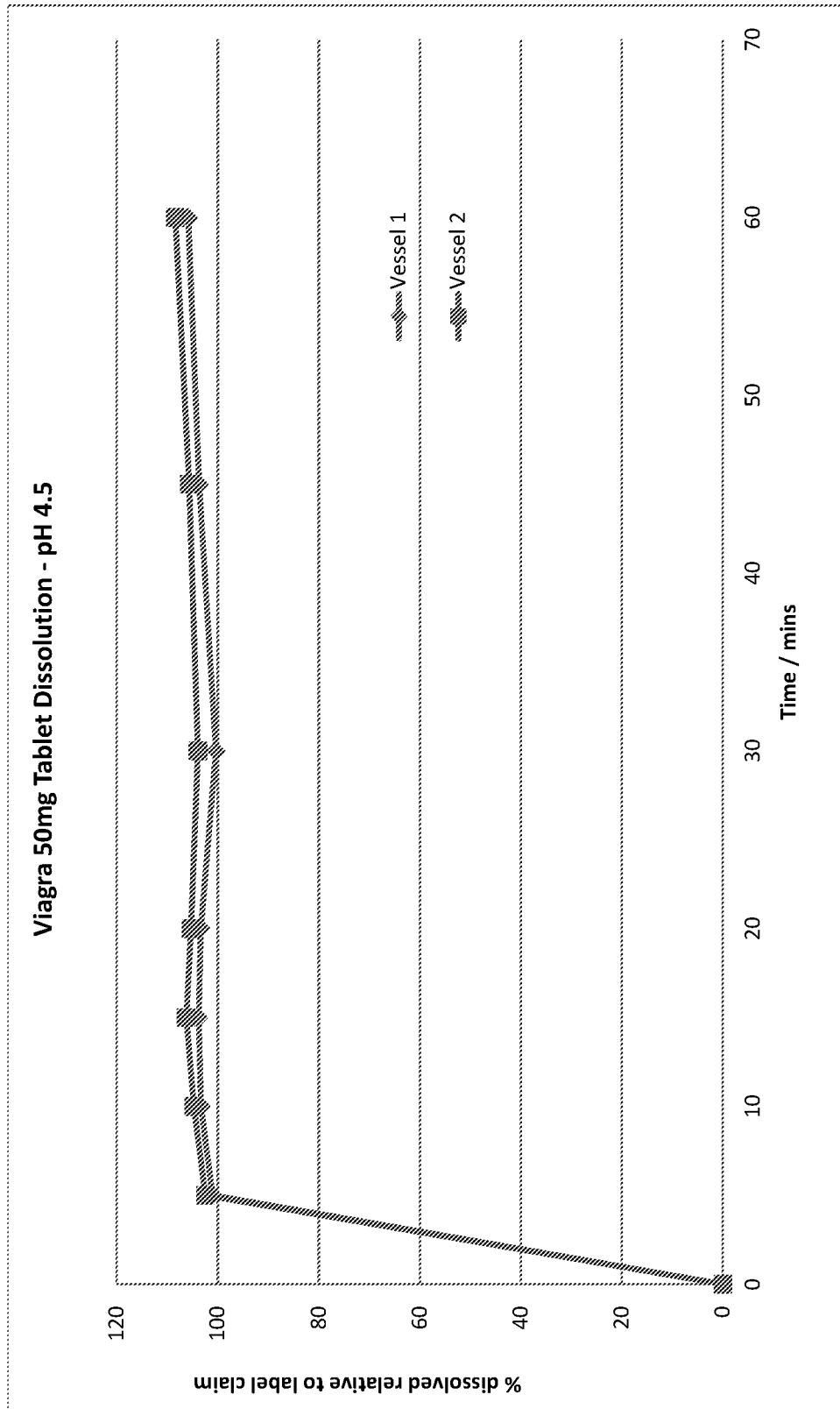


**Fig. 12**



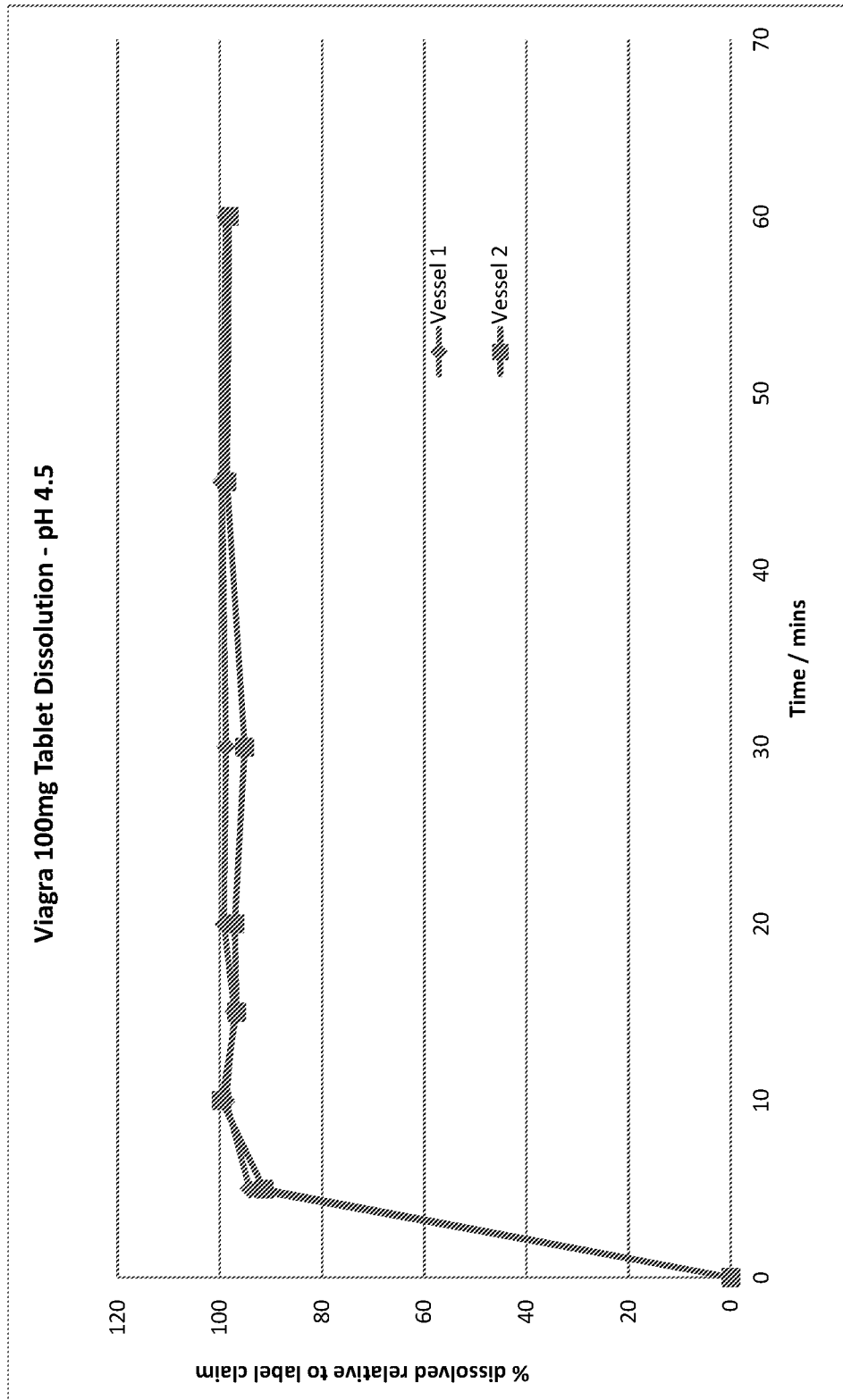
100 % release at 5 minutes

Fig. 13



100 % release at 5 minutes

