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(54) Title: MULTIPLE UNITS CONTROLLED-RELEASE FLOATING DOSAGE FORMS

(57) Abstract: Oral pharmaceutical multiple units controlled release floating composition comprising : - at least one drug containing system comprising at least one active drug, one fusible binder and one gas generating agent, and - either a coating layer surrounding the drug containing system, and/or the drug containing system further comprises a swelling agent.

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Multiple units controlled-release floating dosage forms**5 ABSTRACT**

The present invention relates to oral controlled release floating dosage form, especially multiple units controlled release floating granulated systems which are able to float on the surface of aqueous fluids, including gastric juice, over an extended period of time. The oral dosage form of the invention is preferably for enabling at least a sustained release of one or more active agents.

It also relates to a method of fabrication of said controlled release floating dosage forms, such as granulated multiple units systems which is very simple and based on a melt (thermoplastic) granulation step following by filling into capsules or pelletization and/or compression into mini-tablets or tablets. Melt granulation is a low cost, rapid and solvent-free manufacturing process.

It is further related to the unique composition of the said floating dosage form or granulated multiple units system which is based on at least one drug, at least one fusible (low melting point) binder, at least one gas generating agent and appropriated excipients in order to control efficiently both the release of the drug and the floating properties of the composition. To provide optimal floating properties, a coating layer, can be optionally be added on the dosage form or multiple units (granulates, pellets, mini-tablets) to retain the carbon dioxide produced or alternatively a

gel forming polymer (swelling agent) can be added in the dosage form or in the multiple unit compositions

FIELD OF THE INVENTION

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BACKGROUND OF THE INVENTION

[001] Among the different routes of drug administration, the oral route has achieved the most
10 attention, partly due to the ease of administration and the important flexibility in dosage-form design [reference 1]. Unfortunately, in most cases, the important variability of gastrointestinal tract's physiology and of its transit time leads to an
15 unpredictable bioavailability and non reproducible therapeutic effects.

[002] An orally administrated drug delivery system is exposed to a wide range of highly variable conditions as pH, agitation, intensity and gastric
20 emptying times.

[003] The convenience of administering a single dose of medication which releases an active medicament over an extended period of time as opposed to the administration of a number of singles doses at regular
25 intervals has long been recognised in pharmaceutical field. The advantages to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognised [reference 3].

30 [004] A prolongation of gastric residence time (GRT) of a rate-controlled oral drug delivery system reduces the inter-subject variability, reduces the so

called "peak and valley" effect and leads to a more predictable and a bioavailability increase of the dosage form, especially for molecules with a narrow absorption window. Moreover, the total gastrointestinal transit time is prolonged and thus, the number of dosage regimen can be reduced.

[005] The development of sustained-release dosage forms capable of staying in the stomach over an extended period of time may be particularly useful for drugs that may act locally in the stomach (e.g. antacids, antibiotics for bacterially-origin ulcers), drugs that are absorbed primarily in the stomach (e.g. albuterol), drugs that are poorly soluble in intestinal pHs (weak bases such as dipyridamole), drugs that have a narrow absorption window and absorbed (mainly) from the upper small intestine (e.g. levodopa, riboflavin), drugs that absorbed rapidly from the GI tract (e.g. amoxicillin), drugs having a low bioavailability and drugs that degrade in the colon (e.g. metoprolol) [references 2 to 6]

[006] Several approaches have been pursued to increase the retention of an oral dosage form in stomach.

[007] For instance, expandable gastro retentive dosage forms which don't pass the pylorus sphincter because of their large sizes have been proposed. The final size is obtained by swelling or unfolding process in the gastric juice following ingestion [reference 7]

These types of drug delivery systems were specially made for veterinary applications but it's possible to use them for humans. Furthermore, their preparation seems to be long and hard to make.

[0008] In the same way, swelling tablets are made to swell in the stomach following ingestion, as a result of single gelling or coupled with carbon dioxide emission trapped into hydrocolloid agent [reference
5 7].

[0009] The use of passage-delaying excipients incorporated into and released from the delivery system has been proposed to delay or slow down the gastric transit. This is based on the fact that fatty acids
10 and/or anticholinergic agents can reduce the motility of the stomach [reference 8]. Their use is not harmless because the normal transit is affected.

[0010] Bioadhesive drug delivery systems can be formulated to adhere on the gastric mucous membrane.
15 According to in vivo studies and despite that the principle of bioadhesion has found very interesting applications for other routes of administration, it does not seem that mucoadhesive polymers are able to prolong significantly the GRT of oral drug delivery
20 systems [reference 8].

[0011] The use of solid dosage forms with high density (heavy pellets and tablets), which might remain positioned in the lower part of the antrum during a prolonged period of time, has been also proposed. The
25 success of such systems is limited since the bioavailability depends on a lot of physical and physiological factors [reference 8].

[0012] Magnetic systems and superporous biodegradable hydrogel systems are also described
30 [reference 9].

[0013] The floating drug delivery systems (FDDS) offer the more effective and rational protection

against early and random gastric emptying compared to the other means proposed to prolong the GRT of solid dosage forms.

[0014] Several patents and papers describe buoyant dosage forms which improve efficiently the gastric residence time. Based on the mechanism of buoyancy, two different approaches, the use of polymer-mediated non-effervescent and effervescent systems, have been proposed in the development of FDDS [reference 10]. Floating dosage forms might have a density lower than gastric fluid (less than 1 g/ml) and float on it during a prolonged period of time.

[0015] Most of the floating systems reported in literature are single-unit systems, which are generally unreliable and non-reproducible in prolonging the GRT, owing to their unpredictable all-or-nothing emptying process. On the other hand, multiple-unit dosage forms appear to be better suited since they are claimed to reduce inter-subject variability in absorption and a lower dose-dumping probability [reference 10].

[0016] US Patent no 4,126,672 described a Hydrodynamically Balanced capsule System based on the mixture of drugs and hydrocolloids. In contact with gastric juice the hydrocolloid begins to swell and maintains a relative integrity of shape, a bulk density of less than unity and finally, regulates the drug release [references 11 and 6].

[0017] US Patent no 4,055,178 described a device comprising a drugs reservoir encapsulated in a microporous compartment, to which an independent flotation chamber is attached in order to provoke the flotation of the system [reference 12].

[0018] Iannucelli et al. (1998) have described an air compartment multiple-unit system in which, each unit was formed by coated beads composed of a calcium alginate core separated by an air compartment from a calcium alginate/polyvinyl alcohol membrane [reference 13].

[0019] Kawashima et al (1992) have developed non effervescent hollow polycarbonate microballoons by using an emulsion - solvent evaporation method. Thanoo and al. (1993) have used the same method to make hollow polycarbonate microspheres but they have employed others solvents [references 14 and 15].

[0020] Yuasa et al. (1996) have developed floating granules using Hydroxypropylcellulose (HPC), ethylcellulose and calcium silicate as a floating carrier, which has a characteristically highly porous structure. The granules acquire floating ability from the air trapped in the pores of calcium silicate when they were coated with a polymer [reference 16].

[0021] Whitehead et al. have developed a highly porous multiple-unit floating dosage form. Very low density spherical beads were produced by dropping a sodium alginate solution into aqueous calcium chloride and by freeze-drying the obtained gelled beads [reference 18].

[0022] Ichikawa et al. (1991) have described a gas generating multiple-unit oral floating dosage system consisting of a conventional sustained-release pill coat by two layers. The inner layer was an effervescent layer and the outer layer a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. When the system was immersed in a

buffer solution, it sank at once in the solution and forms swollen pills, like balloons, with a density much lower than 1 g/ml [reference 17].

[0023] Atyabi et al. (1996) have developed a controlled-release gastric retentive system from coated floating ion exchange resin beads. The resin is loaded with bicarbonate anions and coated by a semi-permeable membrane. On exposure to gastric media, exchange of bicarbonate and chloride took place releasing carbon dioxide. The gas is trapped within the membrane causing the particles to float [reference 19].

[0024] US Patent no 3,901,232 and US Patent no 3,786,813 described a very sophisticated osmotically controlled floating system, consisting of two chambers in a capsule. The first chamber contains a drug, while the second one contains a volatile liquid, such as cyclopentane that vaporizes at physiological temperature, enabling drug reservoir to float [references 20 and 21].

[0025] A lot of sustained-release floating tablet systems were described in literature, using effervescent or non effervescent components and which were obtained with or without a granulation step, followed by compression.

[0026] As an example, US Patent no 6,261,601 describes a single-unit pharmaceutical composition in the form of tablets (or capsules) comprising a drug, a gas generating component, a swelling agent, a viscolyzing agent, and (optionally) a gel forming polymer. The swelling agent, the gas entrapping viscolyzing agent and optionally the gel forming polymer form a hydrated gel matrix. The tablets are

prepared by mixing all the compounds. The mixture may be roll compacted and sieved to obtain granules, which may be filled into capsule or compressed into tablets. This invention, however, does not resolve the problem
5 of the high inter and intrasubject variability and the problem of unpredictability of single unit dosage forms [reference 30].

[0027] Accordingly, none of the oral controlled drug delivery systems described hereinbefore is
10 completely satisfactory.

[0028] When a granulation step is used, wet granulation is probably the most popular way to obtain granules from hydrocolloids and bicarbonate sodium after drying to evaporate solvents.

15 **[0029]** Melt (thermoplastic) granulation, in which the granulation is obtained through the melting or softening of a low melting point binder, might be a very interesting alternative to the classical wet granulation as a very short one-step single-pot
20 production process. As it is a solvent free process, the drying phase is eliminated and thus, the process becomes less consuming in terms of time and energy.

[0030] The use of the melt granulation process was thoroughly discussed in the literature for the
25 preparation of immediate release and sustained release granules, pellets and tablets. Hamdani et al. have developed a melt pelletization process allowing a substantial increase of fatty binders content of formulations, up to 80% w/w, in order to obtain
30 prolonged-release pellets for different drugs substances showing very distinct physico-chemical (solubility) properties [reference 22 and 23].

[0031] One of the major limitations for the development of tabletted floating systems is probably the difficulty to modulate both the desired time period for buoyancy and the rate of drug release. Several authors have proposed the use of bilayer or multilayer tabletted systems in which, the buoyancy formulation layer is separated from the drug release formulation layer, and thus, a greater flexibility is possible in release profile adjustment. But the main difficulty is to avoid the separation of the different layers, when the composition is put in contact with gastrointestinal fluids

[0032] Tablets can be presented as a single-unit dosage form or multiple-unit dosage form. According to Hwang et al. (1998), a single-unit dosage form diameter has to be larger than 13 mm in order to be retained in the stomach for a prolonged period of time [reference 13]. Single-unit dosage forms show a higher inter- and intra patients variability resulting from the all-or-none emptying process from stomach. On the other hand, divided systems have a more reproducible gastric residence time, present lower intersubject variability in absorption and show a better dispersion through the gastrointestinal tract.

[0033] In vivo investigations show that the presence of food, rather than buoyancy and/or particulate size, is the most important factor affecting the GRT of floating forms. The GRT of buoyant units depends not only on the initial density but also, on the evolution of their density as function of time [reference 9].

[0034] The present invention relates to buoyant controlled-release dosage forms or granulated formulations, which may be either filled into capsules or compressed into tablets or mini-tablets. The originality of this invention consists in its process of fabrication associated with its composition. The floating granules were fabricated by melt (thermoplastic) granulation in a high shear mixer. As the manufacture method is very simple and well reproducible, the buoyant properties as well as the release properties of the controlled release dosage forms of the invention did substantially not vary from one production batch to another production batch.

