(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/079760 A1

(51) International Patent Classification[7]: A61K 9/16

(21) International Application Number:
PCT/GB2005/050014

(22) International Filing Date: 11 February 2005 (11.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0403100.1	12 February 2004 (12.02.2004)	GB
0501638.1	28 January 2005 (28.01.2005)	GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

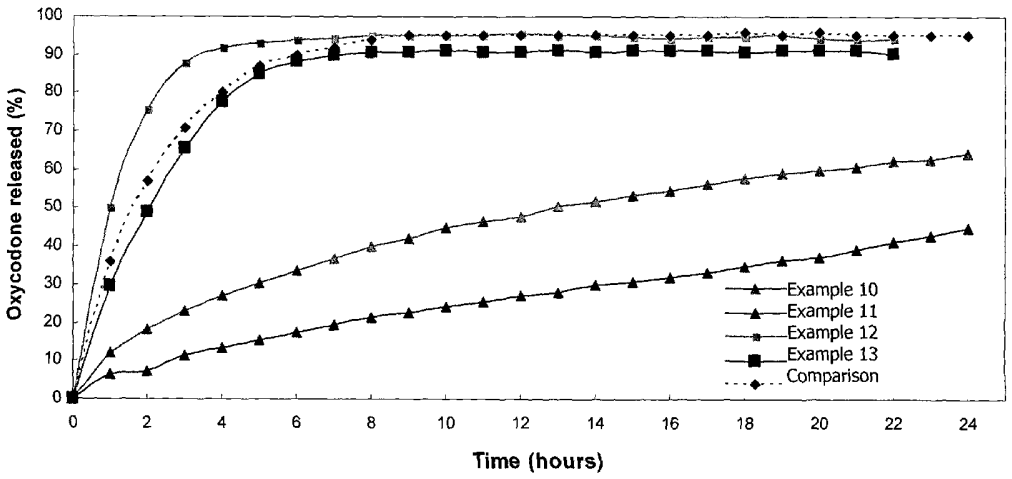
Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PARTICULATES



(57) Abstract: A neutral poly(ethyl acrylate, methyl methacrylate) copolymer is employed as a carrier in the manufacture of pharmaceutical formulations containing an active ingredient. The formulations are preferably made by melt extrusion, and can have rubbery characteristics and can exhibit tamper resistance.

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PARTICULATES

The present invention relates to particulates, and in particular to melt extruded multiparticulates which provide controlled release of an active ingredient.

BACKGROUND OF THE INVENTION

Multiparticulates of uniform dimensions with modified drug release properties can readily be manufactured by melt extrusion technology. Melt extrusion is a solvent-free single-step process for manufacturing multiparticulates and is particularly useful for drug release modification. By selection of suitable thermoplastic polymers and additives, melt extrusion technology can be used both to enhance the solubility, and subsequently the bioavailability, of poorly water soluble drugs as well as to retard drug release of moderate to highly water soluble drugs for controlled release products.

The backbone of melt extrusion technology is the application of thermoplastic materials which act as binders for embedded drugs in solution or dispersion form within the matrix. Thermoplastic polymers with low glass transition temperatures (Tg) are preferred for processing by melt extrusion. Lower processing temperatures are also preferred with respect to the stability of heat sensitive drugs and other necessary excipients. Polymer glass transition temperatures can also be further reduced to facilitate processing at lower temperature with optional addition of plasticisers.

Illustratively, WO 9614058 provides a sustained-release pharmaceutical formulation, comprising a melt-extruded blend of a therapeutically active agent, one or more materials selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof; and one or more hydrophobic fusible carriers which provide a further retardant effect and are selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof, the fusible carrier having a melting point from 30 to 200°C. The melt-extruded blend is divided into a unit dose containing an effective amount of said therapeutically active agent to render a desired therapeutic effect and providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

Furthermore, WO 9614058 describes a method of preparing a sustained-release pharmaceutical extrudate suitable for oral administration. The method comprises:

blending a therapeutically active agent together with (1) a material selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof and (2) a fusible carrier selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof; said retardant material having a melting point between 30-200°C and being included in an amount sufficient to further slow the release of the therapeutically active agent,

heating said blend to a temperature sufficient to soften the mixture sufficiently to extrude the same;

extruding said heated mixture as a strand having a diameter of from 0.1 -3 mm;

cooling said strand; and

dividing said strand to form non-spheroidal multi-particulates of said extrudate having a length from 0.1 -5 mm; and

dividing said non-spheroidal multi-particulates into unit doses containing an effective amount of said therapeutically active agent, said unit dose providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

In certain preferred embodiments of WO 9614058, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methylmethacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Thus, in many of the Examples, the hydrophobic material is Eudragit RS PO (poly(ethyl acrylate, methyl methacrylate, trimethylammonium methacrylate chloride)), optionally in the presence of Eudragit L100 (poly (methacrylic acid, methyl methacrylate)).

SUMMARY OF THE INVENTION

The present invention provides formulations which employ a neutral poly(ethyl acrylate, methyl methacrylate) copolymer as a pharmaceutically acceptable carrier. Such a copolymer can impart controlled release properties to the formulation. Furthermore, with the present invention, we are able to provide a rubbery formulation through the use of melt extrusion.

Neutral poly(ethyl acrylate, methyl methacrylate) copolymer is commercially available in the form of an aqueous dispersion. Two such products, Eudragit NE 30 D and Eudragit NE 40 D, comprise respectively 30% and 40% of the polymer. In particular, Eudragit NE 30 D forms water-insoluble films and is suitable for granulation processes in the manufacture of matrix tablets and sustained-release coatings without any plasticiser addition. Information on the use of Eudragit NE to prepare tablets and coatings can be obtained from the following website: http://www.roehm.de/en/pharmapolymers.html.

For example, the website has a technical article describing how to make ibuprofen sustained release matrix tablets, by wet granulation using Eudragit NE 30 D as a binder and diffusion controlling agent. Granules are made by mixing ibuprofen with the Eudragit dispersion, grinding through a sieve, and drying. The granules are ground, mixed with disintegrant and other ingredients, and then compressed to tablets. The amount of Eudragit NE is relatively low.

In WO 03004009, Eudragit NE is among a list of suggested hydrophobic components for use with hydrophilic erodible components and a poorly compressible pharmaceutical agent. Seemingly the intention was to refer to another Eudragit, since Eudragit NE is a wet dispersion, and an objective of WO 03004009 is to form a compressible formulation by a process other than wet granulation.

Sood *et al.* describe the use of extrusion-spheronization to develop controlled release dosage forms for diltiazem hydrochloride in Pharmaceutical Technology 2004 (April): 62-85. A series of candidate materials were evaluated as pellet matrix-forming agents in a process invloving wet granulation, extrusion of the wet granules, and

spheronisation to form wet pellets which were then dried. Eudragit NE 30 D was tested in formulations D19 and D20, and gave no improvement in controlling drug release.

In the present invention we can employ neutral poly(ethyl acrylate, methyl methacrylate) copolymer as a carrier in a formulation. Typically the formulation of this invention uses a neutral poly(ethyl acrylate, methyl methacrylate) copolymer to provide a matrix within which is dispersed an active ingredient. Thus, for example, the invention provides multiparticulates each with such a matrix.

The formulations of this invention can take the form of a unit dose such as a capsule with a fill of multiparticulates with neutral poly(ethyl acrylate, methyl methacrylate) copolymer as carrier. The multiparticulates can be extrudates formed by extrusion of a dry mix, notably a mixture of dry granulates, which includes a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

Especially by the use of extrusion, the present invention provides controlled release multiparticulates which take the form of a cylinder or are generally spherical, ellipsoidal or disc shaped.

To this end, the invention further provides a dry mix as unfinished composition comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient. Such a composition is substantially free of water and is suited for extrusion as part of a process to provide a formulation of this invention. Typically the unfinished composition is a dry granulate and can be an extruded granulate.

In particular, we provide a dry granulate of neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient,

where the level of neutral poly(ethyl acrylate, methyl methacrylate) copolymer is relativly high in order to impart the desired properties. Typically, amounts of 20 to 66% by weight of neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the dry granulate are employed.

According to the present invention, we also provide a process for preparing a controlled release pharmaceutical extrudate, wherein the mix for extrusion includes a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

Another aspect of this invention resides in a method of administration of an active ingredient, wherein the active ingredient is administered as a controlled release formulation employing a neutral poly(ethyl acrylate, methyl methacrylate) copolymer as pharmaceutically acceptable carrier.

A related aspect of this invention is the use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the preparation of a pharmaceutical formulation to provide resistance to tamper, which is of importance where the active ingredient is open to abuse. The invention provides a method of imparting tamper resistance to a pharmaceutical formulation which comprises the incorporation of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer with the active ingredient in the formulation.

DISCUSSION OF PREFERRED EMBODIMENTS

We find that by utilising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the preparation of controlled release pharmaceutical extrudates, we can obtain melt extruded

multiparticulates which exhibit rubber-like characteristics. Such rubbery extrudates can exhibit enhanced resistance to tamper. In particular, it appears that the rubbery characteristics are imparted by the step of melt extrusion.

In one aspect, the invention provides a controlled release pharmaceutical formulation obtained or obtainable by melt extrusion and including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

In a related aspect, the present invention provides a formulation which includes rubber-like multiparticulates.

The rubber-like characteristics provide multiparticulates which typically are elastic and compressible without breaking, and preferably resilient.