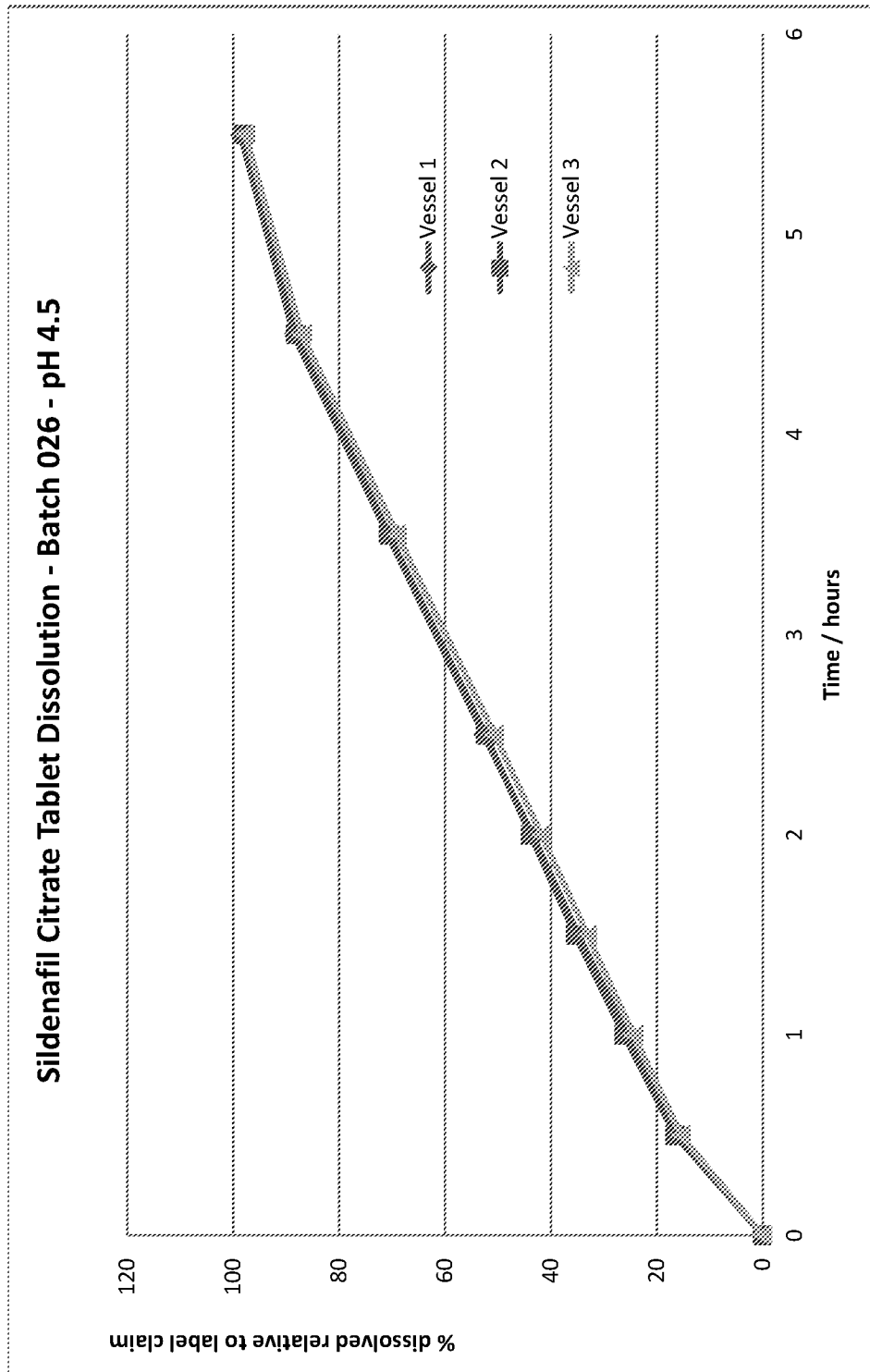
Fig. 14



**>90% release at 5 minutes**

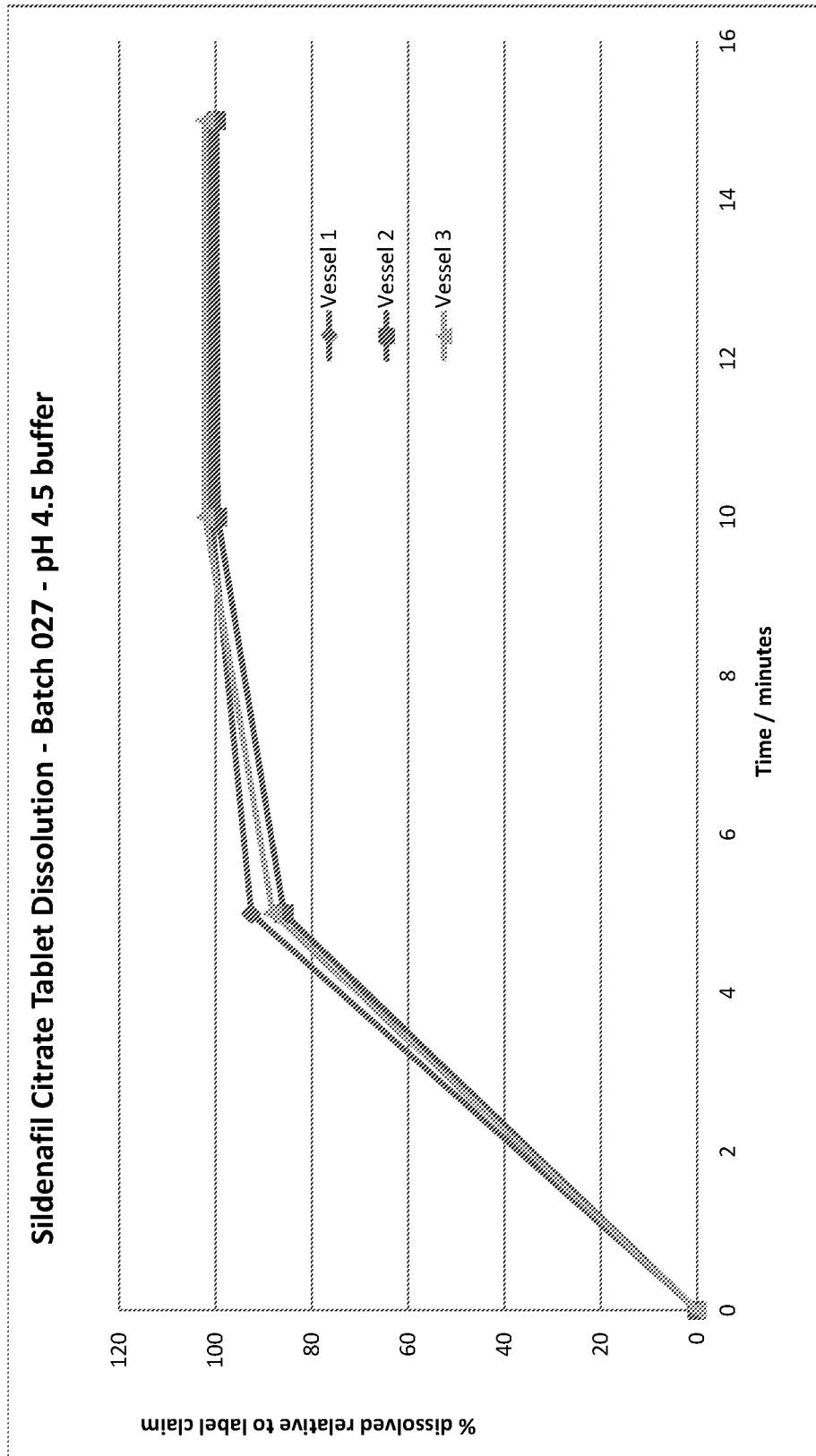
**Fig. 15**