[0035] The granulation mixtures contain at least one drug, one or several meltable binders (preferably lipidic binders), one or more gas-generating agents and, when required, appropriated excipients. Floating tablets or minitables can contain swellable agents and/or be coated by a flexible membrane in order to retain the generated gas inside the dosage form.

[0036] The floating granules compositions according to this invention are preferably compressed into mini-tablets and/or tablets, most preferably into minitables, whose composition and individual size characteristics permit also to modulate both the floating and the dissolution properties of the dosage form. The mini-tablets obtained after compression are preferably filled into capsules in order to obtain multiple-unit sustained-release floating dosage forms.

[0037] Melt granulation can also result in the production of pellets. In the present invention, pellets (also called beads or microgranules) refer to

almost spherical particles containing the drug and the required excipients of the invention and having a mean diameter between 0.5 and 2 mm, preferably between 0.7 and 1.5 mm. Floating pellets may be made by using the same method than the one used to produce floating granulates. The compression step is then avoided. Floating pellets, which is also a multiple-unit dosage form, may contain at least one drug, one fusible binder (preferably lipophilic binders), at least one gas-generating agent and appropriated excipients. Floating pellets may further be coated with a water insoluble coating in order to retain the generated gas inside the dosage form.

BRIEF DESCRIPTION OF THE INVENTION

[0038] The invention relates to an oral
5 pharmaceutical controlled release floating
composition, advantageously in the form of multiple
units composition. The composition of the invention
comprises :

10 a) At least one drug containing system selected
from the group consisting of (I) unit forms
selected from granules, mini tablets, tablets
and pellets comprising at least one active
drug, one fusible binder and one gas
15 generating agent, and (II) multiple unit
forms comprising or formed by more than one
of said unit forms, and

b) either a coating layer surrounding one or
more of said drug containing system, said
coating layer comprising a water insoluble
20 polymer and/or one or more drug containing
systems further comprise a swelling agent.

The compositions of the present invention,
advantageously in the form of multiple units floating
sustained-release granulated systems, are able to
25 float on the surface of aqueous fluids, including
gastric juice, for an extended period of time.

[0039] The drug containing system is advantageously
prepared in the absence of water, so that solid or
semi-solid excipients are bound together by the
30 fusible binder. The active agent can be in solid forms
or in semi solid forms or dissolved or dispersed in one
or more excipients, said active agent being bound to

other excipients particles by means of the fusible binder. The preparation of drug containing system in the absence of water enables to guarantee that the gas generating agent is not wetted with water and is in its optimal condition for generating gas. It enables furthermore that the drug containing system comprises gas generating agents having to react together in presence of water or an aqueous medium for generating gas.

10 **[0040]** Advantageously, the unit form comprises a core comprising at least one active drug, one fusible binder, one gas generating agent and a swelling agent.

[0041] Preferably, the composition further comprises one or more organic acids. Said organic acid or acids are advantageously within the unit forms comprising the drug or active agent.

[0042] According to an advantageous embodiment, the fusible binder has a melting point or a melting range lower than 95°C, preferably lower than 80°C, preferably between 30 °C and 75°C, more preferably between 45 °C and 55°C. The fusible binder can also be a mixture of fusible binders, such as one binder with a low melting temperature or range and another binder with a high melting temperature.

The fusible binder has advantageously a HLB value lower than 7, for example comprised between 1 and 6.

30 **[0043]** Advantageously, the weight ratio between the fusible binder and the gas generating agent in the composition of the invention, preferably in the unit

form, is about 0.1 to 10, preferably from 0.2 to 5, most preferably from 0.5 to 2.

5 **[0044]** Preferably, the unit forms have a weight average size from 0.2mm and 7mm, advantageously between 0.3 and 5mm, preferably between 0.4 and 3mm.

10 **[0045]** According to a preferred embodiment, the unit forms are compressed into tablets or mini tablets or comprised in a capsule forming a multiple unit form

15 **[0046]** According to another embodiment, the multiple unit form is a capsule or a tablet comprising the granules, pellets or mini tablets.

20 **[0047]** The composition comprises advantageously several granules, mini tablets and/or pellets.

25 **[0048]** According to advantageous embodiment, the fusible binder is selected from the group consisting of fats, waxes, fatty alcohols, cetyl alcohol, stearyl alcohol cetostearyl alcohol or fatty alcohols with more than 18 carbon atoms), fatty acids (preferably palmitic acid, or fatty acids with more carbon atoms such as
30 stearic acid, behenic acid, etc.), glycerol esters (e.g. mono-, di-, and tri-glycerides, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate), ethers of fatty alcohols, esters of fatty acids, hydrogenated oils, polyethylene glycols (PEGs), polyoxyethylenated derivatives, phospholipids and any derivatives thereof, as well as mixtures thereof. The use of a mix of fusible binders is advantageous so as

to have a better control of the melting temperature or melting range temperature.

[0049] The gas generating agent is advantageously
5 selected from the group consisting of sodium and potassium hydrogen carbonate, calcium carbonate, sodium glycine carbonate, sulphur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite, and combinations thereof.

10

[0050] The composition advantageously further comprises a second gas generating agent.

[0051] The organic acid is advantageously tartaric
15 acid, citric acid, ascorbic acid or a mix thereof.

[0052] When the composition of the invention is provided with coating, the water insoluble coating polymer is advantageously selected from the group
20 consisting of water insoluble acrylic polymers, water insoluble cellulosic polymers, waxes and combinations thereof. Possibly, the composition of the invention can be provided with more than one coating layer.

[0053] The swelling agent is advantageously selected from the group consisting of gum arabic, Carrageenan, Guar gum, Gum tragacanth, Agar, Sodium Carboxymethyl cellulose, Hydroxyethyl cellulose, Hydroxypropylmethyl cellulose, Sodium alginate, Chitosan, Xanthan gum,
30 Sodium croscarmellose, pectin and combinations thereof.

[0054] The composition of the invention is advantageously formulated in a form suitable for a once-a-day or twice-a-day administration in humans.

5 [0055] According to an embodiment, several unit forms are filled into a pharmaceutically acceptable capsule, preferably hard gelatin capsule or hypromellose capsule. The unit forms can then have a same composition, but can also have different compositions.
10 For example some unit forms comprise a first gas generating agent, while other unit forms comprise a second gas generating agent different from the first gas generating agent. Advantageously, the first and second generating agents are selected so as to react
15 therebetween in presence of an aqueous medium. When using unit forms with different composition, the active agent content is advantageously the same, so as to ensure a correct active agent content of the final composition, for example of the capsule.

20

[0056] According to another possible embodiment, one or more unit forms comprise a first active agent, while one or more other unit forms comprise another active agent.

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[0057] According to still another embodiment, the capsule comprises one or more unit forms having a first controlled release profile, while one or more other unit forms have a second controlled release profile
30 different from the first release profile.

- [0058] According to a further embodiment, the composition further comprises an immediate release form of the same active drug or of another active agent.
- 5 [0059] According to a specific example, the composition comprises a combination of two or more active drugs.
- For example, one drug presents a first controlled release profile (such as an sustained or extended
- 10 release profile), while the other drug presents a release profile different from the first controlled release profile, advantageously an immediate release profile.
- 15 [0060] The composition advantageously further contains one or more classical pharmaceutical excipients like fillers, disintegrants, lubricants, pigments, anti-taching, and combinations thereof.
- 20 [0061] The invention relates also to unit forms as disclosed here above, suitable for the preparation of a composition according to the invention.
- The unit forms are advantageously selected from the group consisting of granules, pellets and mini-tablets,
- 25 said unit forms comprising at least one active agent, one fusible binder and one gas generating agent. The unit forms are characterized in that the unit forms further comprises a swelling agent and/or a coating layer surrounding one or more unit forms, said coating
- 30 layer comprising a water insoluble polymer.

[0062] Advantageously, the unit form comprises a core comprising at least one active drug, one fusible binder, one gas generating agent and a swelling agent.

5 [0063] Preferably, the unit form of the invention further comprises one or more organic acids.
According to an advantageous embodiment, the fusible binder has a melting point or a melting range lower than 95°C, preferably lower than 80°C, preferably
10 between 30 °C and 75°C, more preferably between 45 °C and 55°C. The fusible binder can also be a mixture of fusible binders, such as one binder with a low melting temperature or range and another binder with a high melting temperature. The fusible binder has
15 advantageously a HLB value lower than 7, for example comprised between 1 and 6.

[0064] Advantageously, the weight ratio between the fusible binder and the gas generating agent in the unit
20 form of the invention, preferably in the unit form, is about 0.1 to 10, preferably from 0.2 to 5, most preferably from 0.5 to 2.

[0065] Preferably, the unit form of the invention has
25 a weight average size from 0.2mm and 7mm, advantageously between 0.3 and 5mm, preferably between 0.4 and 3mm.

[0066] According to advantageous embodiment used
30 for the unit form of the invention, the fusible binder is selected from the group consisting of fats, waxes, fatty alcohols, cetyl alcohol, stearyl alcohol

cetostearyl alcohol or fatty alcohols with more than 18 carbon atoms), fatty acids (preferably palmitic acid, or fatty acids with more carbon atoms such as stearic acid, behenic acid, etc.), glycerol esters (e.g. mono-,
5 di-, and tri-glycerides, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate), ethers of fatty alcohols, esters of fatty acids, hydrogenated oils, polyethylene glycols (PEGs), polyoxyethylenated derivatives, phospholipids and any derivatives thereof,
10 as well as mixtures thereof. The use of a mix of fusible binders is advantageous so as to have a better control of the melting temperature or melting range temperature.

15 **[0067]** The gas generating agent used in the unit form of the invention is advantageously selected from the group consisting of sodium and potassium hydrogen carbonate, calcium carbonate, sodium glycine carbonate, sulphur dioxide, sodium sulfite, sodium bisulfite,
20 sodium metabisulfite, and combinations thereof. The unit form of the invention advantageously further comprises a second gas generating agent.

[0068] The organic acid present in the unit form of
25 the invention is advantageously tartaric acid, citric acid, ascorbic acid or a mix thereof.

[0069] When the unit form of the invention is provided with a coating, the water insoluble coating
30 polymer is advantageously selected from the group consisting of water insoluble acrylic polymers, water insoluble cellulosic polymers, waxes and combinations

thereof. Possibly, the unit form of the invention can be provided with more than one coating layer.

[0070] The swelling agent is advantageously selected from the group consisting of gum arabic, Carrageenan, Guar gum, Gum tragacanth, Agar, Sodium Carboxymethyl cellulose, Hydroxyethyl cellulose, Hydroxypropylmethyl cellulose, Sodium alginate, Chitosan, Xanthan gum, Sodium croscarmellose, pectin and combinations thereof.

10

[0071] The unit form of the invention advantageously further contains one or more classical pharmaceutical excipients like fillers, disintegrants, lubricants, pigments, anti-tacking, and combinations thereof.

15

[0072] The invention relates also to a process for manufacturing a composition of the invention or unit forms of the invention. The process comprises at least the step of mixing and melt granulating the drug, the fusible binder, a swelling agent and the gas generating agent together.

[0073] Advantageously, the process for manufacturing composition of the invention or unit forms of the invention comprises at least

25

- the step of mixing and melt granulating the drug, the fusible binder and the gas generating agent together,
- to compress the granulates into mini tablets or tablets, preferably in the forms of mini tablets, and
- 30 - to coat the mini tablets or mini tablets with at least a water insoluble polymer.