In one preferred form, as a demonstration of the rubber-like characteristics, the multiparticulates may be compressed by hand between two rigid surfaces, for example a coin and a table top or between two spoons, without breaking. The multiparticulates usually may be distorted but do not break or shatter and may ideally reassume more or less their original shape.

The rubbery characteristics can help impart resistance to tamper. Tamper resistance is of especial importance for products containing opioid analgesics or other active ingredients which are subject to abuse. The tamper resistance of preferred multiparticulates of the invention can be demonstrated by shaking a dosage amount of multiparticulates in water and/or ethanol, for example 40% ethanol.

For example a dosage amount of multiparticulates may be admixed with 10 ml of the liquid (water and/or ethanol) in a glass flask and then subjected to shaking at 500 to 600 oscillations per minute for 15 minutes using a Stuart Scientific Shaker, Model SF1, optionally after standing for 5 minutes. The amounts of active agent extracted can then be determined by HPLC and detection by UV for instance at 210 nm wavelength.

When tested in this way preferred multiparticulates in accordance with the invention showed at least one of the following release characteristics of active agent:

15 minutes shaking in water at room temperature: less than 10% release of active agent, preferably less than 7.5% release of active agent, more preferably less than 5% release of active agent, for example 1.5 to 4% release of active agent.

5 minutes standing in water at 50°C followed by 15 minutes shaking at the same temperature: less than 20% release of active agent, preferably less than 15% release of active agent, more preferably less than 12% release of active agent, for example 4 to 12% release of active agent.

5 minutes standing at 75°C followed by 15 minutes shaking at the same temperature: less than 25% release of active agent, preferably less than 20% release of active agent, more preferably less than 15% release of active agent, for example 10 to 15% release of active agent.

5 minutes standing at 100°C followed by 15 minutes shaking at the same temperature: less than 30% release of active agent, preferably less than 25% release of active agent, more preferably less than 20% release of active agent, for example 12 to 20% release of active agent.

15 minutes shaking in 40% ethanol at room temperature: less than 35% release of active agent, preferably less than 30% release of

active agent, more preferably less than 25% release of active agent, for example 15 to 25% release of active agent.

Alternatively, the tamper resistance of preferred multiparticulates of the invention can be demonstrated by subjecting a dosage amount of multiparticulates to grinding in a mortar and pestle with 24 rotations of the pestle and the product placed in 900 ml water at 37°C for 45 minutes. The amounts of active agent extracted can then be determined by HPLC and detection by UV for instance at 210 nm wavelength.

When tested using this method, preferred multiparticulates according to the invention showed the following release characteristics of active agent; less than 12.5% release of active agent, preferably less than 10% release of active agent, more preferably less than 7.5% release of active agent, for example 2 to 7.5% release of active agent.

In a further method, the tamper resistance of preferred multiparticulates of the invention can be demonstrated by crushing a dosage amount of multiparticulates between two spoons or in a pill crusher, such as a Pill Pulverizer as sold by Apex Healthcare Products, and then extracting in 2 ml water heated to boiling on a spoon and filtered off. The amounts of active agent extracted can then be determined by HPLC and detection by UV for instance at 210 nm wavelength.

When tested using this method, preferred multiparticulates according to the invention showed the following release characteristics of active agent; less than 27.5% release of active agent, preferably less than 15% release of active agent, more preferably less than 5% release of active agent, for example 1 to 5% release of active agent.

For imparting such tamper resistance, the present invention provides the use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the preparation of a pharmaceutical formulation to provide resistance to tamper. A neutral poly(ethyl acrylate, methyl methacrylate) copolymer is incorporated with the active ingredient in the formulation.

In one aspect, the invention provides a method of imparting tamper resistance in a pharmaceutical formulation, which comprises admixing an active ingredient and a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, and forming a pharmaceutical formulation incorporating the active ingredient with the neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

The neutral poly(ethyl acrylate, methyl methacrylate) copolymer is suitably employed in an amount by weight of up to 66% in the mix for extrusion, say 20 to 66% of the extrusion mix, more typically from 20 to 50% of the extrusion mix, such as 30 to 40% of the extrusion mix. These percentages also apply to the amount of neutral poly(ethyl acrylate, methyl methacrylate) copolymer in a dry granulate of this invention.

The neutral poly(ethyl acrylate, methyl methacrylate) copolymer can be employed with other ingredients including a drug or other active ingredient. The reader is referred to WO 9614058, incorporated herein in full by specific reference. The neutral poly(ethyl acrylate, methyl methacrylate) copolymer can form all or more preferably part of the release controlling material employed in the extrusion method of that patent specification.

In this respect, our preferred compositions include at least one other polymer to modify release. In particular, it appears that the use

of ethyl cellulose or like polymer can assist in imparting resistance to tamper, especially resistance to extraction by alcohol. An alkyl cellulose such as ethyl cellulose is preferably employed for example in an amount of 5 to 60% w/w of the formulation, preferably 10 to 50% w/w of the formulation, most preferably 20 to 45% w/w of the formulation. Other suitable polymers include water insoluble ammonium methacrylate copolymers. The insoluble ammonium methacrylate copolymers may be Eudragit RS PO and Eudragit RL PO, which are ammonio methacrylate copolymers. In particular the at least one other polymer is typically a sparingly water permeable thermoplastic polymer or a relatively highly water permeable thermoplastic polymer which can significantly modify release but is to be used in an amount which does not impair resilience or flexibility.

A plasticiser and/or a lubricant is preferred when using an extruder with a relatively low torque capability such as a Leistritz Micro 18 machine. With a larger extruder, such as a Leistritz Micro 27, similar formulations, without or with relatively low levels of plasticiser and/or lubricant, may be processed.

The plasticiser is normally chosen from water insoluble solids such as cetyl alcohol, stearyl alcohol and cetostearyl alcohol; water soluble solids such as sorbitol and sucrose and high molecular weight polyethylene glycol, water insoluble liquids such as dibutyl sebacate and tributyl citrate and water soluble liquids such as triethyl citrate, propylene glycol and low molecular weight polyethylene glycol. Tributyl citrate is a preferred plasticiser. Stearyl alcohol is also a preferred plasticiser. Another preferred plasticiser is a high molecular weight polyethylene glycol of MW 1000 to 20000, such as PEG 6000.

A lubricant can be included. The lubricant is normally a solid at room temperature, and is suitably chosen from stearic acid, glycerol dibehenate, magnesium stearate, calcium stearate, talc and silicone dioxide (fused silica). The presence of lubricant in the melt extrusion formulation improves blending, kneading and conveying and reduces cohesion and adhesion forces. Smooth extrusion at low to moderate temperatures improves batch to batch reproducibility and reduces the strain on both the product and equipment. Stearic acid, possibly in the form of a salt, is a preferred lubricant. Another preferred lubricant is glycerol dibehenate.

A drug is usually present as active agent in the formulations of the invention. The reader is referred to WO 9614058 for examples. Oxycodone is a typical drug for use in the products and processes of this invention. Other opioids are for example hydromorphone, hydrocodone, fentanyl and analogues thereof, buprenorphine, diamorphine, meperidine, propoxyphene and diphenoxylate. Other active agents which may be formulated in accordance with the invention include stimulants such as dextroamphetamine, amphetamine, methamphetamine, sibutamine, methylphenidate; barbiturates such as methobarbitol and pentobarbital; anti-depressants such as diazepam, bromazepam, chlordiazepoxide, oxazepam, malprazolam, triazolam and etazolam, flunitrazapam and methaqualone; and dissociative anaesthetics such as ketamine; and salts, acid addition salts, and esters thereof.

Preferred multiparticulates of this invention therefore can comprise a neutral poly(ethyl acrylate, methyl methacrylate) copolymer; an active ingredient; at least one other polymer to modify release which is usually an alkyl cellulose; optionally a plasticiser; and optionally a lubricant.

Suitable percentage amounts for the preferred ingredients are given in the following table, based on the total weight of the specified ingredients:

	typical range	preferred range	more preferred range	most preferred range
water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	5 to 66	15 to 50	20 to 45	25 to 45
active agent*	up to 60	5 to 55	5 to 50	10 to 45
further polymer to modify release	0 to 85	5 to 75	5 to 60	5 to 45
plasticiser	0 to 30	0 to 25	3 to 25	3 to 20
lubricant	0 to 25	0 to 25	0 to 20	0 to 15

* The amount of active agent can be 0% in placebo formulations for trials or development work.

A typical formulation may contain as well as for example up to 60% w/w of the active agent or placebo, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w, suitably 15 to 50% w/w, for example 15 to 25% or 25 to 45%, of an alkyl cellulose, preferably ethyl cellulose; and 0 to 25%, preferably 7.5 to 20%, of one or more plasticisers, for example stearyl alcohol and tributyl citrate. For example up to 50% oxycodone can be present as active agent. These ingredients may be the only components, or if desired the formulations may contain additional components such as 5 to 60% of an insoluble ammonium methacrylate copolymer. Illustratively, the formulation can contain 10 to 60%, preferably 35 to 50% of an insoluble ammonium methacrylate copolymer which is of

low permeability, such as Eudragit RS PO, and/or it can contain 5 to 40%, for example 5 to 30%, preferably for example 5 to 25%, of an ammonium methacrylate copolymer which is highly permeable, such as Eudragit RL PO.

Other additives may also be employed to produce multiparticulates within a set of predetermined specifications. Bulking agents for example lactose, microcrystalline cellulose and calcium phosphate, are widely used pharmaceutical excipients and can be used in the present invention to modify the release rates and/or total release. Other release modifying agents may also be considered to modulate the release rate and/or enhance total release.