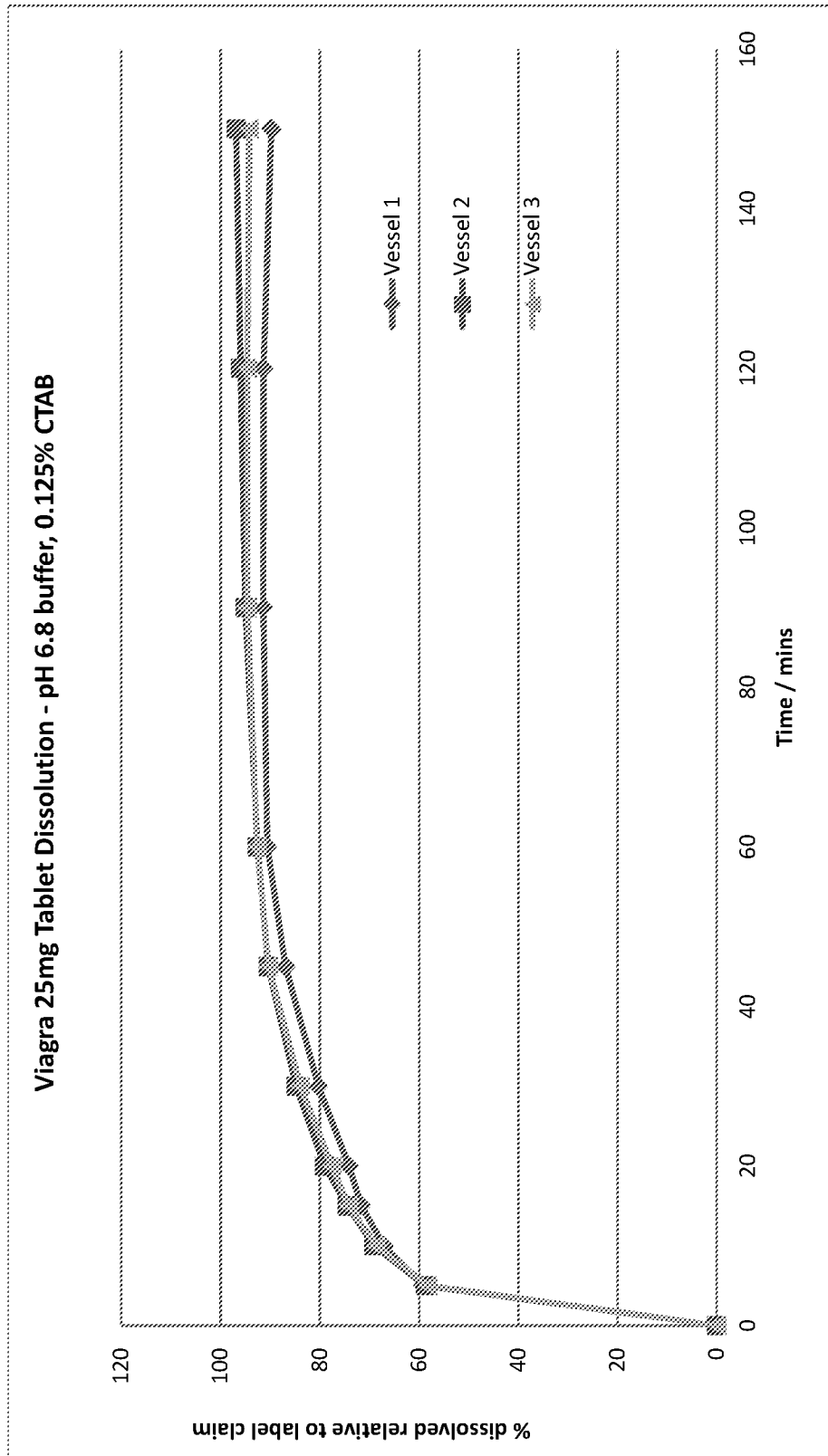


**100 % release at 5.5 hours**

**Fig. 16**

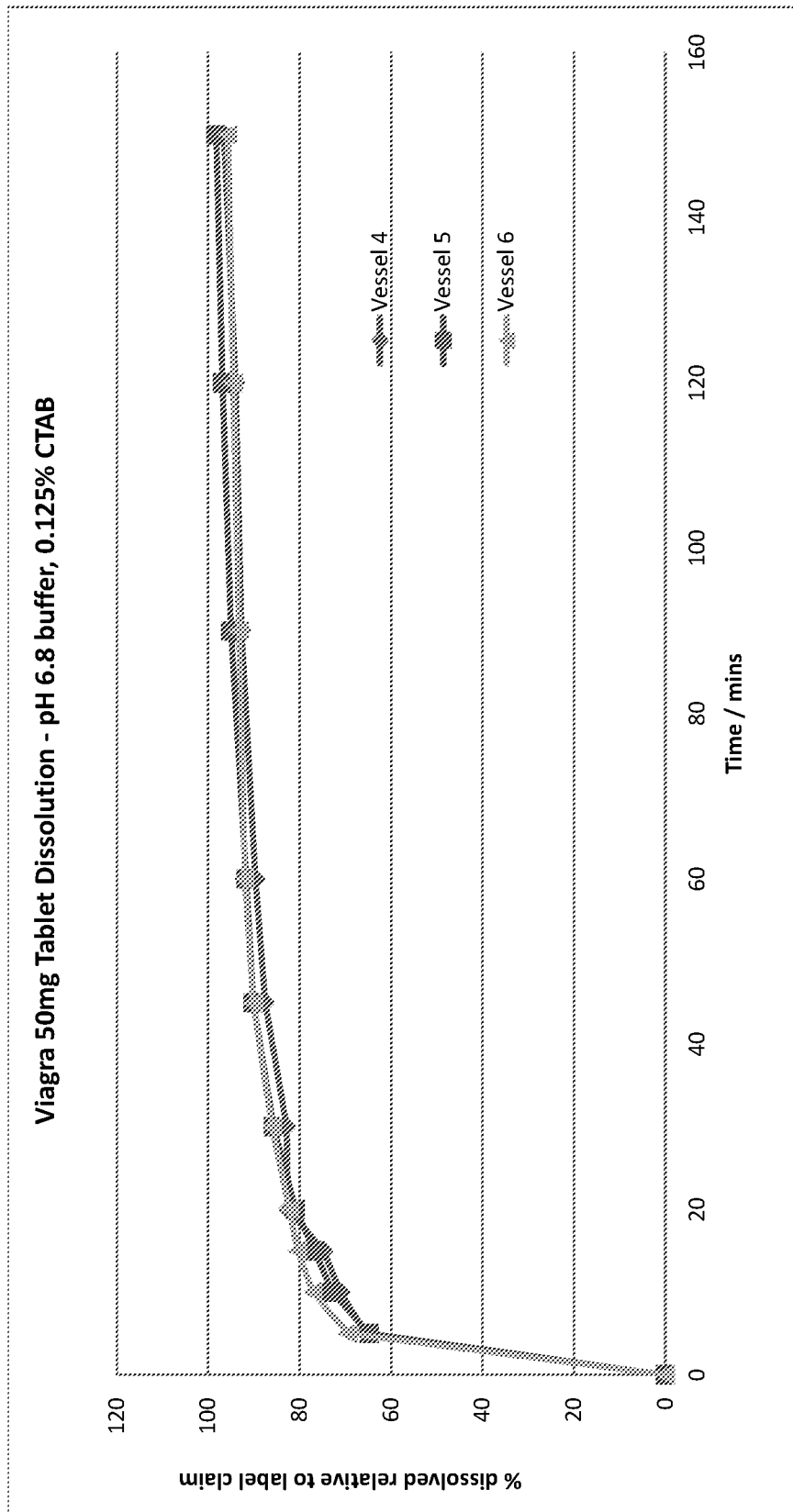


**Fig. 17**



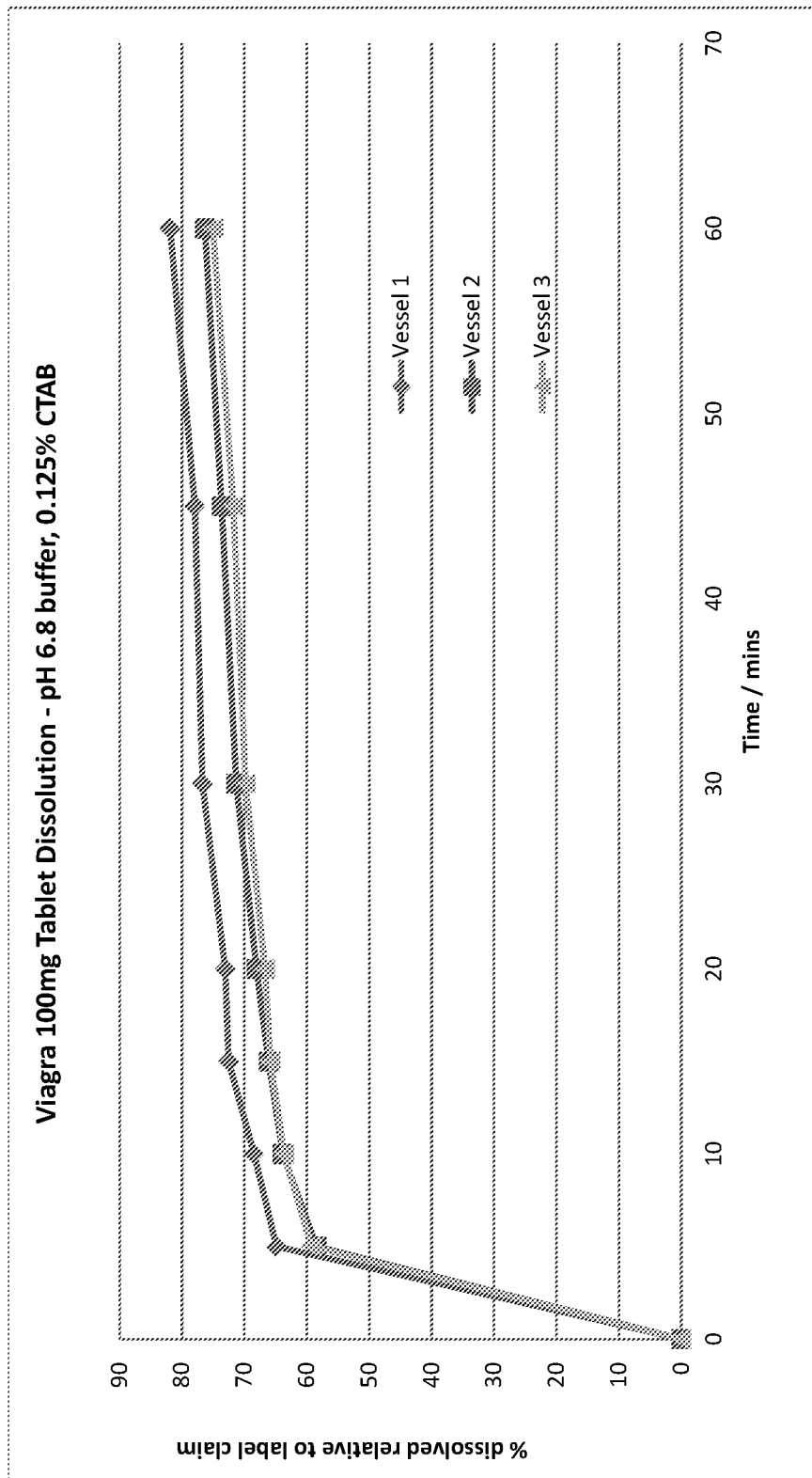