[0074] According to another embodiment, the process for manufacturing unit forms of the invention comprises at least

- the step of mixing the drug, the molten fusible binder and the gas generating agent together,
- to form pellets or granules or beads or mini tablets from said mixture, and
- to coat the pellets or granules or beads or mini tablets with at least a water insoluble polymer.

10

[0075] According to still another embodiment of the process of the invention, the process comprises at least

- the step of mixing, melt granulating and pelletized the drug, the fusible binder and the gas generating agent together and
- to coat the pellets with at least a water insoluble polymer.

- 20 **[0076]** The present invention also relates to the manufacturing process of said granulated systems which is very simple and based on a melt (thermoplastic) granulation step followed by filling into capsules or compression into mini-tablets. Alternatively, pellets
- 25 can be produced after or during melt granulation.

- [0077]** The present invention further relates to the unique composition of the said floating granulated system which is based on the mixture of at least one therapeutically active ingredient or drug, at least one
- 30 fusible (meltable) binder, at least one gas generating agent, and appropriated excipients in order to control efficiently both the release and the floating

properties of the composition. A swellable agent (gel forming polymer), or more preferably a polymer coating, can optionally be used, to further improve floating and/or release properties.

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BRIEF DESCRIPTION OF THE DRAWINGS

[0078] Figure 1 shows the influence of the mini tablet diameter on the drug release profiles (n=5). The pharmaceutical composition of the granulates of the invention used for the preparation of the mini tablets of the invention is given in Table 1.

[0079] Figure 2 shows the influence of the minitabulet diameter on the resultant-weight results and thus, on the floating properties (n=3). The pharmaceutical composition of the granulates is given in Table 1.

[0080] Figure 3 shows the influence of the pharmaceutical composition on the drug release profiles (n=5). The pharmaceutical compositions of granulates are given in Table 4

[0081] Figure 4 shows the influence of the pharmaceutical composition on the resultant-weight results and thus, on the floating properties (n=3). The pharmaceutical compositions of granulates are given in Table 4.

[0081] Figure 5 shows the influence of the pharmaceutical composition of the core, in the case of coated mini tablets, on the drug release profiles (n=5). The pharmaceutical compositions of the core and the formulation used in the coating are shown in Table 6.

[0082] Figure 6 shows the influence of the coating level, in the case of coated mini tablets, on the drug release profiles (n=5). The pharmaceutical composition of the core and the formulation used in the coating are given in Table 8.

[0083] Figure 7 shows the influence of the formulations used in the coating, in the case of coated minitabets, on the drug release profiles (n=5). The pharmaceutical composition of the core and the formulations used in the coating are shown in Table 10.

[0084] Figure 8 shows that is possible to obtain a sustained-release profile with several different drugs (n=5). The pharmaceutical compositions are given in Table 12.

[0085] Figure 9 shows the mean amount $\pm$ SD of riboflavin excreted in urine (mg), following administration of floating mini tablets and non-floating mini tablets in (a) fasted (n=5) and (b) fed (n=4) conditions.

[0086] Figure 10 shows the mean riboflavin urinary excretion rate ($\mu\text{g}/\text{min}$) following administration of floating mini tablets and non-floating mini tablets in (a) fasted (n=5) and (b) fed conditions (n=4).

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DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

[0087] The object of the present invention is to provide multiple units solid dosage forms able to float on the surface of aqueous fluids and to deliver one or

more therapeutic agents incorporated therein over an extended period of time.

[0088] The present invention provides floating controlled-release (CR) granulated formulations that
5 can be filled into capsules or compressed into mini tablets or pelletized.

[0089] The present invention provides also new compositions of the said floating CR granules based on the use of very simple compositions comprising at least
10 one drug, one fusible (low melting point) binder, one gas generating agent and other pharmaceutically acceptable excipients. The composition has to be designed to obtain an optimal floating properties and dissolution rate of the drug.

[0090] Advantageously, a composition of the said floating granules further comprises one or more inert (insoluble) polymer(s) and /or a swellable agent gel forming hydrocolloid(s) in order to improve the floating capabilities of the solid dosage form by
20 entrapping carbon dioxide generated by the effervescent components.

[0091] More advantageously, floating mini tablets according to a composition of the invention are coated by a flexible membrane in order to retain the generated
25 gas inside the dosage form.

[0092] Furthermore, the swellable agent and/or the coating layer may participate to the control of the drug release in addition to the sustained-release provided by the fusible binder, which is preferably
30 lipophilic.

[0093] The swellable agents and the coating can also preserve the cohesion of the system.

[0094] A method of preparation of the floating CR granules according to the invention comprises the process of melt granulation in a high shear mixer.

[0095] Advantageously, the fusible binder which has
5 a low melting point or melting range is a lipophilic or optionally a hydrophilic compound selected from the group consisting of fats, waxes, fatty alcohols (preferably cetyl alcohol, stearyl alcohol cetostearyl alcohol or fatty alcohols with more than 18 carbon
10 atoms), fatty acids (preferably palmitic acid, or fatty acids with more carbon atoms such as stearic acid, behenic acid, etc.), glycerol esters (e.g. mono-, di-, and tri-glycerides, in particular, glyceryl monostearate, glyceryl palmitostearate, glyceryl
15 behenate), ethers of fatty alcohols, esters of fatty acids, hydrogenated oils, polyethylene glycols (PEGs), polyoxyethylenated derivatives, phospholipids and any derivatives thereof.

[0096] Advantageously, the low melting point
20 ingredient, used as fusible (meltable) binder, is a solid material at ambient temperature with a melting point or a melting range lower than 95°C, preferably lower than 80°C, preferably between 30 °C and 75°C, more preferably between 45 °C and 55°C.

[0097] Advantageously, the gas generating system may
25 consist of one or more substances known to produce carbon dioxide (e.g. sodium or potassium hydrogen carbonate, calcium carbonate, sodium glycine carbonate) or sulphur dioxide (e.g. sodium sulfite, sodium
30 bisulfite or sodium metabisulfite) upon contact with gastric fluid. The composition of the invention may further comprise acidic substances, preferably organic

acids (e.g. tartaric acid, citric acid) to increase the gas generation in fed conditions even when the gastric pH is substantially increased, i.e. in presence of high fat meals. The acid source may be one or more of an edible organic acid, a salt of an edible organic acid, an edible mineral acid, a salt of an edible mineral acid or mixtures thereof.

[0098] Although application of the present invention has not to be limited to any medicament or class of medicaments. The drug may be pharmacologically or chemotherapeutically active itself, or may be converted into a pharmacologically or chemotherapeutically active species by a chemical or enzymatic process in the body (prodrug). The floating solid dosage forms of this invention are particularly useful for drugs which have narrow absorption window, drugs having a higher solubility in the stomach than in the intestine, drugs having a local action in the stomach or drugs absorbed by a saturable transport process.

[0099] Illustrative examples of drugs that are predominately absorbed from the upper part of the gastrointestinal tract include ofloxacin, ciprofloxacin, metoprolol, oxprenolol, allopurinol, baclofen, cyclosporin, sumatriptan, benazepril, enalapril, quinapril, imidapril, benazeprilat, cilazapril, delapril, moexipril, indolapril, olindapril, retinapril, pentopril, perindopril, altiopril, ramipril, spirapril, lisinopril, zofenopril, captopril and the like.

[0100] Advantageously, the present invention can be used for drug substances active against *Helicobacter pylori* like bismuth salts such as rantidine bismuth

citrate, bismuth subsalicylate, tripotassium dicitratobismutate and the like; H-2 receptor antagonists such as cimetidine, ranitidine, famotidine, nifentidine, roxatidine, nizatidine, bifentidine, 5 erbrothidine and the like ; antacids like aluminium hydroxide, magnesium oxide, magnesium carbonate and the like ; cytoprotective agents such as misoprostol, carbenoxolone sodium, sucralfate and the like ; antimuscarinic agents like propantheline bromide, 10 pirenzepine , telenzepine and the like ; antibiotics and anti-parasite agents such as amoxycillin, clarithromycin, minocycline, tetracycline, metronidazole and the like.

[0101] Advantageously, the present invention can be 15 used for drug substances having higher solubilities in acidic pH or one with absorption site in upper part of the gastro-intestinal tract and those that are subjected to gastrointestinal first pass metabolism.

[0102] These are antihypertensive agents like 20 nicardipine, nimodipine, amlodipine, nifedipine, verapamil, diltiazem, cinnarizine, propranolol, atenolol, prazosin, ketanserin, hydralazine, guanabenz acetate, carvedilol and the like ; Antivirals like acyclovir, inosine pranobex, gancyclovir, zidovudine, 25 vidarabine, tribavirin and the like ; lipid lowering agents like atorvastatin, pravastatin, simvastatin, lovastatin and the like ; And others therapeutic agents like ascorbic acid, folic acid, riboflavin, cyanocobalmin, prednisolone, diazepam, levodopa, 30 methyldopa, carbidopa, isosorbide, quinidine, sotalol, theophylline, salbutamol, alendronate, glipizide, metformine, prazosin, ketanserin, selegiline,

midalozam, mriseofulvine, terfenadine aspirin, Ibuprofene, Diclofenac, Indomethacine and Ketoprofene. Advantageously, the drug itself or its pharmacologically active salt, ester or pro-drug can be used in the present invention. Moreover, combination of two or more active drugs or doses combinations may be included as the drug component. In this case, the release of each active ingredient may be identical or different (for instance combination of two active ingredients in which the first one is presented as an immediately release form and the second one as a controlled release. Similarly, a combination of immediate release and controlled release form may also be obtained for the same active ingredient, in order to provide a rapid and sustained effect.

[0103] The floating granules compositions according to this invention are preferably compressed into mini-tablets, whose composition and individual size characteristics permit also to modulate both the floating and the dissolution properties of the dosage form.

[0104] Mini-tablets can be present as single layered or multi-layered dosage forms in order to separate different active ingredients or dosages of active ingredient(s).

[0105] Pellets but preferably mini tablets obtained after compression are preferably filled into hard gelatin capsule, hydroxypropylmethyl-cellulose (HPMC) or other pharmaceutically acceptable capsules in order to obtain multiple-unit sustained-release floating dosage form.

[0106] The present invention relates to floating sustained-release granulated systems which are able to float on the surface of aqueous fluids and delivering one or more therapeutic agents incorporated therein
5 over an extended period of time. A sustained release or controlled release composition is a composition suitable for a once-a-day or a twice-a-day administration in mammals, preferably in human.

[0107] Granulates are made by melt granulation in a high shear mixer. Melt granulation is a low cost very short solvent-free process, consisting in the blending of the drug and at least the fusible binder and the gas generating agent. The fusible binder presents the property to be solid or pasty (semi-solid) at ambient
15 temperature (20-25°C) and to become liquid at the temperature of the process (30°C to 90°C), so playing the role of granulating liquid. concentrations. Granulates can be compressed, pelletized, or filled into capsules. Optionally a step of sieving of
20 granulates can be added before compression.

[0108] Granulates can be incorporated in a one, two or multiple layered minitabets. Pellets and minitabets made by this process can be coated by hydrophilic, hydrophobic or inert, pH dependent or
25 independent coating agents.