The multiparticulates are preferably produced by melt extrusion of a granulate, and in particular by a process comprising wet granulation of the ingredients and drying of the granulates, and melt extrusion of the granulate.

The granulation step may be carried out using conventional procedures, for example using a high shear mixer such as a Gral mixer or a fluid bed granulator or a fluid bed granulator with a rotary insert.

When using a high shear mixer the process may comprise the following steps;

a) granulation, preferably wet granulation;
b) optionally extrusion of the granulate;
c) drying of the granulate or the extruded granulate, preferably by means of a fluid bed dryer;
d) optionally screening and/or milling the dried granulate or the dried extruded granulate from step c); and
e) melt extrusion of the product from step c) or d).

When using a fluid bed granulator with or without a rotary insert the process may comprise the following steps;

a) granulation;
b) optionally extrusion of the granulate;
c) drying of the granulate or the extruded granulate, preferably by means of a fluid bed dryer;
d) optionally screening and/or milling the product from step c) ; and
e) melt extrusion of the dried granulate or screened or milled product from step c) or step d).

The product from step (c) or (d) which is to be loaded into the melt extruder, that is the optionally milled or screened dried granulate, is itself a novel product of this invention.

The granulation step may be carried out using conventional procedures, for example using a high shear mixer such as a Gral. Typically the dry ingredients are added first; these are mixed by operation of the high shear mixer and then the dispersion of polymer is added by spraying or dropwise, and mixing continued.

Alternatively, for example, a liquid plasticiser may be added to the dry ingredients and mixed by operation of the high shear mixer and the dispersion of polymer is then added by spraying or dropwise and mixing continued.

The granulate may then be extruded in optional step (b), for example using an Alexanderwerk extruder. The extrudate is then dried using preferably a fluid bed dryer. The extrudate may be produced directly of a suitable size for fluid bed drying using a suitable extruder such as the aforementioned Alexanderwerk where

the small blade breaks up the pellets, or may be broken down to a suitable size. Alternatively the granules produced by high shear mixing may be of a suitable size or broken down to a suitable size for drying followed by melt extrusion.

The dried material will typically contain less than 5% w/w water for example 2 to 3% w/w water, or less, such as trace amounts.

The melt extrusion process may be carried out in a manner similar to that described in WO 9614058.

For the present invention, we prefer to employ a twin screw extruder. Essentially, the dried granulate or milled product is fed by a feeder into the first segment of an extruder barrel preferably at relatively low temperature (for example 10-20°C) to ensure a constant flow of material to the high temperature barrels. The feeder provides a uniform current of the material to the extruder. Consistency is desirable as irregular and variable feeding rates can produce multiparticulates with various physical properties, such as density and porosity.

The preferred extruder is designed with twin screws, which may have co-rotating or counter-rotating screws, for the tasks of conveying, blending and compressing the blend as well as providing mechanical energy. The extruder will be equipped with heating means and cooling means as required. The screws which perform a significant part of this melt extrusion process are built of different smaller elements. The mixing and kneading process can be significantly altered by changing the type, length and configuration of the screws elements. Short residence times and moderate to low shear forces contribute to safe processing and stable product even with heat sensitive drugs.

Screw rotating speeds may play a part in the quality of the multiparticulates produced. High rotation speeds without appropriate compensation of the feed rate may produce high porosity multiparticulates with a variable drug release rate. On the other hand slow screw rotation would induce unnecessary long residence times. A vacuum connected to the extruder barrel is desirable to remove trapped air and residual moisture from within the plastified material and thus produce dense multiparticulates ideally of low porosity.

The extrusion head is typically designed to produce multiple strands of fixed diameter, for example 1.0 mm. The number, shape and diameter of the orifices can be changed to suit a predetermined specification.

In addition to the screw speed, the other main influential parameters are the screw torque, individual barrel temperature, and extrusion head pressure and temperature.

In accordance with one cutting procedure of this invention, the extruded strands are carried away from the die-head on a conveyer. Strand diameter is affected by the starting material feed rate, the screws speed, barrel temperature, die-head orifice diameter and conveying speed and nip rolls speed. Conveying is appropriate to carry the extruded strands to a laser gauge or other measuring device. During this conveying process the strands cool down gradually, but essentially remain flexible. Flexible strands retain integrity on the laser gauging device, between the pelletiser feed nip rolls and during entry to the pelletiser. Rapidly cooled strands, depending on the formulation, may lose their integrity and shatter during passage

through the nip rolls and pelletiser into uneven-shaped and irregular-sized multiparticulates.

A laser gauge may be used to provide a continuous measurement of strand diameter, for example 1.0 mm.

The measured strands are fed into the pelletiser by nip rollers. The pelletiser cuts the fed strands, for instance using a rotary knife cutter, to a pre-determined length, for example 1.0 mm. The feeding rate of the strands and the pelletiser cutter speed determine the length of the multiparticulates.

Overall, the co-ordination/interaction between the feeder, extruder, conveyor, and pelletiser is an important parameter affecting the quantity, quality and reproducibility of the final multiparticulate products.

Multiparticulates produced by this cutting procedure where the extruded strands are carried away from the die-head typically take the form of cylinders. Preferably the cylinders have a diameter of about 1 mm and a length of about 1 mm.

In another preferred cutting procedure, a cutter cuts the extruded mix as it emerges under pressure and still molten from the orifices of the die-plate. The cutter is suitably a rotary cutter with one or more blades which sweep over the surface of the die-head to pass the orifices. Two diametrically opposed blades are preferred. Ideally, the outer surface of the die-head is coated with a non-stick material, for example polytetrafluoroethylene (PTFE). As the cut extrudate multiparticulates expand and cool, they tend to form rounded surfaces. By appropriate adjustment of the rate of extrusion and the speed of the cutter blade, as well as generally cylindrical

multiparticulates, it is possible for example to arrange for spherical or substantially spherical, ellipsoidal or disc shaped multiparticulates to be obtained. In one embodiment a stream of air is directed into the region of the surface of the die-head, the air being at a reduced temperature to cool the extrudate and to speed solidification.

Spherical multiparticulates produced by this method offer a number of advantages:

Better batch to batch reproducibility.

Easier coating and lower coating weight required.

Better capsule filling and higher yield.

More stable at elevated temperature.

More tamper resistant.

Reduce or eliminate some problems that arise during conveying and pelletising the strands such as strands fracturing to different length pellets and possible static charge.

The multiparticulates may be divided into unit doses such that each individual unit dose includes a dose of drug for administration to a mammal, preferably a human patient. For the preferred drug, oxycodone or a salt thereof, preferably the hydrochloride, a suitable dose of the active agent is 5 to 400 mg, especially 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg unit dosages. In this respect, a unit dose contains an effective amount of the therapeutically active agent to produce pain relief and/or analgesia to the patient. The dose of oxycodone administered to a patient will vary due to numerous factors, including the weight of the patient, tolerance, the severity of the pain, the metabolic status and the nature of any other therapeutic agents being administered.

The resultant multiparticulates can be employed as a fill in a capsule. Thus, the present invention provides a capsule suited for

once or twice a day dosing. Other dosage forms of the controlled release formulation can be provided.

In one preferred embodiment, the multiparticulates are filled into gelatin capsules each containing a unit dose. The fill weight in the capsule is preferably in the range 80 to 500 mg, more preferably 120 to 500 mg. In a variation of this invention, the unit doses of multiparticulates may be incorporated into other solid pharmaceutical dosage formulations, for example using compression or shaping or forming into tablets, or by forming the extruded product into the form of a suppository.

The preferred capsules or other unit dose forms of this invention preferably are designed for administration at intervals of about 12 hours or 24 hours.

A preferred drug for inclusion in the multiparticulates is oxycodone or salt thereof, preferably the hydrochloride. A unit dose form suitable for 12-hourly dosing then suitably has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

A unit dose form containing oxycodone or a salt thereof, preferably the hydrochloride, suitable for 12 hourly dosing may also, suitably have the following dissolution rate *in vitro* when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without

enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; from 0 to 40%, preferably 25 to 35% at 1 hour; from 20 to 70%, preferably 40 to 60%, at 2 hours; from 40 to 80%, preferably 55 to 75%, at 3 hours; from 60 to 95%, preferably 65 to 90%, at 4 hours; and greater than 70% at 5 hours.

Furthermore, we prefer that the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

More information on desirable characteristics for such oxycodone formulations is given in WO 9310765 which is incorporated herein in full by specific reference.

As an alternative, the oxycodone capsules or other unit dose forms of this invention are designed for administration at intervals of about 24 hours. To this end, the unit dose form suitably has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

Furthermore, we prefer that the peak plasma level of oxycodone obtained *in vivo* is reached at about 2 hours to about 17 hours after administration at steady state of the dosage form.

A unit dose form containing oxycodone or a salt thereof, preferably the hydrochloride, suitable for dosing every 24 hours, may also suitably have the following dissolution rate *in vitro* when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100

rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; from 10 to 30%, preferably 17 to 23%, at 1 hour; from 20 to 35%, preferably 24 to 32%, at 2 hours; from 35 to 75%, preferably 48 to 66%, at 8 hours; and greater than 50%, preferably 68 to 92%, at 16 hours.

More information on desirable characteristics for such oxycodone formulations is given in WO 02087512 which is incorporated herein in full by specific reference.

In a variation, the present invention provides unit doses which contain an opioid and an opioid antagonist effective to prevent tampering. In this respect, reference is made to WO 0313433 which is incorporated herein in full by specific reference. In particular, the unit dose can contain oxycodone and naltrexone.