60 % release at 5 minutes (slower release of remaining drug possibly due to coning effect due to insoluble sample matrix)

Fig. 18



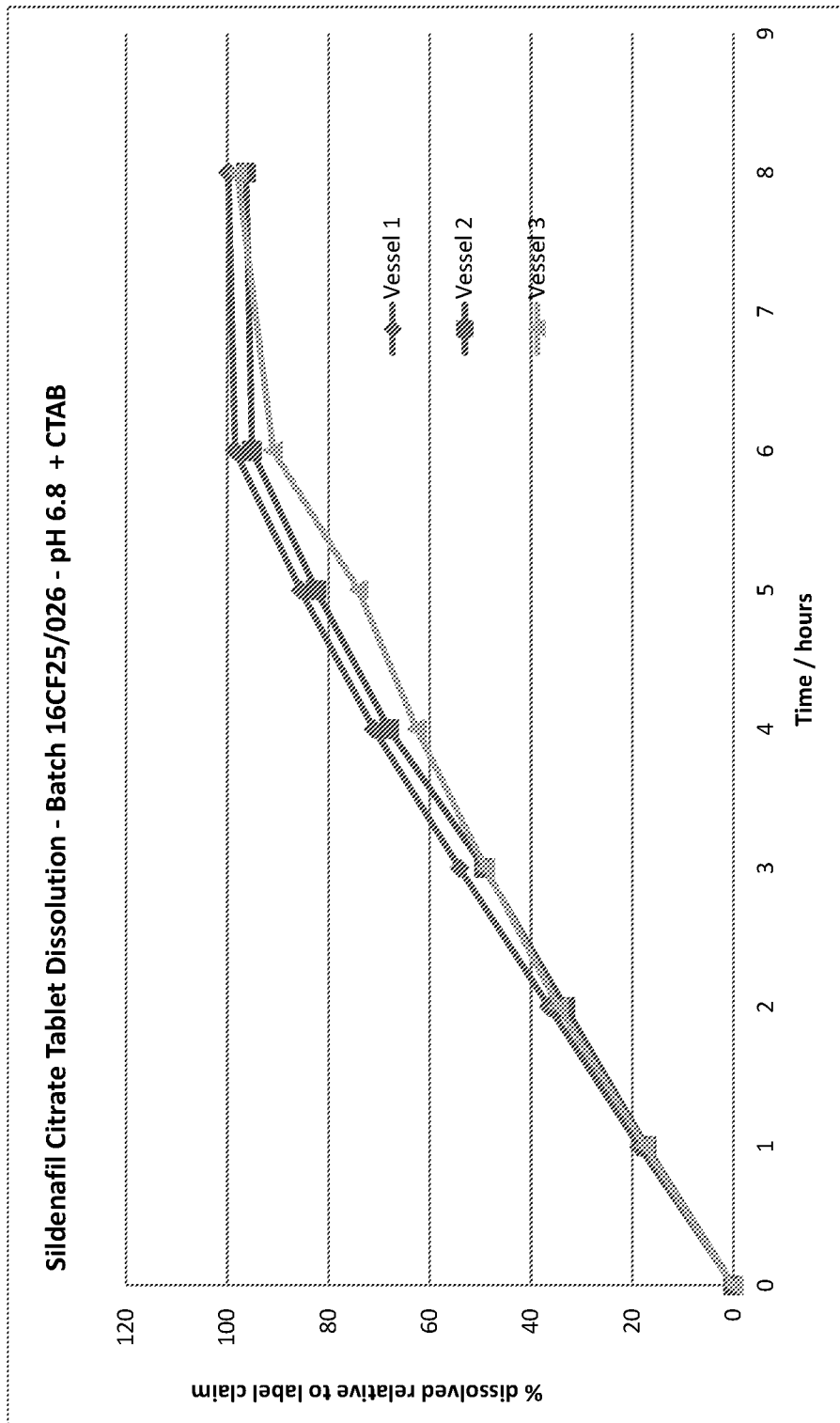
66 % release at 5 minutes (slower release of remaining drug possibly due to coning effect due to insoluble sample matrix)