[0109] Minitabets present a diameter comprised between are contained between 1 and 7 mm, in order to design a multi-particulate pharmaceutical dosage form. Minitabets can be filled into hard gelatin capsule or
30 hypromellose capsules with or without disintegrating agent (for example: Ac-Di-Sol®, croscarmellose sodium NF, FMC Corporation, Philadelphie). When it's

necessary, the disintegrant prevents the mini-tablets from sticking when hydrocolloid is swelling into capsule and thus, reduce the variability in drug diffusion through mini-tablets.

5 **[0110]** Pellets present a diameter between 0.5 and 2 mm, preferably between 0.7 and 1.5 mm.

The new compositions described here are multiple-units dosage form for reasons described above. Multiple units in the present invention refers to a pharmaceutical
10 form (which can be monolithic like a capsule or a tablet)but containing several separate units (granulates, pellets, mini tablets) which will be released once the pharmaceutical form is in contact with gastro-intestinal fluids. Examples of those forms
15 are mini tablets contained in a capsule, pellets contained in a capsule, pellets compressed to form a tablet, granulates in a capsule, granulate in a sachet,...

[0111] It's supposed that the Gastric Residence Time
20 of the compositions of the invention depends on presence of food like all floating forms. In fed condition, the gastric mixing is increased and the peristaltic movements are decreased. These physiological processes allow the floating of dosage
25 form.

[0112] The present invention preferably consists of one-layered mini tablets obtained by compression. Granulates contain at least one drug, at least one fusible (meltable) binder, one or more gas generating
30 agents, and optionally hydrophilic or lipophilic diluent(s) or inert diluent(s), preferably swelling (hydrocolloid) agent(s). Pellets, granulates or mini

tablets may be coated with a suitable coating layer to help to control the drug release.

[0113] These dosage forms have sufficient
5 mechanical stability and hardness so that they will withstand the normal stress of production, packaging and dispensing.

[0114] The optimum concentration of therapeutic agent depends of its physical properties, chemical properties
10 and its optimum therapeutic dosage.

[0115] The fusible (binder concentration depends of its capabilities of binding the different powders present in the mix and the drug release properties pursued. The content of the gas generating agents and
15 the one of the several diluents, especially the hydrocolloid vary with the floating properties and the drug release capabilities pursued. The amount and the composition of the coating depend on the floating properties and the drug release capabilities pursued.

20 [0116] The fusible binder of the invention may be any lipophilic, hydrophilic or amphiphilic agent having a melting range between 30 and 80°C, preferably between 45°C and 65°C and which can act as binder during the melt granulation process. Lipidic agents have to be
25 solid at ambient temperature. The HLB values of lipidic diluents and lipidic binders can be between 0 and 7, preferably around 2. They have to be chemically inert and safe for humans and animals.

[0117] The fusible binder may be present in an amount
30 from about 5% to about 80%, preferably from about 10% to about 50%, and more preferably from about 12 to

about 20%, by weight of the total weight of the composition.

[0118] Optionally, a lipidic diluent may be present in an amount from about 0% to 80%, preferably from about 0% to about 20%, and more preferably from about 0% to about 10%, by weight of the total weight of the composition.

[0119] Every agent or every mixture of agents that can produce carbon dioxide in the presence of water or gastro intestinal fluids can be used as gas generating agents. Particle sizes of these agents are preferably not too big ($< 500 \mu\text{m}$, preferably inferior to $200 \mu\text{m}$) to avoid production of too big bubbles of gas, which can reduce the system cohesion. The association of acid substances permits to allow the gas generation in fed conditions even when the gastric pH is substantially increased by creating a micro acid pH area just around minitablets borders.

[0120] The gas generating component such as carbonates and bicarbonates may be present in amounts from about 0.5% to about 50%, preferably from about 3% to about 20%, an more preferably from about 3% to about 15%, by weight of the total weight of the composition.

The acid source may be present in an amount from about 0% to about 50%, preferably from about 0.5% to about 10%, and more preferably from about 1% to about 3%, by weight of the total weight of the composition.

[0121] Swellable agents hydrate and form viscous barrier when they are in contact with aqueous fluids, including gastric juice. The hydrocolloid agent preserves the system cohesion, traps the carbone

dioxide to acquire a dosage form density lower than one (1 g/ml) and provides a sustained-release of the drug by both diffusion and erosion. Thus, the density of tablets or minitabets becomes lower than one (1 g/ml) when they are in contact with gastric fluid. The polymer is progressively hydrated and water diffusion into the dosage form and drug diffusion through the dosage form influence the drug release. The presence of lipidic agents may also slow down the water diffusion and thus, the drug release. Inert agents, as Ethylcellulose or Cellulose acetate, have the same effect on water diffusion as lipidic agents. The swelling or gelling agent that can be used are gum arabic, Carrageenan, Guar gum, Gum tragacanth, Agar, Sodium Carboxymethyl cellulose, Hydroxyethyl cellulose, Hydroxypropylmethyl cellulose, Sodium alginate, Chitosan, Xanthan gum, Sodium croscarmellose, pectin [2, 4].

[0122] The swelling agent may be present in an amount from about 0% to about 80%, preferably from about 0% to about 50%, and more preferably from about 0% to about 25%, by weight of the total weight of the composition. To retain the gas generated in the composition, a non-toxic film coating may be preferably used. The composition and the level of the coating influence the dissolution rate of the active drug. The coating composition comprises at least one coating agent which may be, but is not limited to, any water insoluble polymer derivative of acrylic acid, any water insoluble polymer derivative of cellulose or a wax, a plasticizer, a detackifying agent, an anti-foam, or the

likes. All additives commonly used in coating composition may be used.

[0130] As used herein, the term "coating composition" refers to a mixture of designated compounds that when
5 applied to the surface of the pharmaceutical dosage form produces a coating layer through which the drug is released.

[0131] As used herein, the term "plasticizer" refers to a component of the coating composition that has a
10 low vapor pressure and whose presence in the composition modifies the flexibility and diffusion properties of the coating composition.

[0132] As used herein, the term "detackifying agent" refers to a compound whose presence in the coating
15 composition reduces the stickiness or adhesion of the coated dosage form.

[0133] Depending on the pharmaceutical form and the floating and dissolution properties required, all water insoluble coating agents commonly used may be employed
20 alone or in combination, preferably acrylic polymers or cellulosic, more preferably insoluble pH-independent acrylic polymers (e.g. EUDRAGIT ® RL, RS or NE30D). The coating agents may be available as aqueous or organic dispersions, as a powder or as granules. The amount of
25 film-coating materials should not be limited because they vary with the kind or the amount of additives. The amount of dry coating (expressed as a weight percentage of the uncoated dosage form) may be comprised between 5% and 50%, preferably between 15 and 25% (w/w).

[0134] The detackifying agent may be, but is not
30 limited to talc, aluminium hydrate, glyceryl monostearate, kaolin, and the like, or mixtures thereof

and is used principally to reduce the incidence of tablet-to-tablet sticking that can occur during the film coating of pharmaceutical tablets and the like when aqueous dispersions are used. Preferably, the
5 anti-agglomerating agent comprises about 5% to 50% by weight of the dry coating composition.

[0135] The plasticizer may be but is not limited to a derivative of the groups consisting of phthalic esters, citric esters, phosphoric esters, of acid esters, oils,
10 oleic acid, stearic acid, cetylic acid, myristic acid, propylen glycol, glycerin, polyethylene glycol having a molecular weight in the range of 200 to 800, and the like or a mixture of thereof. Preferably, the amount plasticizer is between 0% to about 20% by weight of the
15 dry coating composition.

[0136] Additives commonly used in coating dispersion are pigments, water-soluble materials, less water-soluble materials, no water-soluble materials, pore-forming agents. Their amount in the coating
20 composition, if any, depends on the physicochemical properties required.

[0137] Lactose may be used as a hydrophilic diluent. Other suitable diluents are mannitol, sorbitol, glucose, microcrystalline cellulose, gelatin, starch,
25 dicalcium phosphate, PVP, and all hydrophilic or lipophilic diluents which have no toxicity and are compatibles with other agents present in the granulation mixture.

[0138] Hydrophilic, lipophilic or inert, pH-depedent
30 or -independent coating agents can be used.

[0139] There may also be incorporated into these sustained-release formulations additional edible non-

toxic ingredients recognized in pharmaceutical compounding such as excipients, preservatives, stabilisers and tableting lubricants.

[0140] The choice, the amount and/or the composition
5 of each agents described above depend on the pharmaceutical dosage form properties wanted by the formulator.

[0141] A swellable agent and a coating can possibly
10 be used together to retain the generated gas inside the dosage form.

[0142] The procedure of making unit dosage form includes at least two steps.

[0143] The first step consists in the manufacturing
of granulates or pellets by melt granulation. The
15 granules or pellets are, for instance, made in a high shear mixer by using the appropriate operating conditions. A high shear mixer is equipped with a bowl containing the mix, an impeller to mix, a chopper to break agglomerates, an optionally with infra-red
20 temperature detector (it's also possible to use a borer directly in contact with the mix), an air inlet (it's possible to regulate the air flow) and sometimes with a heating jacket. During the process, a computer records the temperature, the impeller speed (IS), the chopper
25 speed (CS) and the resistance supported by the impeller during the mix. This resistance is called "the torque". A jump of the torque, because of the melting of the lipidic binder, indicates the formation of the granules. Then, IS is generally decreased and CS is
30 generally increased. From this moment, the massing time (MT) begins. The size of granulates increases by increasing the massing time. In order to reduce the

total duration of the process, to obtain granules having acceptable diameters and to avoid sticking, four parameters have to be controlled: the double-jacket temperature, the CS, the IS and the massing time. The
5 granules have to provide good flow properties.

[0144] After granulation, the granulates size distribution is measured by laser diffractometry, using a dry sampling system with a suitable SOP (Standard Operating Procedure), (Scirocco®, Mastersizer 2000,
10 Malvern, UK) to appreciate the size distribution.

[0145] The second step consists to fill granulates into capsules or compress them into tablets or mini tablets. Tablets and mini tablets can be manufactured by using an alternative or rotative tableting machines.

15 The choice of the punch determines the tablet's diameter. The punches can be convex or flat.

[0146] All excipients generally used for compression process can be employed.

[0147] When a coating is needed, the detackifying
20 agent is previously dispersed in water in the presence of anti-foam and mixed with the others water-soluble additives commonly used in coating composition. All the components of the coating dispersions have to be blended. The stirring may be continued for one hour
25 before starting the coating process. The tablets or, preferably mini tablets, are transferred in a suitable coating apparatus. The coating parameters depend on the physicochemical properties required.

[0148] The mini tablets (800g) were transferred into
30 a fluidized bed coating apparatus (Uni-Glatt, Glatt GmbH, Germany) equipped with a bottom-spray coating process in a Würster column. During the coating

operations, the coating dispersion has to be stirred continuously to prevent sedimentation of insoluble particles. The inlet and outlet temperatures of the drying air were $40\pm 2^{\circ}\text{C}$ and $32\pm 2^{\circ}\text{C}$, respectively. The
5 coating dispersion was pumped at a flow rate of 5ml/min and the pneumatic spraying pressure was 1 bar. The total weight of the coating dispersion sprayed on the mini tablets was 1450g. The coated mini tablets were then dried in the same apparatus for 10min at the
10 above-mentioned temperatures. The coated tablets or mini tablets may be cured or not.

[0149] Up to 1990, bulk density and floating duration have been the main parameters used to describe the adequacy of the dosage forms buoyancy (= floating
15 properties). However, Those parameters don't reflect the magnitude of the floating forces produced by the dosage form [25]. In 1990, J. Timmermans has proposed the resultant-weight measurement concept and an in vitro measuring apparatus was conceived.