To this end, the present invention provides melt extruded multiparticulates of an opioid such as oxycodone, and melt extruded multiparticulates of an opioid antagonist such as naltrexone. In a preferred formulation antagonist multiparticulates do not release the antagonist on conventional administration, and for example have a non-release coating. Both populations of opioid and opioid antagonist are preferably visually and physically identical.

An important aspect of this invention is a capsule with a unit dose fill of less than 500 mg, comprising up to about 350 mg of oxycodone multiparticulates, and up to about 200 mg of tamper-proof oxycodone antagonist multiparticulates. For example, there can be 120 to 300 mg of oxycodone multiparticulates, and 125 to 175 mg of tamper-proof oxycodone antagonist multiparticulates.

SUMMARY OF THE DRAWINGS

Reference is made in the following experimental section to the accompanying drawings, in which:

Figure 1 shows the dissolution of oxycodone from pellets made in Example 5.

Figure 2 shows the dissolution of oxycodone from pellets made in Examples 10 to 13.

Figure 3 shows dissolution of oxycodone from the crushed pellets of Examples 11 to 13.

Figure 4 shows the dissolution of oxycodone from the pellets of Examples 11 to 13 after milling using a pestle and mortar.

Figure 5 shows the dissolution in solvents of oxycodone from the pellets of Examples 10 to 13.

EXAMPLES OF THE INVENTION

Examples 1, 2 and 3

Three batches (Examples) of multiparticulates were manufactured following a similar procedure:

Step 1. Initially, the following items were placed into a Gral 10 high shear mixer, pre-heated to 40°C, and dry blended at high speed for 2 minutes:

Oxycodone Hydrochloride

Eudragit RS PO

Stearyl Alcohol

Stearic Acid

Step 2. The Eudragit NE 40 D dispersion was screened through a 350 micron mesh to eliminate aggregates and transferred into a suitably sized container.

Step 3. The screened Eudragit NE 40 D dispersion was sprayed at low atomising pressure on to the dry blended materials from step 1 in the mixing bowl, whilst maintaining mixing/chopping.

Step 4. The application of Eudragit NE 40 D was continued until granule formation occurred.

Step 5. The application of Eudragit NE 40 D was periodically halted to scrape the sides of the mixing bowl.

Step 6. After all the Eudragit NE 40 D had been applied, the granules were dried under the same temperature conditions and at reduced mixing/chopping speeds.

Step 7. The granules were then fed at a controlled rate to a Leistritz Micro 18 extruder equipped with a conveyor and pelletiser. The extruder had a 1.5 mm die-plate, and heated Stations as follows; Stations 3 to 8, 90°C to 100°C; Stations 9 and 10, 100°C. The feed rate was 2.0 to 2.6 kg/hr and the screw speed 100 to 141 rpm, with a torque/melt pressure of 50 to 60% / 40 to 50 bar.

The extruded strands were carried away from the die-head on a conveyer and cut into cylindrical multiparticulates.

Material	Examples (% w/w)		
	Example 1	Example 2	Example 3
Lactose anhydrous	10.0	10.0	
Oxycodone hydrochloride			10.0

Eudragit RS PO	40.0	32.0	32.0
Stearyl alcohol	10.0	10.0	10.0
Stearic acid	6.0	6.0	6.0
Eudragit NE*	34.0	42.0	42.0
Total	100	100	100

* As Eudragit NE 40 D (water removed by drying)

Example 4

For this example, the alternate cutting procedure was employed. Extrudate emerges from the twelve orifices of the die-head of a Leistritz Micro 18 extruder. A rotary cutter with two blades is used to cut the extruded mix as it emerges under pressure and still molten from the orifices of the die-plate. The blades sweep over the surface of the die-head to pass the orifices. As they expand and cool, the cut extrudate particles tend to form rounded surfaces.

The following formulation was employed to produce placebo product containing lactose as a pharmaceutical non-active ingredient.

Material	Example 4 (% w/w)
Lactose anhydrous	10.0
Eudragit RS PO	37.0
Stearyl alcohol	10.0
Stearic acid	6.0
Eudragit NE 40 D	37.0*
Total	100

* Value stated as solids content

By appropriate adjustment of the extrusion parameters including temperature and rates of extrusion, spherical or substantially spherical multiparticulates may be obtained.

Examples 5 and 6

Two batches of multiparticulates were planned using tributyl citrate as plasticiser (circa 43% w/w drug load). The percentage contents, w/w, were as follows.

Material	Examples (% w/w)	
	5	6
Oxycodone hydrochloride	42.2	42.2
Ethyl cellulose N10	14.7	19.6
Eudragit NE 40 D*	35.3 (S), [88.3 (D)]	29.4 (S), [73.5 (D)]
Tributyl citrate	5.9	6.9
Glycerol dibehenate	2.0	1.9
Total	100	100

S = solid weight

D = dispersion weight

* 40% dispersion (% w/w), water lost by evaporation

A procedure for preparing multiparticulates of Example 5 in the form of pellets is as follows:

Step 1. The tributyl citrate was slowly added to ethyl cellulose in a Gral 10 high shear mixer and blended.

Step 2. The oxycodone was added to the blend from Step 1 in the Gral 10 high shear mixer and blended for 5 minutes.

Step 3. The Eudragit NE 40 D dispersion was screened through a 350 micron mesh to eliminate aggregates and transferred into a suitably sized container. The screened Eudragit NE 40 D dispersion was then slowly added by aid of a peristaltic pump onto the blended

materials from Step 2 in the Gral 10 mixing bowl, pre-warmed to 38°C, whilst maintaining mixing/chopping.

Step 4. The application of Eudragit NE 40 D was continued until granule formation occurred – all the Eudragit NE 40 D was added.

Step 5. The application of Eudragit NE 40 D was periodically halted to permit scraping of the sides of the mixing bowl.

Step 6. After all the Eudragit NE 40 D had been added, the wet granules were extruded through a conventional extruder and the dried in a fluid bed dryer at approximately 42°C.

Step 7. The dried granules were cooled to room temperature and collected.

Step 8. The granules were then fed at a controlled rate to a Leistritz Micro 18 extruder equipped with a 1.0 mm die-plate, a conveyor and pelletiser under the same conditions as in Example 1. The extruded strands were carried away from the die-head on a conveyer and cut into cylindrical multiparticulates.

The procedure for the preparation of the formulation of Example 6 was the same as for Example 5 except in the following respects:

- No plasticiser (tributyl citrate) was added in Step 1. Instead Step 1 was excluded and Step 2 consisted of mixing the oxycodone hydrochloride and the ethyl cellulose in the Gral 10 high shear mixer.
- The granules were sieved (1.5 mm mesh) and the oversized granules milled (1.0 mm mesh) and recombined with the other granules.
- Lubricant (glycerol dibehenate) was added to the dried granules immediately before feeding to the extruder at the end of Step 7.
- The extruder had a die-plate with 1.5 mm orifices.

An alternate cutting procedure can be considered. Extrudate emerges from the orifices of the die-head of a Leistritz extruder. A rotary cutter with two blades is used to cut the extruded mix as it emerges under pressure and still molten from the orifices of the die-plate. The blades sweep over the surface of the die-head to pass the orifices. As they expand and cool, the cut extrudate particles tend to form rounded surfaces.

Although in the above Examples a Leistritz Micro 18 extruder was used, a larger extruder, for example a Leistritz Micro 27, may be preferred to handle materials requiring a higher torque for processing.

Extruded pellets obtained in Example 5 were dissolution tested using the USP Basket Method «711» Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength and gave the following results which are plotted in the accompanying Figure 1 along with a preferred profile for a once-a-day product.

Time (Hours)	Example 5 % oxycodone released
0	0
1	30
2	41
3	48
4	53
5	58
6	62
7	66
8	69
9	71

10	74
11	76
12	78
13	78
14	81
15	82
16	82
17	84
18	85
19	85
20	86
21	87
22	88
23	88
24	88

Examples 7, 8 and 9

Using the same procedure and extrusion conditions as for the previous Examples apart from temperatures ranging from 100 to 120°C, a screw speed of up to 240 rpm and die-plate dimensions of 1.5 mm diameter (Examples 7 and 8) and 1.0 mm (Example 9), the following formulations were processed to produce multiparticulates.

Material	Examples (% w/w)		
	Example 7	Example 8	Example 9
Oxycodone HCl	43	43	43
Ethyl cellulose N10	19	19	18
Eudragit NE 40 D*	29	29	27

Tributyl citrate	6	6	6
Stearyl alcohol		3	
Glycerol dibehenate	3		6
Total	100	100	100

* Value stated is solids content only. Liquid dispersion weight is (value/40)x100

Examples 10 to 13

Using procedures similar to those of the previous Examples multiparticulates were produced with the following formulations.

Material	Examples (% w/w)			
	Example 10	Example 11	Example 12	Example 13
Oxycodone HCl	10.0	10.0	10.0	10.0
Ethyl cellulose N10	41.8	nil	32.0	nil
Eudragit RS PO	nil	41.8	nil	22.0
Eudragit RL PO	nil	nil	10.0	20.0
Stearyl alcohol	14.0	14.0	14.0	14.0
Eudragit NE 40 D*	34.2 (S), [85.5 (D)]	34.2 (S), [85.5 (D)]	34.0 (S), [85.0 (D)]	34.0 (S), [85.0 (D)]
Total	100	100	100	100

S = solid weight

D = dispersion weight

* 40% dispersion (% w/w), water lost by evaporation

The above multiparticulates from Examples 10 to 13 were subjected to testing by dissolution using the USP Basket Method described above in Example 5. The results are shown in Figure 2. These demonstrate that the release profiles of the multiparticulates of Examples 12 and 13 are similar in this test to the release profile of a preparation (Example 5 of our co-pending application publication number WO 2005/000310) which, when tested *in vivo* is substantially bio-equivalent to OxyContin tablets.