**Fig. 19**



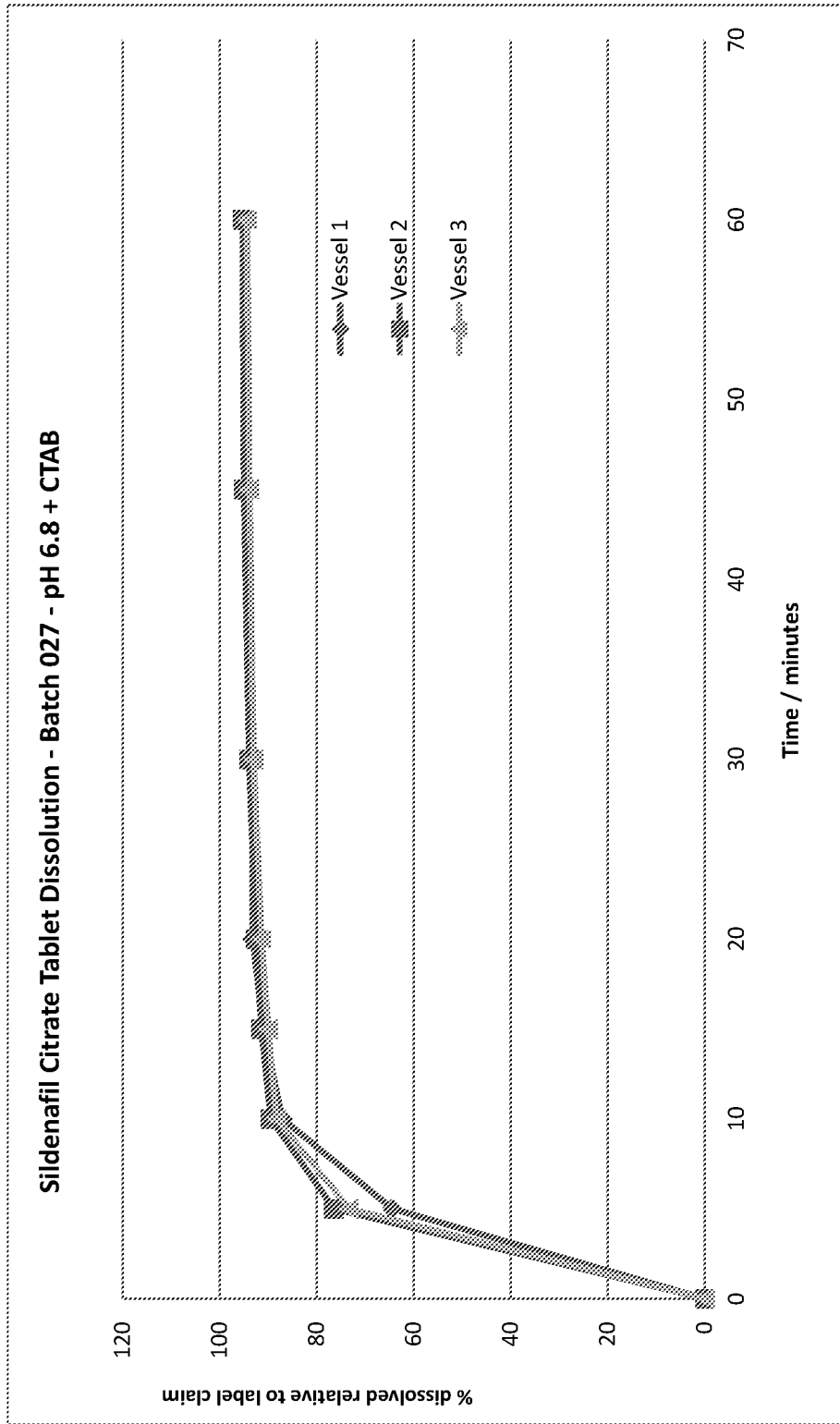
60% release at 5 minutes (slow release of remaining drug possibly due to coning effect due to insoluble sample matrix)