20 **[0150]** The total force acting on an immersed object, F , can be given by this equation :

$$F = F_{\text{buoy}} - F_{\text{grav}}$$

F_{buoy} is the buoyant force and F_{grav} is the gravity force exerted on the object [26]

25 **[0151]** Conventionally, F is positive when the object floats and F is negative when the object sinks. The resultant-weight apparatus measures F values as a function of time. When these values are divided by the experimental weighing, it possible to obtain the
30 resultant-weight values in percent.

[0152] The resultant-weight apparatus comprises a balance, a force transmitter device (FTD), a test bath

(the bath temperature can be regulate), a liquid level compensating system, a digital/analog converter and a recorder (computer) [reference 26]

[0153] The interfering factors can be the temperature
5 of electromagnetic measuring module, the draft and room ventilation, the magnetization of LTD, the surface tension of test solvent, the fluid density, air bubble adherence onto FTD, liquid level lowering by evaporation and the condensation of solvent vapour onto
10 the FTD [reference 26].

[0154] With this method, it's possible to evaluate the lag time (time period between placing the pharmaceutical composition in the medium and its floating), the maximal system magnitude and the
15 floating duration.

[0155] The medium used for resultant-weight measurement is a HCl 0.1N solution containing 0.05% (w/v) of Polysorbate 20 (pH 1.2, 37°C).

[0156] The lag time can also be measured by an other
20 way. Pharmaceutical dosage forms can be placed in a becher containing the medium and subjected to an horizontal shaking of 100 cycles per minute.

[0157] The medium used for this test is a HCl 0.1N solution containing 0.05% (w/v) of Polysorbate 20 (pH
25 1.2, 37°C).

[0158] Drug release can be evaluated by usual measurement processes as a dissolution testing by UV spectrophotometry or HPLC analysis. In this case, dissolution studies were carried out using a Distec
30 2100C USP 29 dissolution apparatus (Distec Inc., North Brunswick, NJ, USA) Type II (paddle method). Dipotassium hydrogen phosphate/Acetic acid (0.05M each)

buffer solutions containing 0.05% (w/v) Polysorbate 20 were used as the dissolution fluid at suitable pHs. The volume and temperature of the dissolution medium were 900ml and $37.0 \pm 0.2^\circ\text{C}$, respectively. The drug releases
5 from tablets or minitables was determined at a suitable wavelength, using an Agilent 8453 UV/visible Dissolution Testing System (Agilent, USA). The percentages of drug release were measured at fixed time intervals and averaged ($n=5$).

10 **[0159]** The present invention is illustrated by, but is by no means limited to, the following examples.

[0160] The examples described below were realized by using levodopa, ciprofloxacin and riboflavin as models of drugs which are absorbed in the upper part of small
15 intestine.

[0161] Levodopa is used for the treatment of Parkinson's disease. Parkinson disease is a progressive neurological disorder with a prevalence of 1-2% in people over the age of 50. It has a world-wide
20 distribution and has no gender preference [reference 28].

[0162] Ciprofloxacin is a broad spectrum, fluoroquinolone antibiotic that is administered every 12h to treat a wide range of bacterial infections.
25 Design of such an once daily dosage form with conventional sustained-release is problematic because ciprofloxacin is poorly absorbed in the terminal part of the small intestine and in the colon.

EXAMPLES OF PREFERRED EMBODIMENTS**Example 1**

5

[0163] Example 1 illustrates the influence of the minitabulet diameter on the drug release profiles and the floating properties. The pharmaceutical composition is given in Table 1.

10 TABLE 1

Ingredients	% w/w
Levodopa	37.5
Glyceryl palmito-stearate (Precirol®)	12.0
Calcium carbonate	10.0
15 Sodium bicarbonate	4.0
Tartaric acid	3.0
Hydroxypropyl methylcellulose (Methocel® K15M)	25.0
Lactose 450mesh	8.5

20 [0164] During the granulation step, the double-jacket temperature of the mixer was set at 60°C. Before the formation of the granulates, the IS was set at 1800rpm and the CS was set at 130rpm. After the formation of the granulates, the IS is decreased at
25 600rpm and the CS is increased at 2000rpm. Massing time was fixed to 5 minutes.

[0165] Mini tablets were prepared by compression of granulates. Table 2 shows the weight and the hardness of the mini tablets in function of their
30 diameter. The hardness was measured in accordance to the method described in the European Pharmacopoeia (chapter 2.9.8 - resistance to crushing of tablets)

TABLE 2

	Diameter	Weight (mg)	Hardness (Newton)
	3mm	20.0	14
5	4mm	40.0	22
	5mm	60.0	not performed

[0166] The mini-tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP 29 Apparatus II with paddle speed at 60rpm. The dissolution results are given in Figure 1.

[0167] Lag time was visually determined for each diameter by using the horizontal shaking method described above. Results are shown in Table 3.

TABLE 3

3 mm	4 mm	5 mm
1 min	16 min	45 min

[0168] Resultant-weights were recorded as a function of time by using the apparatus described above. Results are shown in Figure 2.

Example 2

[0169] Example 2 illustrates the influence of the pharmaceutical composition on the drug release profiles and on the floating properties. The pharmaceutical compositions are given in Table 4.

TABLE 4

Indredients	Formulations	1	2	3	4
		<u>% w/w</u>			
	Levodopa	37.5	37.5	37.5	37.5
5	Glyceryl palmito-stearate (Precirol®)	12.0	12.0	12.0	12.0
	Glyceryl behenate (Compritol®)	0.0	0.0	0.0	6.0
	Calcium carbonate	10.0	10.0	5.0	5.0
	Sodium bicarbonate	4.0	4.0	4.0	4.0
10	Tartaric acid	3.0	3.0	3.0	3.0
	Hydroxypropyl methylcellulose (Methocel® K15M)	25.0	15.0	15.0	15.0
	Lactose 450mesh	8.5	18.5	23.5	17.5

15 **[0170]** Suitable parameters (described above) were applied to granulate these formulations by melt granulation. Granulates were filled into the die of an instrumented single-punch tableting machine to produce mini tablets, using 4 mm concaved-face punches and

20 dies. The weight and the hardness were kept constant and were 40mg and 22N, respectively.

[0171] The mini tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP

25 29 Apparatus II with paddle speed at 60rpm. The dissolution results are given in Figure 3.

[0172] Lag time was determined visually for each formulation by using the horizontal shaking method described above. Results are shown in Table 5.

TABLE 5

Formulation 1	Formulation 2	Formulation 3	Formulation 4
16 min	1 min	25 min	1h 15min

[0173] Resultant-weights were recorded as a
 5 function of time by using the apparatus described
 above. Results are shown in Figure 4.

Example 3

10 [0174] Example 3 illustrates the influence of the
 composition of the core, in the case of coated
 minitables, on the drug release profiles and the
 floating lag time. The pharmaceutical compositions of
 the cores and the formulation used for the coating are
 15 given in Table 6.

TABLE 6

Core Formulation 1

20		<u>% w/w</u>
	Levodopa	37.5
	Glyceryl palmito-stearate (Precirol®)	12.0
	Calcium carbonate	10.0
	Sodium bicarbonate	4.0
25	Tartaric acid	3.0
	Lactose 450mesh	33.5

	Core Formulation 2	% w/w
	Levodopa	37.5
	Glyceryl palmito-stearate (Precirol®)	12.0
5	Calcium carbonate	5.0
	Sodium bicarbonate	4.0
	Tartaric acid	3.0
	Lactose 450mesh	38.5
10	Core Formulation 3	% w/w
	Levodopa	37.5
	Glyceryl palmito-stearate (Precirol®)	12.0
	Calcium carbonate	1.7
	Sodium bicarbonate	1.36
15	Tartaric acid	1.02
	Lactose 450mesh	46.42
	Coating Formulation	
	EUDRAGIT RL 30D (dry basis)	200g
20	Citroflex 2	40g
	Talc	50g
	Antifoam	2g
	Water	842g
	Coating level (%)	20
25	(expressed as a weight percentage of the uncoated dosage form)	
	[0175] Suitable parameters (described above) were applied to granulate these formulations by melt granulation. Granulates were filled into the die of an	
30	instrumented single-punch tableting machine to produce mini tablets, using 3 mm concaved-face punches and	

dies. The weight and the harness were kept constant and were 20mg and 7N, respectively.

[0176] To perform the coating, the inlet temperature, the flow rate, the pneumatic spraying pressure and the total spraying time were controlled.

[0177] The mini tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP 29 Apparatus II with paddle speed at 50rpm. The dissolution results are given in Figure 5.

[0178] Lag time was determined visually for each formulation by using the horizontal shaking method described above. Results are given in Table 7.

TABLE 7

Formulation 1	Formulation 2	Formulation 3
10 min	9 min	120 min

Example 4

[0179] Example 4 illustrates the influence of the coating level, on the drug release profiles and the floating lag time in the case of coated mini-tablets. The pharmaceutical compositions of the core and the formulation used for the coating are given in Table 8.

TABLE 8

Formulation of the core		% w/w
25	Levodopa	37.5
	Glyceryl palmito-stearate (Precirol®)	12.0
	Calcium carbonate	10.0
	Sodium bicarbonate	4.0
	Tartaric acid	3.0
30	Lactose 450mesh	33.5

Formulation used for the coating

	EUDRAGIT RL30D (dry basis)	200g
	Citroflex 2	40g
5	Talc	50g
	Antifoam	2g
	Water	842g
	Coating level (%)	0 - 11 - 15 - 20
10	(expressed as a weight percentage of the uncoated dosage form)	

[0180] Suitable parameters (described above) were applied to granulate these formulations by melt granulation. Granulates were fed into the die of an instrumented single-punch tableting machine to produce mini-tablets, using 3 mm concaved-face punches and dies. The weight and the hardness were kept constant and were 20mg and 7N, respectively.

[0181] To perform the coating, the inlet temperature, the flow rate, the pneumatic spraying pressure and the total spraying time were controlled.

[0182] The mini-tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP 29 Apparatus II with paddle speed at 50rpm. The dissolution results are given in Figure 6.

[0183] Lag time was determined visually for each coating level by using the horizontal shaking method described above. Results are given in Table 9.

TABLE 9

Coating level (%)	0	11	15	20
Lag time (min)	Early breaking	7	5	10

Example 5

[0184] Example 5 illustrates the influence of the formulations used for the coating, in the case of coated mini-tablets, on the drug release profiles and the floating lag time. The pharmaceutical composition of the core and the formulations used for the coating are given in Table 10.

10 TABLE 10

Formulation of the core

	% w/w
Levodopa	37.5
Glyceryl palmito-stearate (Precirol®)	12.0
15 Calcium carbonate	10.0
Sodium bicarbonate	4.0
Tartaric acid	3.0
Lactose 450mesh	33.5

Formulations used for the coating

20 Coating 1 Coating 2 Coating 3

Acrylic polymer			
(dry basis)	200g	200g	200g
Methocel® E5	0g	20g	40g
Citroflex 2	40g	40g	40g
25 Talc	50g	50g	50g
Antifoam	2g	2g	2g
Water	842g	822g	802g
Coating level (%)	20	20	20
(expressed as a weight percentage of the uncoated			
30 dosage form)			

[0185] Suitable parameters (described above) were applied to granulate this formulation by melt granulation. Granulates were filled into the die of an instrumented single-punch tableting machine to produce
5 mini-tablets, using 3 mm concaved-face punches and dies. The weight and the harness were kept constant and were 20mg and 7N, respectively.