The multiparticulates from Examples 10 and 11 have slower release profiles which may indicate they would be suitable for use in dosage forms for dosing at 24 hour intervals.

The multiparticulates from Examples 10 to 13 were tested to determine their potential for tamper resistance as follows:

1) 400 mg of the multiparticulates from Examples 10 to 13 were either crushed between two spoons or in a pill crusher, such as a Pill Pulverizer as sold by Apex Healthcare Products, and then extracted in 2 ml water heated to boiling on a spoon and filtered off. The amounts of oxycodone extracted were then determined by HPLC and detection by UV at 210 nm wavelength and are shown in the chart of Figure 3.

2) 400 mg of the multiparticulates from Examples 10 to 13 were subjected to grinding in a mortar and pestle with 24 rotations of the pestle and the product placed in 900 ml water at 37°C for 45 minutes. The amount of oxycodone dissolved was then determined by the method described in 1) above and the results are represented in the bar chart of Figure 4.

3) In each of extractions a) to e) 400 mg of the multiparticulates from one of Examples 10 to 13 were treated respectively as follows: the

multiparticulates were placed in the solvent indicated in a glass flask which was then heated (if heating is indicated) over a water bath. The flask was then subjected to shaking for the time indicated using a Stuart Scientific Flask Shaker Model SF1 set at 500 to 600 oscillations per minute. After extraction the amount of oxycodone dissolved was then determined by the method used in 1).

a) 15 minutes shaking in 10 ml water at room temperature;
b) heating for 5 minutes in 10 ml water at 50°C followed by 15 minutes shaking;
c) heating for 5 minutes in 10 ml water at 75°C followed by 15 minutes shaking;
d) heating for 5 minutes in 10 ml water at 100°C followed by 15 minutes shaking;
e) 15 minutes shaking in 10 ml 40% ethanol at room temperature.

The test results are shown in the attached bar chart of Figure 5.

Claims

1. A controlled release pharmaceutical formulation comprising a rubbery matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

2. A formulation according to claim 1, wherein the active agent is an opioid, a stimulant, a barbiturate, an anti-depressant or a dissociative anaesthetic.

3. A formulation according to claim 2, wherein the active agent is oxycodone.

4. A formulation according to any preceding claim, which is resistant to tampering by reducing the release of the active agent upon extraction in a liquid which is water, ethanol or aqueous ethanol.

5. A formulation according to any preceding claim, which comprises multiparticulates.

6. A formulation according to any preceding claim, which shows at least one of the following characteristics (a) to (e) when tested by a test method comprising admixing a dosage amount of multiparticulates with 10 ml of the liquid in a glass flask and shaking at 500 to 600 oscillations per minute for 15 minutes using a Stuart Scientific Shaker Model SF1:

(a) 15 minutes shaking in water at room temperature: less than 7.5% release of active agent;

(b) 5 minutes standing in water at 50°C followed by 15 minutes shaking at the same temperature: less than 15% release of active agent;

(c) 5 minutes standing at 75°C followed by 15 minutes shaking at the same temperature: less than 20% release of active agent;

(d) 5 minutes standing at 100°C followed by 15 minutes shaking at the same temperature: less than 25% release of active agent;

(e) 15 minutes shaking in 40% ethanol at room temperature: preferably less than 25% release of active agent.

7. A formulation according to any preceding claim, wherein the tamper resistance reduces release of the active agent upon grinding of the formulation and extraction.

8. A formulation according to claim 7, which releases less than 10% of active agent when tested by a test method comprising subjecting a dosage amount of the formulation to grinding in a mortar and pestle with 24 rotations of the pestle and placing in 900 ml water at 37°C for 45 minutes.

9. A formulation according to claim 7, which releases less than 15% of active agent when tested by a test method comprising crushing a dosage amount in a pill pulverizer sold by Apex Healthcare Products,

and then extracting in 2 ml water heated to boiling on a spoon and filtering.

10. A formulation according to any preceding claim, wherein the matrix includes at least one other polymer to modify release.

11. A formulation according to claim 10, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

12. A formulation according to claim 11, wherein the other polymer is ethyl cellulose.

13. A formulation according to claim 12, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

14. A formulation according to any of claims 10 to 13, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
plasticiser	0 to 25
lubricant	0 to 25.

15. A formulation according to claim 14, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
plasticiser	3 to 25
lubricant	0 to 20.

16. A formulation according to claim 14, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45
other polymer to modify release	5 to 45
plasticiser	3 to 20
lubricant	0 to 15.

17. A formulation according to any preceding claim, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

18. A formulation according to claim 17, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

19. A formulation according to claim 18, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

20. A formulation according to any preceding claim, which contains a bulking agent.

21. A formulation according to any preceding claim, which contains an opioid and an opioid antagonist.

22. A formulation according to claim 21, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

23. A formulation according to claim 21 or 22, which contains oxycodone and naltrexone.

24. A formulation according to claim 21, 22 or 23, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

25. A unit dose of a pharmaceutical formulation according to any preceding claim suited for administration to a human.

26. A unit dose according to claim 25, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

27. A unit dose according to claim 25 or 26 suited for once a day dosing.

28. A unit dose form according to claim 27, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

29. A unit dose according to claim 28, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

30. A unit dose form according to claim 27, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37A unit dose form with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

31. A unit dose according to claim 25 or 26 suited for twice a day dosing.

32. A unit dose form according to claim 31 and which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

33. A unit dose form according to claim 31 which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at 2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

34. A unit dose according to claim 33, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

35. A controlled release pharmaceutical formulation obtainable by melt extrusion and including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

36. A formulation according to claim 35, and which exhibits rubber-like characteristics.

37. A formulation according to claim 35 and 36 with enhanced resistance to tampering by extraction with water or alcohol or aqueous ethanol

38. A formulation according to claim 35, 36 or 37, wherein the active agent is an opioid, a stimulant, a barbiturate, an anti-depressant or a dissociative anaesthetic.

39. A formulation according to claim 38, wherein the active agent is oxycodone.

40. A formulation according to any of claims 35 to 39, which comprises multiparticulates.

41. A formulation according to any of claims 35 to 40, wherein the matrix includes at least one other polymer to modify release.

42. A formulation according to claim 41, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

43. A formulation according to claim 42, wherein the other polymer is ethyl cellulose.

44. A formulation according to claim 43, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

45. A formulation according to any of claims 41 to 44, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
plasticiser	0 to 25
lubricant	0 to 25.

46. A formulation according to claim 45, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
plasticiser	3 to 25
lubricant	0 to 20.

47. A formulation according to claim 46, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45

other polymer to modify release	5 to 45
plasticiser	3 to 20
lubricant	0 to 15.

48. A formulation according to any of claims 35 to 47, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

49. A formulation according to claim 48, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

50. A formulation according to claim 49, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

51. A formulation according to any of claims 35 to 50, which contains a bulking agent.

52.A formulation according to any of claims 35 to 50, which contains an opioid and an opioid antagonist.

53.A formulation according to claim 52, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

54.A formulation according to claim 52 or 53, which contains oxycodone and naltrexone.

55.A formulation according to any of claims 52, 53 or 54, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

56.A unit dose of a pharmaceutical formulation according to any of claims 35 to 55 suited for administration to a human.

57.A unit dose according to claim 56, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

58.A unit dose according to claim 56 or 57 suited for once a day dosing.

59.A unit dose form according to claim 58, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to

about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

60. A unit dose according to claim 58, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

61. A unit dose form according to claim 58, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37° C with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

62. A unit dose according to claim 56 or 57 suited for twice a day dosing.

63. A unit dose form according to claim 62, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the US Pharmacopoeia XXII 1990) at 100 rpm in 900ml aqueous buffer (p H between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt)

oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

64. A unit dose form according to claim 62 which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at 2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

65. A unit dose according to claim 64, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

66. A controlled release pharmaceutical formulation obtained by melt extrusion and including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active ingredient.

67. A dry granulate comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

68. A dry granulate comprising 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and a pharmaceutically active compound.

69.A dry granulate according to claim 68, wherein the pharmaceutically active compound is an opioid.

70.A dry granulate according to claim 69, wherein the opioid is oxyocodone or a salt thereof.

71.A dry granulate which comprises a matrix of the neutral poly(ethyl acrylate, methyl methacrylate) copolymer incorporating the opioid analgesic.

72.A dry granulate according to claim 71, which is an extruded granulate.

73.A dry granulate according to claim 71 or 72, which comprises up to 66% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

74.A dry granulate according to claim 71, 72 or 73, which comprises 20 to 50% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

75.A dry granulate according to claim 74, which comprises 30 to 40% neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

76. Multiparticulates each comprising a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

77. Multiparticulates according to claim 76, formed by melt extrusion.

78. Multiparticulates according to claim 78, which take the form of a cylinder or are generally spherical, ellipsoidal or disc shaped.

79. Multiparticulates each comprising 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and a pharmaceutically active compound.