Fig. 20



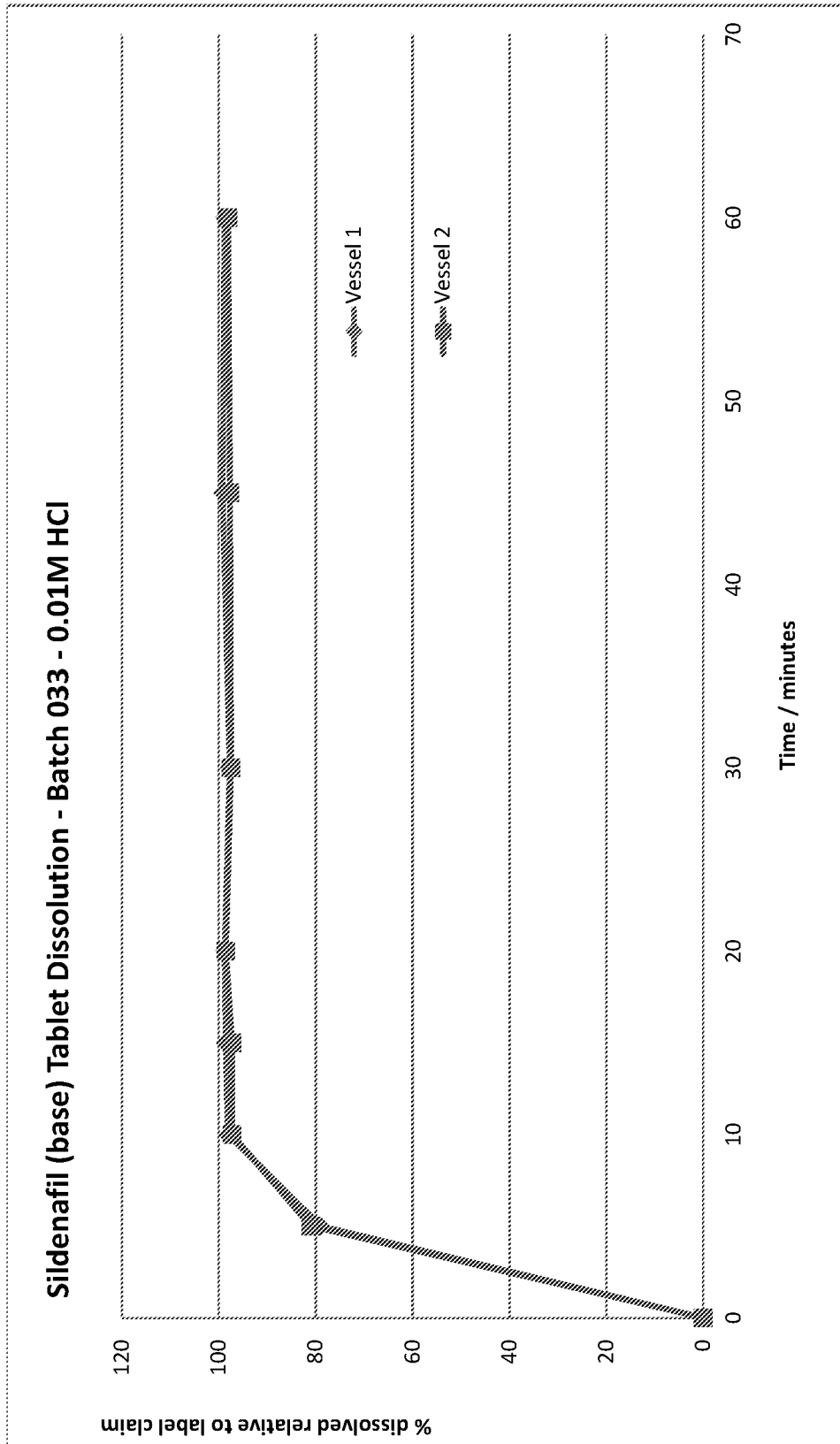
100 % release at 6 hours

Fig. 21



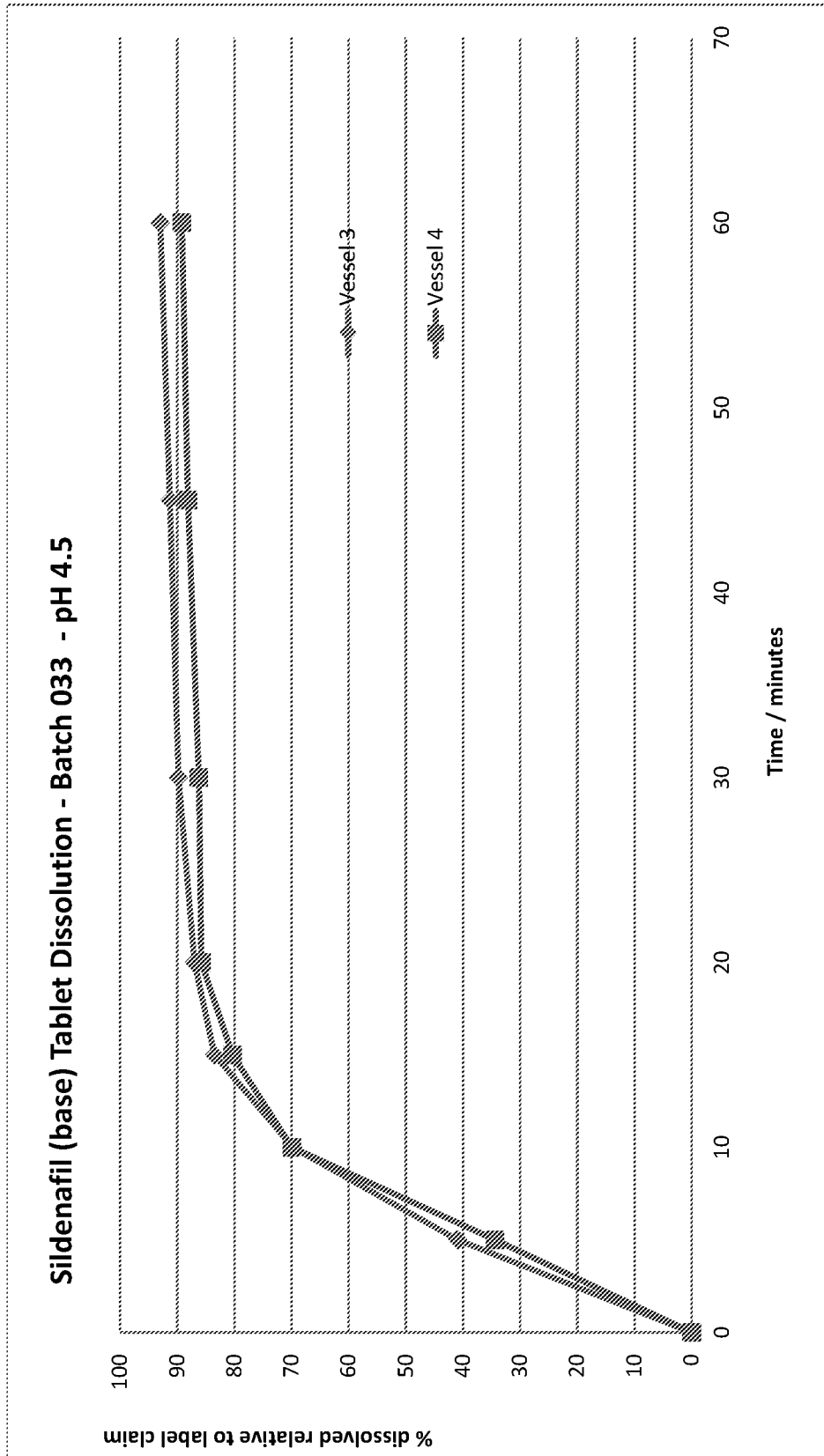
**> 90 % release at 15 minutes**

**Fig. 22**



**Fig. 23**





**Fig. 24**

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/GB2017/050921

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K31/519 A61P15/00 A61P17/10 A61K9/52  
 ADD.  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 EPO-Internal, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 374 460 A1 (SIEGFRIED RHEIN S A DE C V [MX]) 12 October 2011 (2011-10-12)  Compositions comprising sildenafil citrate in two different forms providing a dual-release: the first form comprises from 5 to 100mg of sildenafil in immediate release form and the second comprising 25 to 150 mg of sildenafil in controlled release form: see paragraphs 1, 11-17; examples 1-3; the claims and figures 1, 2 ----- -/--	1,3-13, 36,41, 42,44, 45,47, 58-68, 76,77, 80,81, 85,86, 89-91, 111-122

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>
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Date of the actual completion of the international search  9 June 2017	Date of mailing of the international search report  17/08/2017
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Veronese, Andrea
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## INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2017/050921

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 2005/013937 A2 (ELAN PHARMA INT LTD [IE]; RYDE TUULA A [US]; HOVEY DOUGLAS C [US]; BOS) 17 February 2005 (2005-02-17)</p> <p>Composition comprising sildenafil nanoparticles for treating sexual dysfunctions, where the sildenafil is distributed providing a dual-release, and the composition comprises both a fast-acting formulation and a long-lasting formulation, preferably in form of tablets: see paragraphs 41, 42, 71, 98-101, claim 10</p> <p style="text-align: center;">-----</p>	<p>1,3-8, 36,41, 42, 111-122</p>
X	<p>WO 00/24383 A1 (PFIZER RES &amp; DEV [IE]; PFIZER [US]; PFIZER LTD [GB]; KING ELIZABETH [G]) 4 May 2000 (2000-05-04)</p> <p>Composition comprising sildenafil nanoparticles where the sildenafil is distributed providing a dual-release, and the composition comprises both a fast-acting formulation and a long-lasting formulation, preferably in form of tablets: see the section between page 4, line 10 and page 5, line 20; claims 1, 8-11, 21, 29</p> <p style="text-align: center;">-----</p>	<p>1,3-8, 36,41, 42, 111-122</p>