[0186] To perform the coatings, the inlet temperature, the flow rate, the pneumatic spraying
10 pressure and the total spraying time were controlled.

[0187] The mini-tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP
29 Apparatus II with paddle speed at 50rpm. The
15 dissolution results are given in Figure 7.

[0188] Lag time was determined visually for each formulation used for the coating by using the horizontal shaking method described above. Results are shown in Table 11.

20

TABLE 11

Percentage of Methocel® E5 used in the coating	0 %	10 %	20 %
Lag time (min)	10	13	13

Example 6

25

[0189] Example 6 illustrates the fact that it is possible to obtain a sustained-release profile with several different drugs. The pharmaceutical compositions are given in Table 12.

TABLE 12

Formulation 1		% (w/w)
	Levodopa	37.5
5	Glyceryl palmito-stearate (Precirol®)	12.0
	Calcium carbonate	10.0
	Sodium bicarbonate	4.0
	Tartaric acid	3.0
	Hydroxypropyl methylcellulose	
10	(Methocel® K15M)	25.0
	Lactose 450 mesh	8.5
Formulation 2		% (w/w)
	Ciprofloxacin	31.25
15	Glyceryl palmito-stearate (Precirol®)	18.0
	Calcium carbonate	10.0
	Sodium bicarbonate	4.0
	Tartaric acid	3.0
	Hydroxypropyl methylcellulose	
20	(Methocel® K15M)	25.0
	Lactose 450 mesh	8.75
Formulation 3		% (w/w)
	Riboflavin	5.0
25	Glyceryl palmito-stearate (Precirol®)	12.0
	Calcium carbonate	10.0
	Sodium bicarbonate	4.0
	Tartaric acid	3.0
	Hydroxypropyl methylcellulose	
30	(Methocel® K15M)	25.0
	Lactose 450 mesh	41.0

[0190] Suitable parameters (described above) were applied to granulate these formulations by melt granulation. Granulates were fed into the die of an instrumented single-punch tableting machine to produce minitables, using 4 mm concaved-face punches and dies. The weights were kept constant and were 40mg.

[0191] The mini-tablets were tested for dissolution in a di-potassium hydrogen phosphate/acetic acid (0.05M each) buffer solution at pH 3.0 using USP 29 Apparatus II with paddle speed at 50rpm. The dissolution results are given in Figure 8.

[0192] Lag time was determined visually for each formulation by using the horizontal shaking method described above. Results are shown in Table 12.

TABLE 12

Drugs	Levodopa	Ciprofloxacin	Riboflavin
Lag time (min)	16	7	0.5

Exemple 7

[0193] Example 7 illustrates some results obtain after an in vivo study on human volunteers. The aim of this investigation was to evaluate the intragastric buoyant properties of the floating sustained-release mini-tablets using fasted and fed healthy volunteers. Riboflavin was chosen as drug tracer because its absorption occurs mainly in the proximal small intestine. It has been establish by Levy et al., 1971 [reference 27] that all variations in gastric transit time for a dosage form containing riboflavin affect both the absorption rate of the compound and the

quantity absorbed. This allows indirect demonstration of an increase in the residence time of the dosage form above the absorption area: any increase of the gastric residence time of the dosage form increases the quantities of absorbed and thus eliminated riboflavin. To assess the usefulness of the intragastric buoyancy properties of the floating mini-tablets (FMT), non-floating mini-tablets (NFMT) with in vitro riboflavin release profiles equivalent to the floating mini-tablets prepared. The mini-tablets compositions are shown in Table 13.

TABLE 13

Formulations (% w/w)

Floating minitables		
15	Sodium riboflavin-5'-phosphate	5
	Glyceryl palmito-stearate Precirol®	12
	Calcium carbonate	10
	Sodium bicarbonate	4
	Tartaric acid	3
20	Methocel® K15M	25
	Lactose 450 mesh	41
Non floating minitables		
	Sodium riboflavin-5'-phosphate	5
25	Glyceryl palmito-stearate Precirol®	18
	Methocel® K15M	55
	Lactose 450 mesh	22

[0194] As shown in Figure 9, when compared to the NFMT, the cumulative urinary excretions tends to be higher after administration of the FMT, whether the ingestion protocol is fasted or fed, with this trend

increasing under fed condition. Moreover, the amount of riboflavin in urine increases more particularly following ingestion of food. This increasing is characteristic of the behaviour of a floating form.

5 **[0195]** As shown in Figure 10, the maximal urinary excretion rate (UER) values for the FMT were higher than the NFMT, whether the ingestion protocol was fasted or fed. Furthermore, in both groups, the time needed to reach the maximal UER value (Tmax) was
10 delayed with the FMT in comparison with that one of the NFMT. Indeed, under the fasted condition, Tmax was delayed for 2h, while it was delayed for 3h by feeding. Compared to the UER curve corresponding to the NFMT, the one obtained with the FMT was more evenly
15 distributed, especially in the fed condition. This suggests that the FMT might be able to float on the stomach juice sufficiently in the fed condition to increase the GRT and delay drug arrival at the absorption site.

20

Example 8

[0196] This example shows the pharmaceutical composition of floating sustained-release pellets when
25 the active ingredient is ciprofloxacin hydrochloride (Table 14).

TABLE 14

	Indredients	% w/w
	Ciprofloxacin HCl	55.0
5	Glyceryl palmito-stearate (Precirol®)	15.0
	Glyceryl behenate (Compritol®)	22.0
	Sodium bicarbonate	8.0

[0197] During the granulation step, the double-jacket temperature was set at 50°C. Before the formation of the granulates, the IS was set at 1800rpm and the CS was set at 130rpm. After the formation of the granulates, the IS is decreased at 800rpm and the CS is increased at 4000rpm to form pellets. Massing time was fixed to 12 minutes.

[0198] To perform the coatings, the inlet temperature, the flow rate, the pneumatic spraying pressure and the total spraying time were controlled.

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WHAT WE CLAIM IS :

1. An oral pharmaceutical multiple units controlled
5 release floating composition comprising :
 - At least one drug containing system selected from the group consisting of (I) unit forms selected from granules, mini tablets, tablets and pellets comprising at least one active drug,
10 one fusible binder and one gas generating agent, and (II) multiple unit forms comprising or formed by more than one of said unit forms, and
 - either a coating layer surrounding one or more of said drug containing system, said coating
15 layer comprising a water insoluble polymer and/or one or more drug containing systems further comprise a swelling agent.
2. The composition of claim 1, in which the unit form comprises a core comprising at least one active drug,
20 one fusible binder, one gas generating agent and a swelling agent.
3. The composition of claim 1 further comprising an organic acid, advantageously in one or more unit forms.
- 25 4. The composition of claim 1 wherein the fusible binder has a melting point or a melting range lower than 95°C, preferably lower than 80°C, preferably between 30 °C and 75°C, more preferably between 45 °C and 55°C.
- 30 5. The composition of claim 1 wherein the fusible binder has a HLB value lower than 7.

6. The composition of claim 1 wherein the weight ratio between the fusible binder and the gas generating agent, advantageously in the unit form, is about 0.1 to 10, preferably from 0.2 to 5, most preferably from 0.5 to 2.
7. The composition of claim 1, in which the unit forms have a weight average size from 0.2mm and 7mm, advantageously between 0.3 and 5mm, preferably between 0.4 and 3mm.
8. The composition of claim 1 wherein the unit forms are compressed into tablets or mini tablets or comprised in a capsule forming a multiple unit form.
9. The composition of claim 1 wherein the multiple unit form is a capsule or a tablet comprising the granules, pellets or mini tablets.
10. The composition of claim 8 or 9, which comprises several granules, mini tablets and/or pellets.
11. The composition of claim 1 wherein the fusible binder is selected from the group consisting of fats, waxes, fatty alcohols, cetyl alcohol, stearyl alcohol cetostearyl alcohol or fatty alcohols with more than 18 carbon atoms), fatty acids (preferably palmitic acid, or fatty acids with more carbon atoms such as stearic acid, behenic acid, etc.), glycerol esters (e.g. mono-, di-, and tri-glycerides, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate), ethers of fatty alcohols, esters of fatty acids, hydrogenated oils, polyethylene glycols (PEGs), polyoxyethylenated derivatives, phospholipids, derivatives thereof and mixtures thereof.

12. The composition of claim 1 wherein the gas generating agent is selected from the group consisting of sodium and potassium hydrogen carbonate, calcium carbonate, sodium glycine carbonate, sulphur dioxide, sodium sulfite, sodium bisulfite, sodium metabisulfite, and combinations thereof.
13. The composition of claim 1 further comprising a second gas generating agent.
14. The composition of claim 3 wherein the organic acid is selected from the group consisting of tartaric acid, citric acid, ascorbic acid and combinations thereof.
15. The composition of claim 1 wherein the water insoluble coating polymer is selected from the group consisting of water insoluble acrylic polymers, water insoluble cellulosic polymers, waxes and combinations thereof.
16. The composition of claim 1 wherein the swelling agent is selected from the group consisting of gum arabic, Carrageenan, Guar gum, Gum tragacanth, Agar, Sodium Carboxymethyl cellulose, Hydroxyethyl cellulose, Hydroxypropylmethyl cellulose, Sodium alginate, Chitosan, Xanthan gum, Sodium croscarmellose, pectin and combinations thereof.
17. The composition of claim 1 suitable for a once-a-day or twice-a-day administration in humans.
18. The composition of claim 1 wherein several unit forms are filled into a pharmaceutically acceptable capsule, preferably a hard gelatine capsule or hypromellose capsule.

19. The composition of claim 1 further comprising an immediate release form of the same active drug or of another active agent.
20. The composition of claim 1 comprising a
5 combination of two or more active drugs.
21. The composition of claim 20 wherein one drug presents a first controlled release profile, while the other drug presents a release profile different from the first controlled release profile,
10 advantageously an immediate release profile.
22. The composition of claim 1 further containing one or more classical pharmaceutical excipients like fillers, disintegrants, lubricants, pigments, anti-taching.
- 15 23. A unit form suitable for the preparation of a composition according to any one of the preceding claims, whereby said unit form is selected from the group consisting of granules, pellets and mini-tablets, said unit forms comprising at least one
20 active agent, one fusible binder and one gas generating agent, whereby the unit form is characterized in that the unit form further comprises a swelling agent and/or a coating layer surrounding the unit form or a combination of unit forms, said
25 coating layer comprising a water insoluble polymer.
24. The unit form of claim 23, said unit form having one or more characteristics as disclosed in any one of the claims 2 to 22.
25. A process for manufacturing composition of claim 1
30 comprising at least the step of mixing and melt granulating the drug, the fusible binder, a swelling agent and the gas generating agent together.

26. A process for manufacturing composition of claim 1 comprising at least
- a) the step of mixing and melt granulating the drug, the fusible binder and the gas generating agent together and
 - b) to compress the granulates into mini tablets or tablets
 - c) to coat the mini tablets or tablets with at least a water insoluble polymer.
27. A process for manufacturing composition of claim 1 or unit forms of claim 23 comprising at least
- a) the step of mixing, melt granulating and pelletized the drug, the fusible binder and the gas generating agent together and
 - b) to coat the pellets with at least a water insoluble polymer.
28. A process for manufacturing a composition of claim 1 or unit forms of claim 23 comprising at least
- the step of mixing the drug, the molten fusible binder and the gas generating agent together,
 - to form pellets or granules or beads or mini tablets from said mixture, and
 - to coat the pellets or granules or beads or mini tablets with at least a water insoluble polymer.