80. Multiparticulates according to claim 79, wherein the pharmaceutically active compound is an opioid analgesic.

81. Multiparticulates according to claim 80, wherein the opioid is oxycodone or a salt thereof.

82. Multiparticulates according to claim 80 and 81, formed by melt extrusion of a dry mix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

83. Multiparticulates according to claim 82, which take the form of a cylinder or are generally spherical, ellipsoidal or disc shaped.

84. A controlled release pharmaceutical formulation comprising a matrix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an opioid analgesic.

85. A controlled release pharmaceutical formulation comprising a matrix including 20% to 66% by weight of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and pharmaceutically active compound.

86. A formulation according to claim 85, and which exhibits rubber-like characteristics.

87. A formulation according to claim 85 or 86 with enhanced resistance to tampering by extraction with water or alcohol or aqueous ethanol

88. A formulation according to any of claims 84 to 87, wherein the opioid analgesic is oxycodone.

89. A formulation according to any of claims 84 to 88, which comprises multiparticulates.

90.A formulation according to any of claims 84 to 89, wherein the matrix includes at least one other polymer to modify release.

91.A formulation according to claim 90, wherein the other polymer is an alkyl cellulose or a water insoluble ammonium methacrylate copolymer.

92.A formulation according to claim 91, wherein the other polymer is ethyl cellulose.

93.A formulation according to claim 92, wherein the amount of ethyl cellulose is 10 to 50% by weight of the formulation.

94.A formulation according to claim 93, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	15 to 50
active agent	5 to 55
other polymer to modify release	5 to 75
Plasticiser	0 to 25
Lubricant	0 to 25.

95.A formulation according to claim 94, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	20 to 45
active agent	5 to 50
other polymer to modify release	5 to 60
Plasticiser	3 to 25
Lubricant	0 to 20.

96.A formulation according to claim 95, which contains the following amounts of ingredients, based on the total weight of the specified ingredients:

water-insoluble neutral poly(ethyl acrylate, methyl methacrylate) copolymer	25 to 45
active agent	10 to 45
other polymer to modify release	5 to 45
Plasticiser	3 to 20
Lubricant	0 to 15.

97.A formulation according to any of claims 85 to 96, which comprises up to 60% w/w of the active agent, 15 to 50% w/w of neutral poly(ethyl acrylate, methyl methacrylate) copolymer; 5 to 60% w/w of ethyl cellulose; and 7.5 to 20% of plasticiser.

98. A formulation according to claim 97, which further contains 5 to 60% of an insoluble ammonium methacrylate copolymer.

99. A formulation according to claim 98, which contains 35 to 50% of an insoluble ammonium methacrylate copolymer which is of low permeability and/or 5 to 30% of an ammonium methacrylate copolymer which is highly permeable.

100. A formulation according to any of claims 85 to 99, which contains a bulking agent.

101. A formulation according to any of claims 85 to 100, which contains an opioid and an opioid antagonist.

102. A formulation according to claim 101, which comprises 120 to 300 mg of oxycodone multiparticulates and 125 to 175 mg of oxycodone antagonist multiparticulates.

103. A formulation according to claim 101 or 102, which contains oxycodone and naltrexone.

104. A formulation according to claim 101, 102 or 103, which comprises melt extruded multiparticulates of an opioid and melt extruded multiparticulates of an opioid antagonist.

105. A unit dose of a pharmaceutical formulation according to any of claims 87 to 104 suited for administration to a human.

106. A unit dose according to claim 105, which contains 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 120 mg or 160 mg of oxycodone.

107. A unit dose according to claim 105 or 106 suited for once a day dosing.

108. A unit dose form according to claim 107 which has an oxycodone dissolution rate *in vitro*, when measured by the USP Basket Method at 100 rpm in 900 ml aqueous buffer at a pH between 1.6 and 7.2 at 37°C of from 0% to about 40% at 1 hour, from about 8% to about 70% at 4 hours, from about 20% to about 80% at 8 hours, from about 30% to about 95% at 12 hours, from about 35% to about 95% at 18 hours, and greater than about 50% at 24 hours.

109. A unit dose according to claim 107, wherein the peak plasma level of oxycodone obtained *in vivo* occurs at 2 hours to 17 hours after administration of the dosage form.

110. A unit dose form according to claim 107, which has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method <<7 11>> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37A unit dose form C with detection by HPLC with UV at 206 nm wavelength; from 10 to 30% at 1 hour; from 20 to 35% at 2 hours; from 35 to 75%, at 8 hours; and greater than 50% at 16 hours.

111. A unit dose according to claim 105 or 106 suited for twice a day dosing.

112. A unit dose form according to claim 111, which has an oxycodone dissolution rate *in vitro*, when measured by the USP Paddle Method (see the U.S. Pharmacopoeia XXII 1990) at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C of between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours.

113. A unit dose form according to claim 111 has an oxycodone dissolution rate *in vitro*, when measured using the USP Basket Method << 7 11 >> Apparatus 1 at 100 rpm in 900 ml aqueous buffer at pH 1.2 (simulated gastric fluid without enzyme) at 37°C with detection by HPLC with UV at 206 nm wavelength; of from 0 to 40% at 1 hour; from 20 to 70%, at

2 hours; from 40 to 80%, at 3 hours; from 60 to 95%, at 4 hours; and greater than 70% at 5 hours.

114. A unit dose according to claim 113, wherein the peak plasma level of oxycodone obtained *in vivo* occurs between 2 and 4.5 hours after administration of the dosage form.

115. A process for preparing a controlled release formulation which comprises melt extrusion of a mix including a neutral poly(ethyl acrylate, methyl methacrylate) copolymer and an active agent.

116. A process according to claim 115, wherein the neutral poly(ethyl acrylate, methyl methacrylate) copolymer is provided in the form of an aqueous dispersion comprising 40% of the polymer which is mixed with the active agent and dried to give the mix for melt extrusion.

117. A process according to claim 115 or 116, wherein the mix includes a plasticiser.

118. A process according to claim 117, wherein the plasticiser is tributyl citrate, stearyl alcohol or a high molecular weight polyethylene glycol.

119.A process according to any of claims 115 to 118 wherein the mix includes a lubricant.

120.A process according to claim 119, wherein the lubricant is stearic acid, a stearic acid salt, or glycerol dibehenate.

121.A process according to any of claims 115 to 120, which comprises wet granulation of the ingredients for the mix to be extruded to give a wet granulate, drying the granulate, and melt extrusion of the dried granulate.

122.A process according to claim 121, wherein the wet granulate is extruded before drying.

123.A process according to claim 122, wherein the dried granulate contains less than 3% w/w water.

124.A process according to any of claims 115 to 123, wherein the melt extrusion of the dry granulate is performed in a twin screw extruder.

125.A process according to any of claims 115 to 127, wherein extruded strands are conveyed to a pelletiser and cut to multiparticulates.

126.A process according to any of claims 115 to 125, wherein each multiparticulate has a dimaeter of about 1 mm and a length of about 1 mm.

127.A process according to any of claims 115 to 124, wherein a cutter cuts the extruded mix as it emerges from the extruder.

128.The use of a neutral poly(ethyl acrylate, methyl methacrylate) copolymer in the preparation of a pharmaceutical formulation to provide resistance to tamper.

129.A method of imparting tamper resistance in a pharmaceutical formulation, which comprises admixing an active ingredient and a neutral poly(ethyl acrylate, methyl methacrylate) copolymer, and forming a pharmaceutical formulation incorporating the active ingredient in a matrix with the neutral poly(ethyl acrylate, methyl methacrylate) copolymer.

130.A method of administration of an active ingredient, wherein the active ingredient is administered as a controlled release formulation according to any of claims 1 to 104.