X	<p>WO 2010/146407 A1 (NANOFORM HUNGARY LTD [HU]; FILIPCSEI GENOVEVA [HU]; OETVOES ZSOLT [HU]) 23 December 2010 (2010-12-23)</p> <p>Formulations comprising co-crystals of sildenafil where the sildenafil can be in mixed immediate and controlled release forms: see claims 1, 17, 23, 24</p> <p style="text-align: center;">-----</p>	<p>1,3-8, 32,33,43</p>
Y	<p>PALASH SANPHUI ET AL: "Salt and Cocrystals of Sildenafil with Dicarboxylic Acids: Solubility and Pharmacokinetic Advantage of the Glutarate Salt", MOLECULAR PHARMACEUTICS, vol. 10, no. 12, 2 December 2013 (2013-12-02), pages 4687-4697, XP055375732, US</p> <p>ISSN: 1543-8384, DOI: 10.1021/mp400516b</p> <p>Co-crystals of sildenafil and other co-crystalizing agents</p> <p style="text-align: center;">-----</p>	<p>1-94, 111-122</p>
Y	<p>WO 2007/080362 A1 (PLIVA ISTRAZIVANJE I RAZVOJ D [HR]; MCLEISH NICHOLAS ALASTAIR MAXW [GB]) 19 July 2007 (2007-07-19)</p> <p>Co-crystals of sildenafil and acetylsalicylic acid: see claims and examples</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/--</p>	<p>1-94, 111-122</p>

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2017/050921

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/044457 A1 (FAOUR JOAQUINA [AR] ET AL) 6 March 2003 (2003-03-06) Compositions comprising a core comprising an osmotic device, for the controlled release of a drug and an external compositions providing immediate release of said drug -----	1-94, 111-122
Y	WO 2013/001516 A1 (RANBAXY LAB LTD [IN]; BHAVARISETTI MURALI KRISHNA [IN]; VIVEK KUMARAVE) 3 January 2013 (2013-01-03) Multi-coated compositions comprising three different layers of active agents -----	1-94, 111-122

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2017/050921

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-94(completely); 111-122(partially)

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-94(completely); 111-122(partially)

A composition comprising sildenafil (possibly in salt or co-crystal form), wherein the composition comprises a first component capable of releasing sildenafil rapidly, and a second component for delivering sildenafil "from dose to dose" within the therapeutic window.

---

2. claims: 95-104(completely); 111-122(partially)

A co-crystal of sildenafil, as defined in claims 95-103 and pharmaceutical compositions thereof.

---

3. claims: 105-110(completely); 111-122(partially)

A salt of sildenafil, as defined in claims 105-11 and pharmaceutical compositions thereof.

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2017/050921

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 2374460	A1	12-10-2011	AR 071970 A1	28-07-2010
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