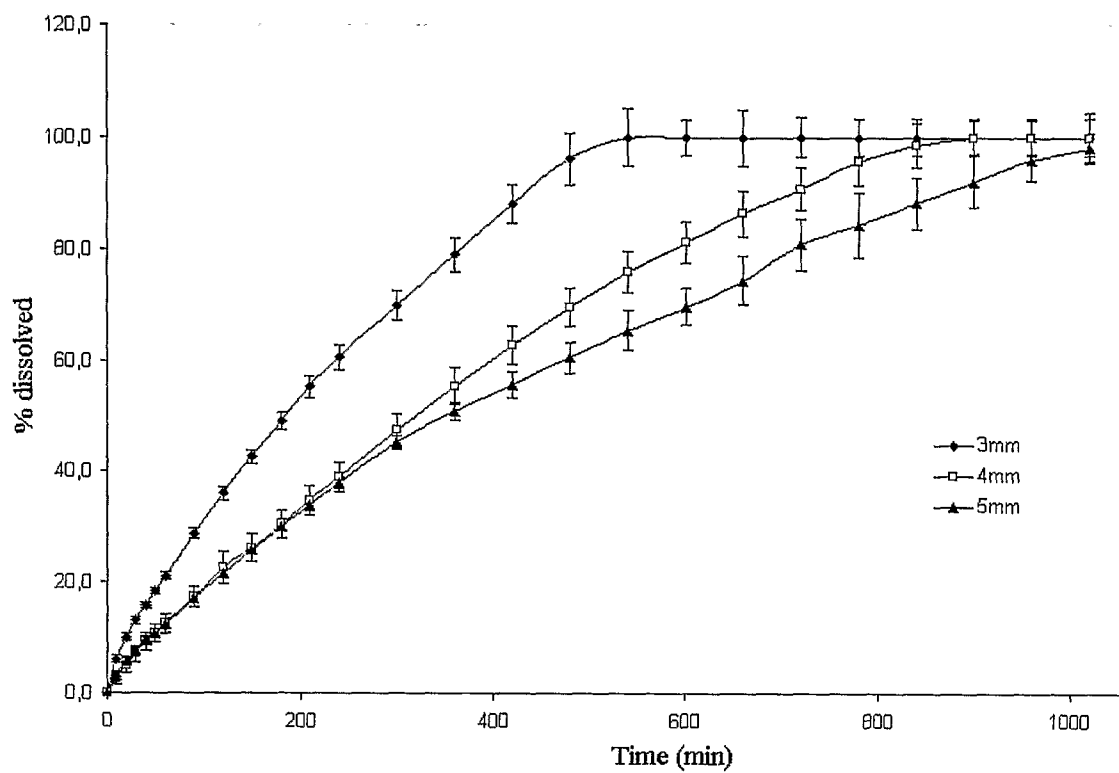
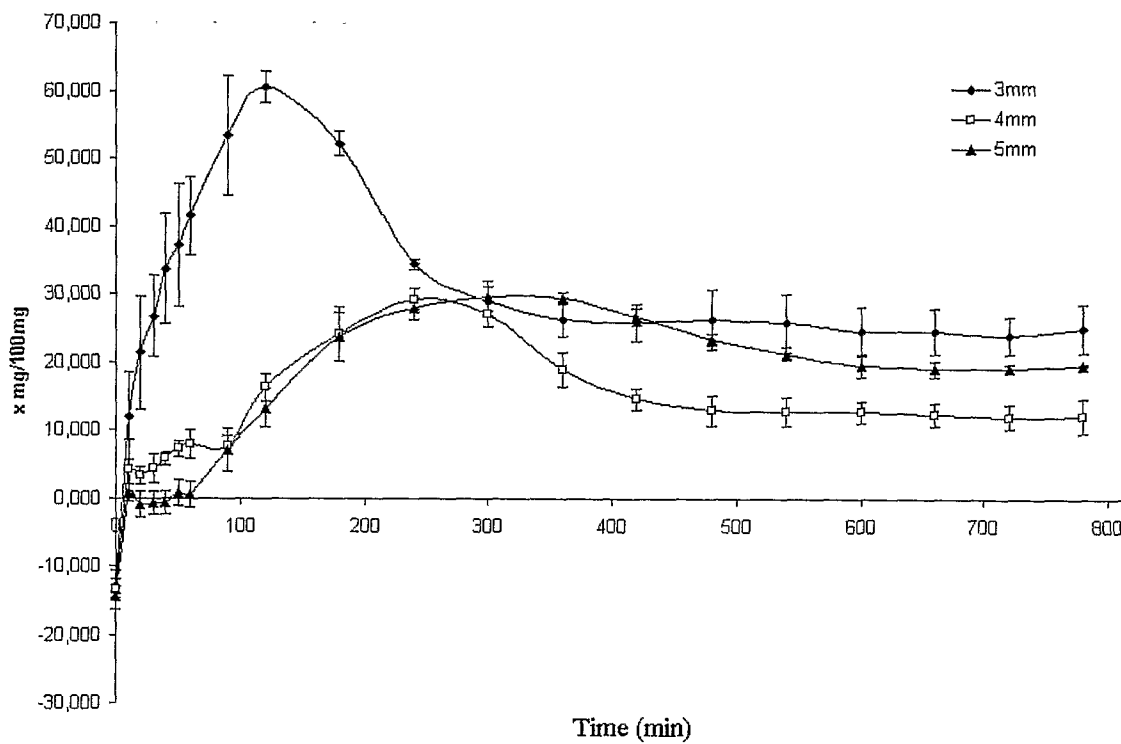
Figure 1**Figure 2**

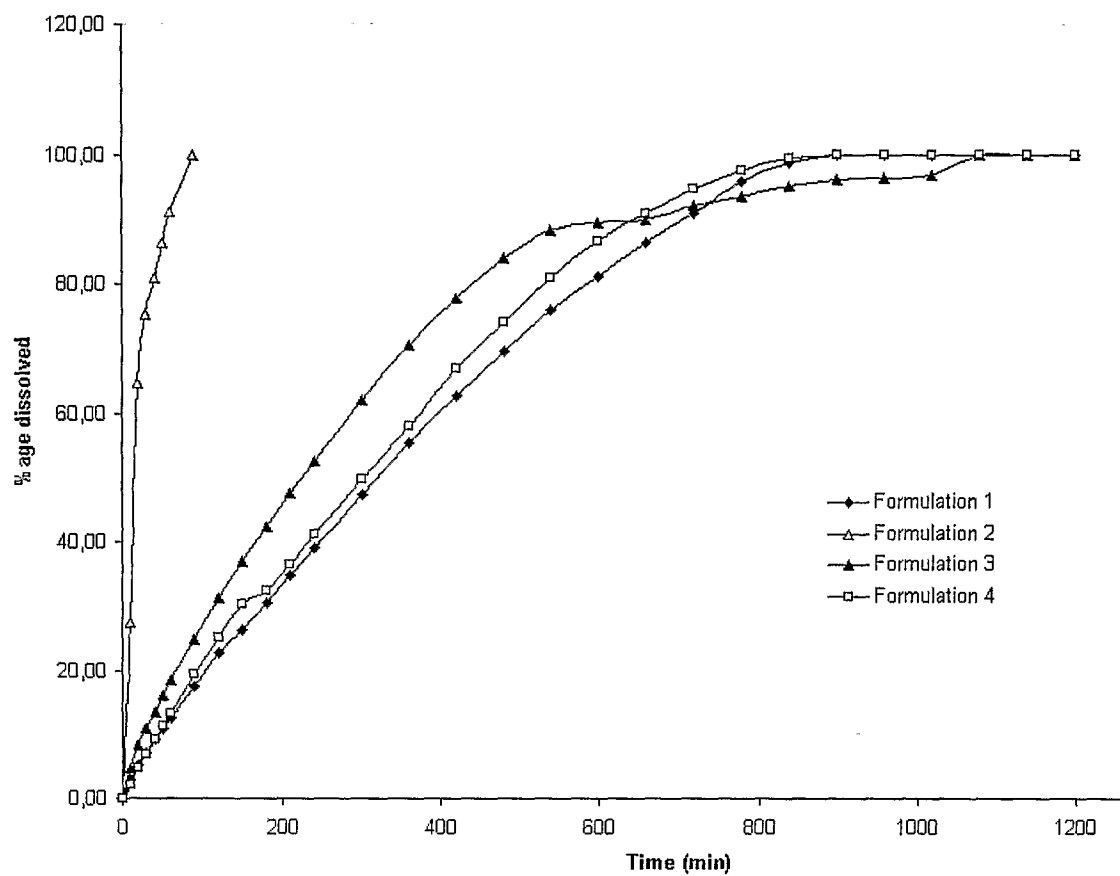
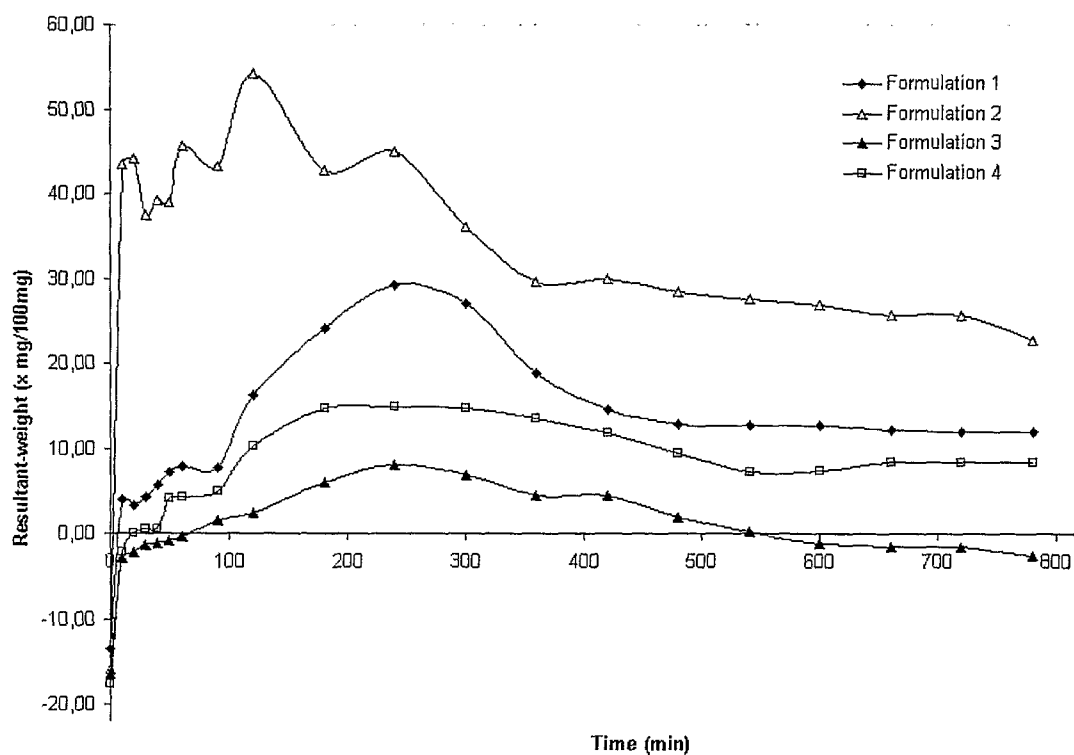
Figure 3**Figure 4**