Figure 1

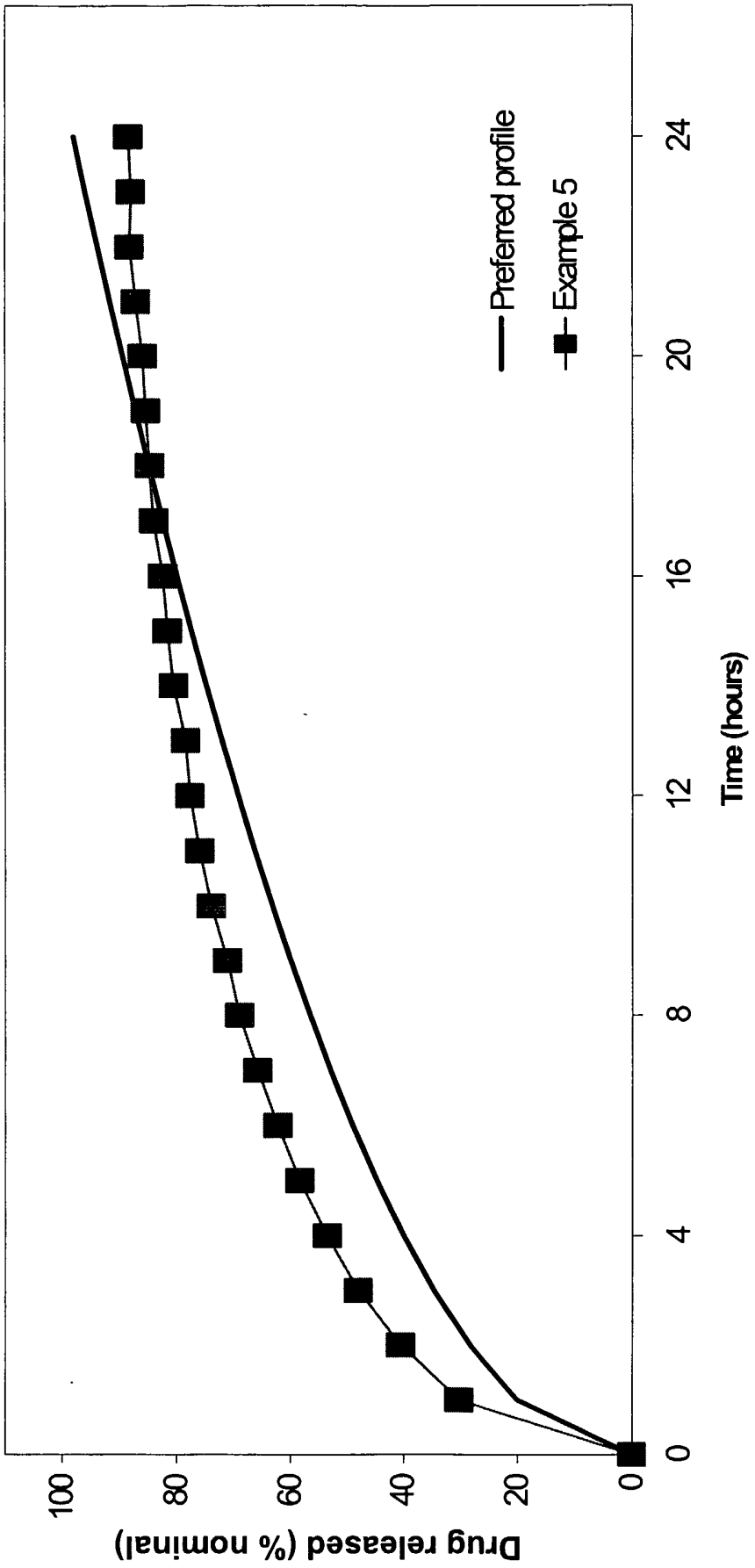

Drug released (% nominal)
0
20
40
60
80
100
Time (hours)
0
4
8
12
16
20
24
Preferred profile
Example 5

Figure 2

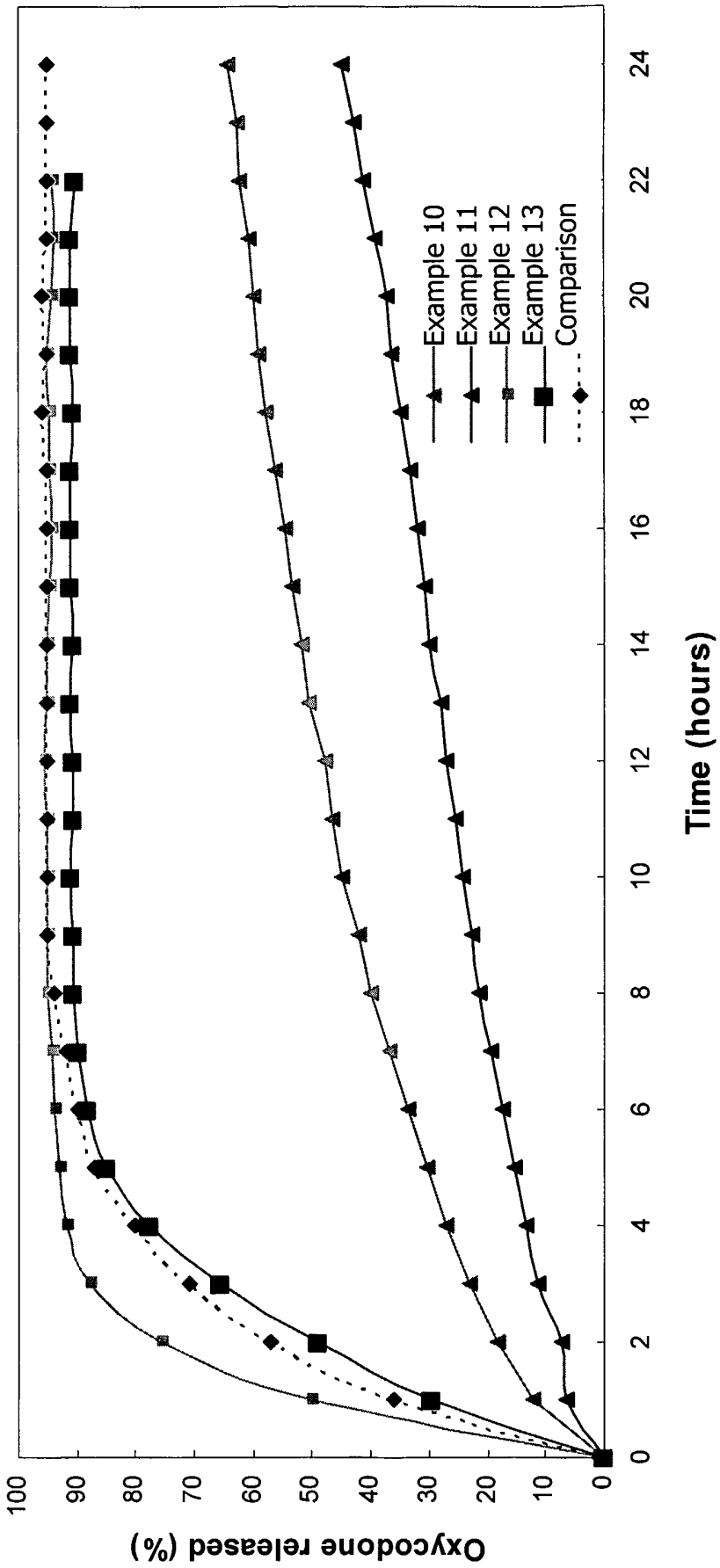

Oxycodone released (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours)
Example 10
Example 11
Example 12
Example 13
Comparison

Figure 3

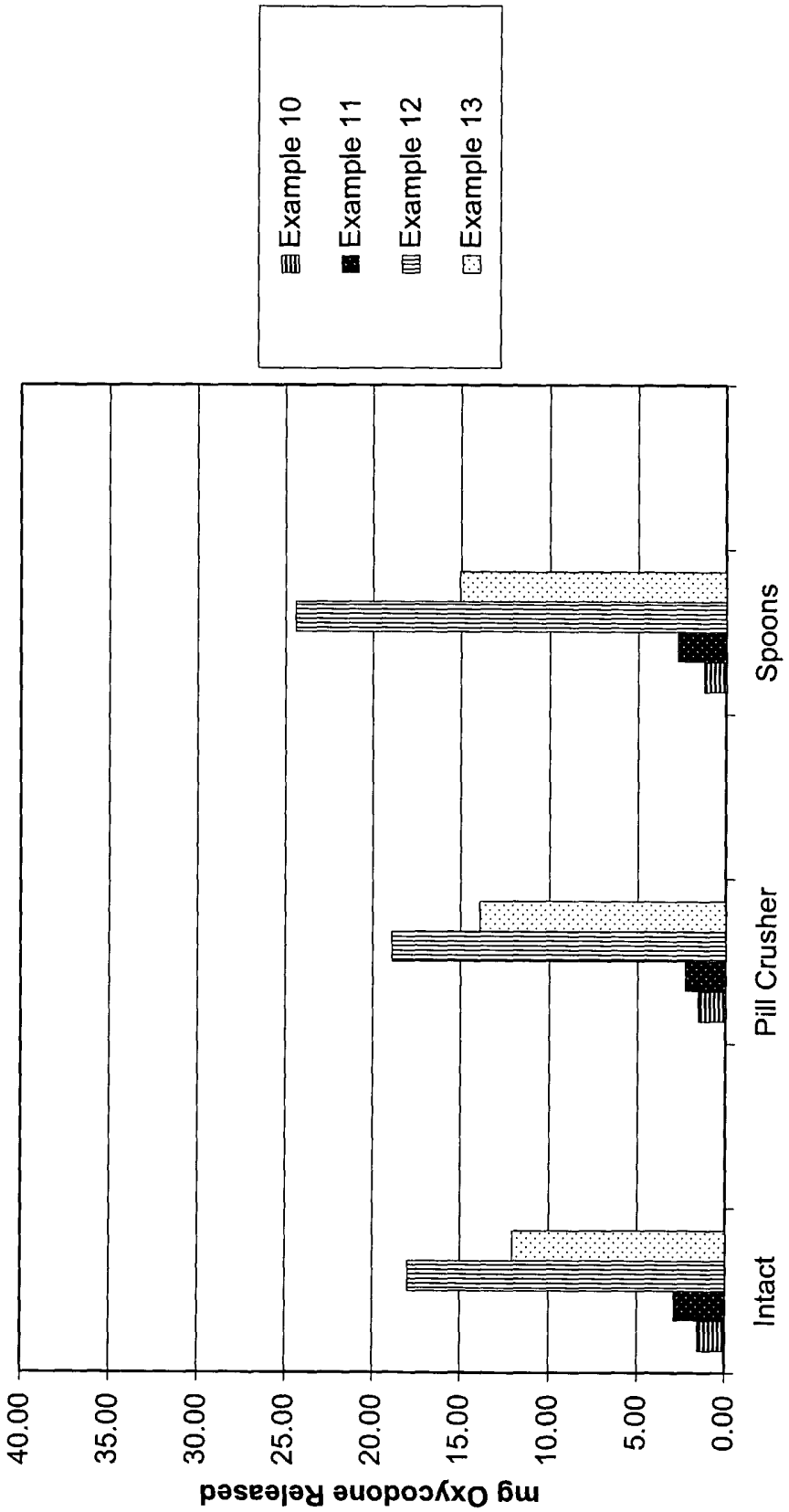

Example 10
Example 11
Example 12
Example 13
mg Oxycodone Released
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Intact
Pill Crusher
Spoons

Figure 4

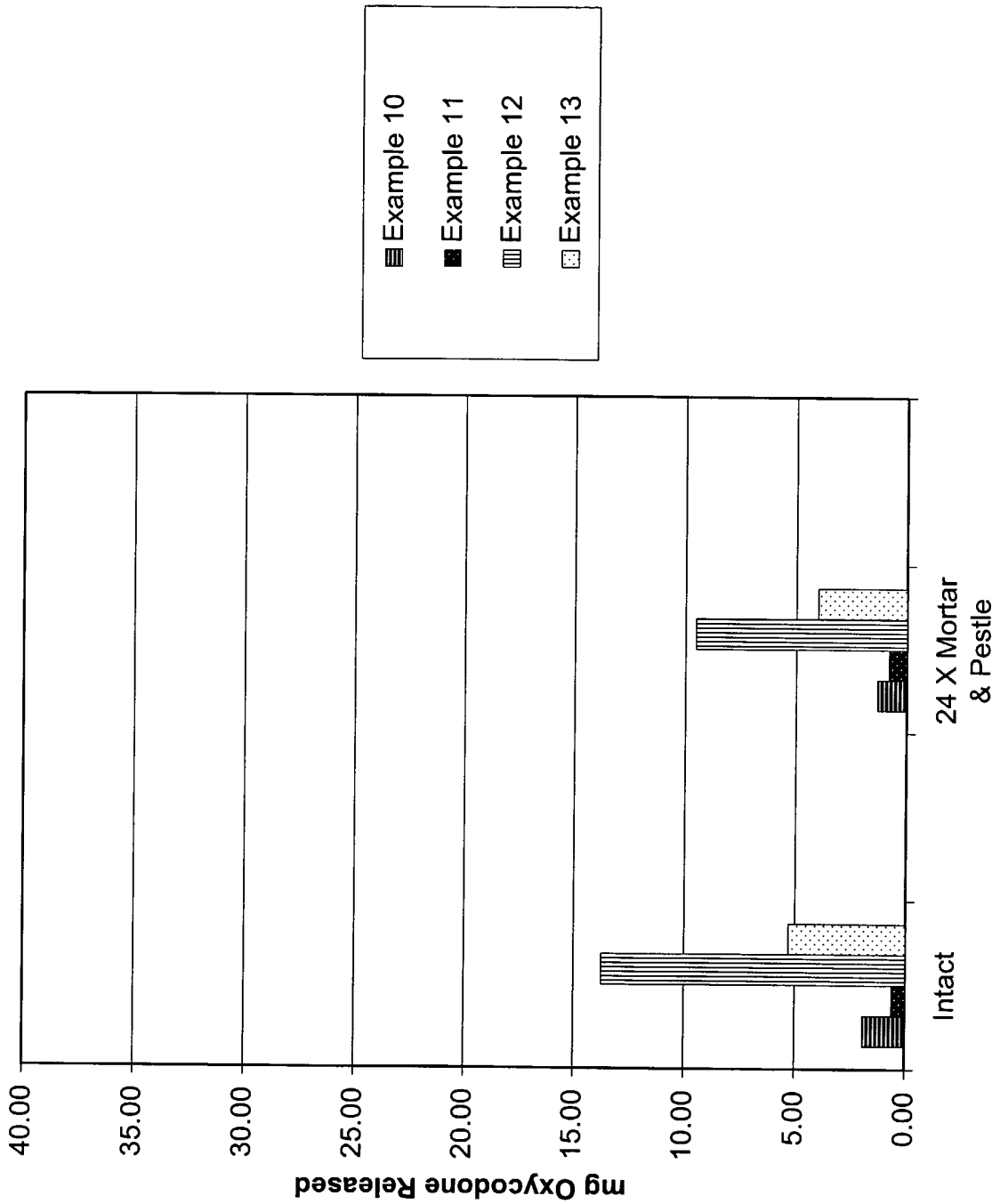
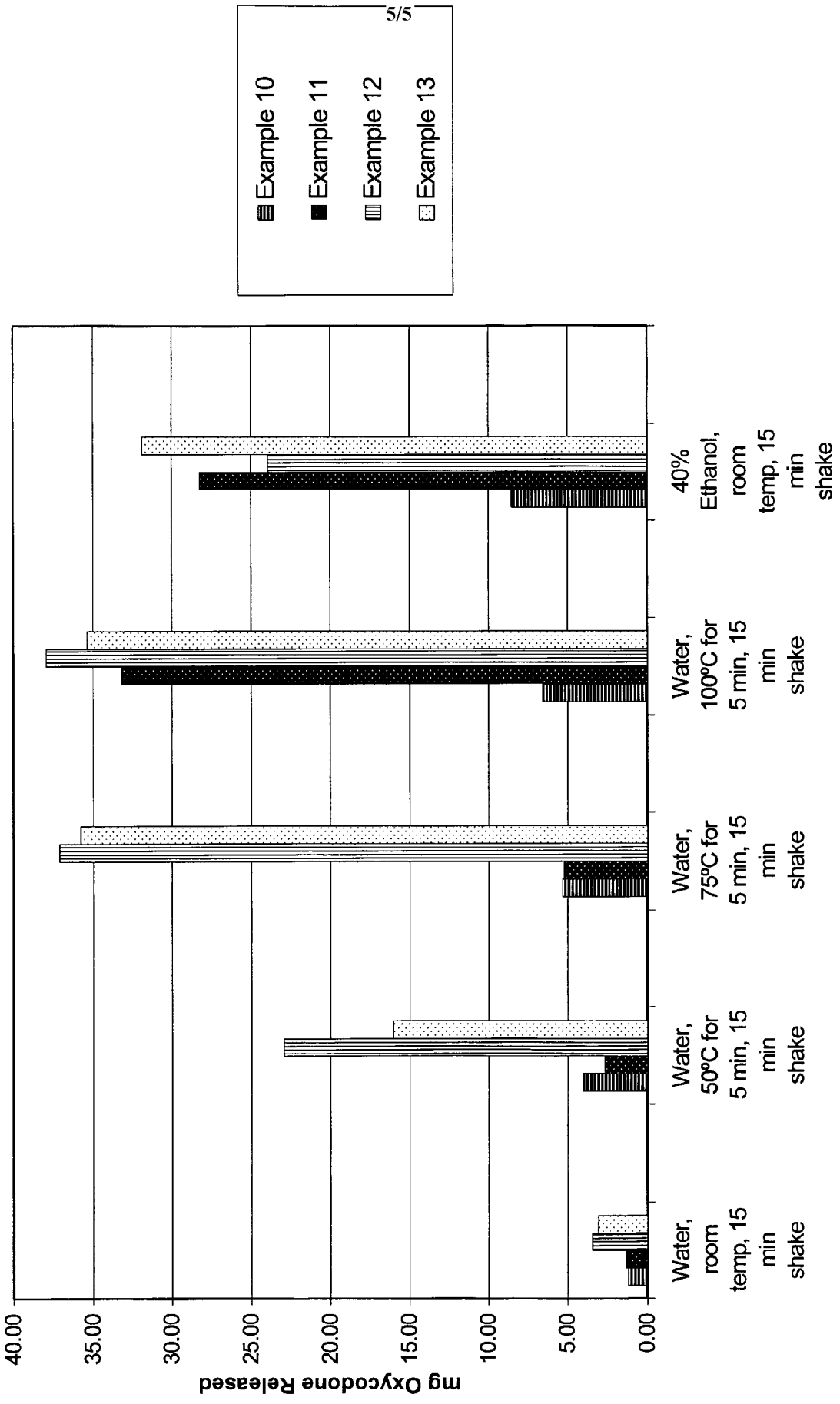

Example 10
Example 11
Example 12
Example 13
mg Oxycodone Released
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Intact
24 X Mortar & Pestle

Figure 5


Example 10
Example 11
Example 12
Example 13
mg Oxycodone Released
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Water, room temp, 15 min shake
Water, 50°C for 5 min, 15 min shake
Water, 75°C for 5 min, 15 min shake
Water, 100°C for 5 min, 15 min shake
40% Ethanol, room temp, 15 min shake

INTERNATIONAL SEARCH REPORT

Inter I Application No
PCT/GB2005/050014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16

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)
IPC 7 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 practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/004009 A (GENEVA PHARMACEUTICALS, INC; MATHARU, AMOL, SINGH; PATEL, MAHENDRA, R) 16 January 2003 (2003-01-16) cited in the application the whole document claims 1-29	1-130
A	EP 1 348 429 A (EURO-CELTIQUE S.A) 1 October 2003 (2003-10-01) the whole document claims 1-25; figures 1-17	1-130
P,A	WO 2005/000310 A (EURO-CELTIQUE S.A; WALDEN, MALCOLM; HAYES, GEOFF; MOHAMMAD, HASSAN; TA) 6 January 2005 (2005-01-06) the whole document	1-130

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2005	04/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Felder, C

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INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB2005/050014

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 958 452 A (OSHLACK ET AL) 28 September 1999 (1999-09-28) the whole document -----	1-130
A	US 5 965 161 A (OSHLACK ET AL) 12 October 1999 (1999-10-12) the whole document -----	1-130

INTERNATIONAL SEARCH REPORT

ional application No.
PCT/GB2005/050014

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 130 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 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:

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 fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB2005/050014

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INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/GB2005/050014

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		DE 69532415 T2	30-12-2004
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