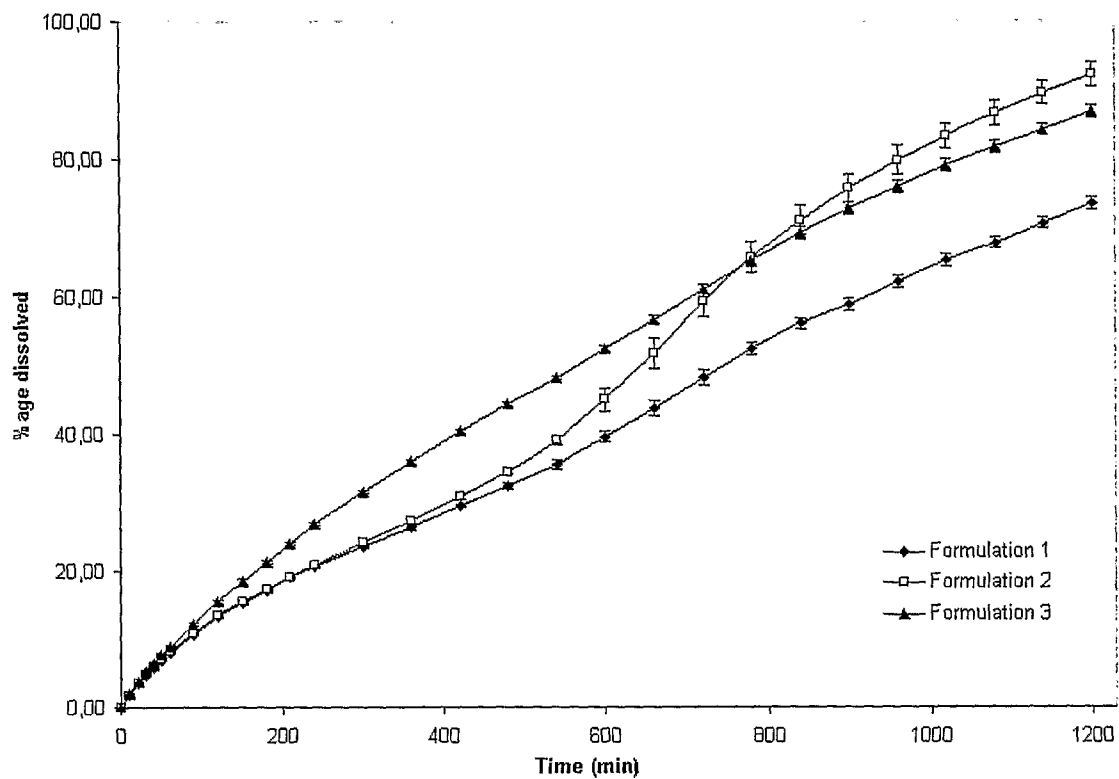
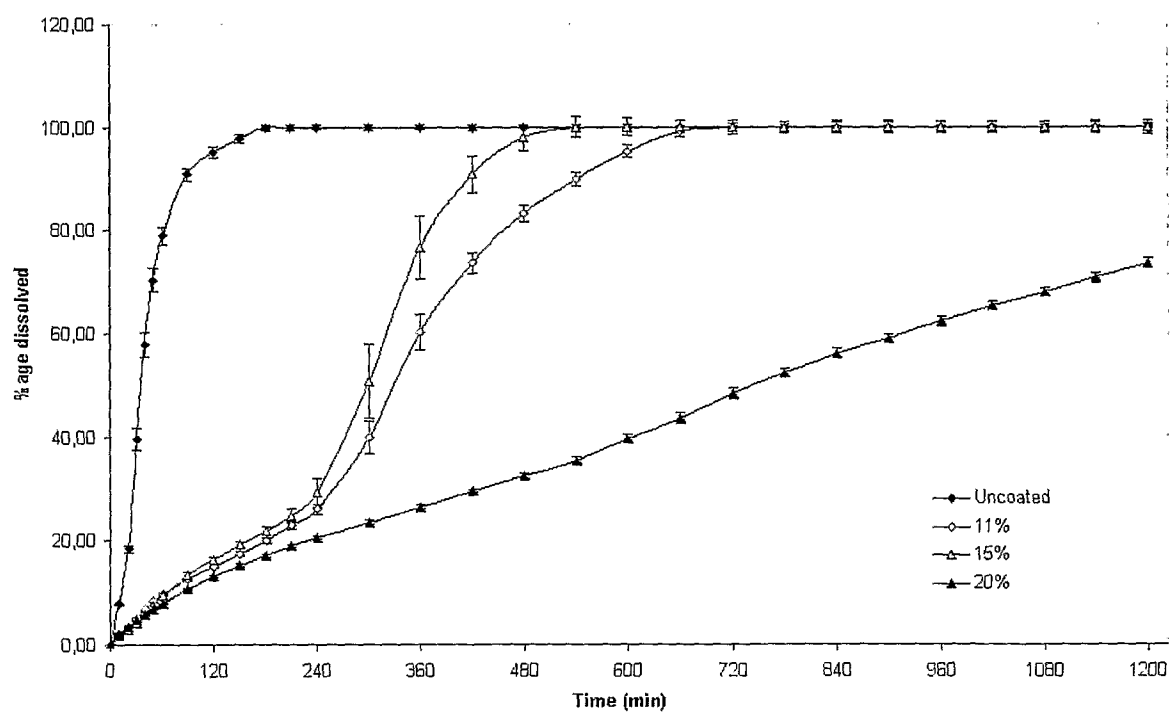
Figure 5**Figure 6**

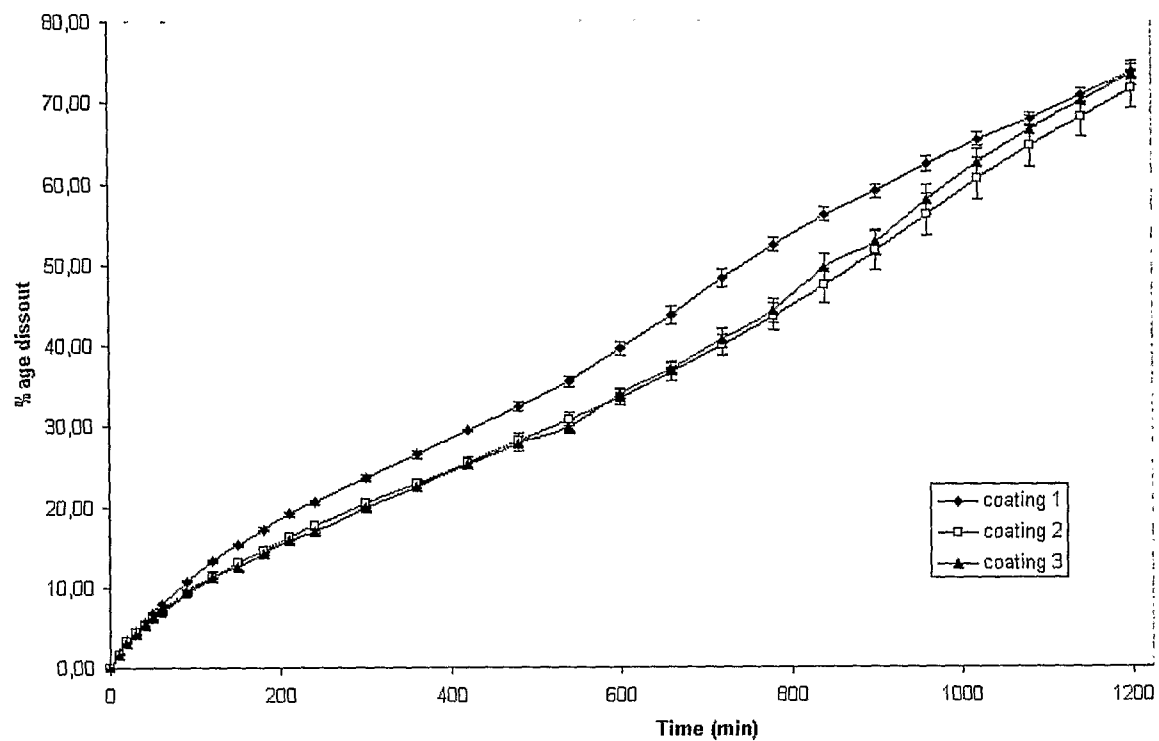
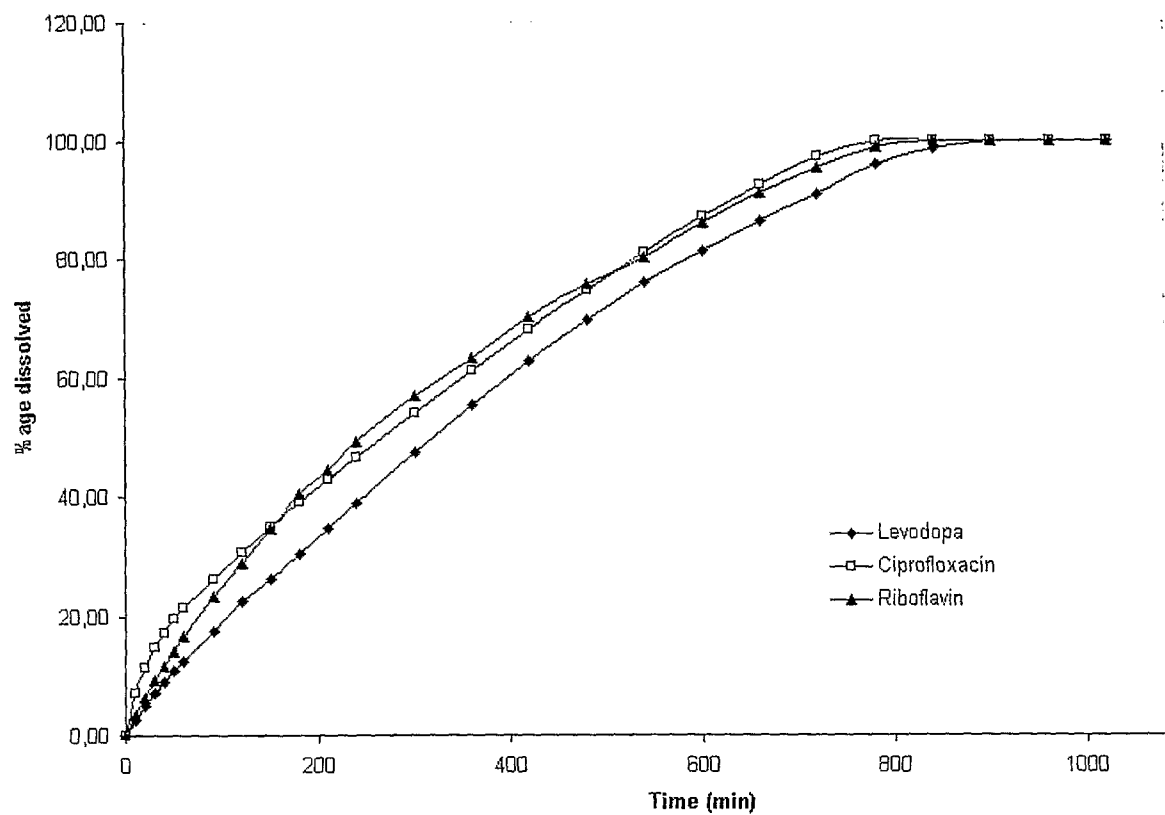
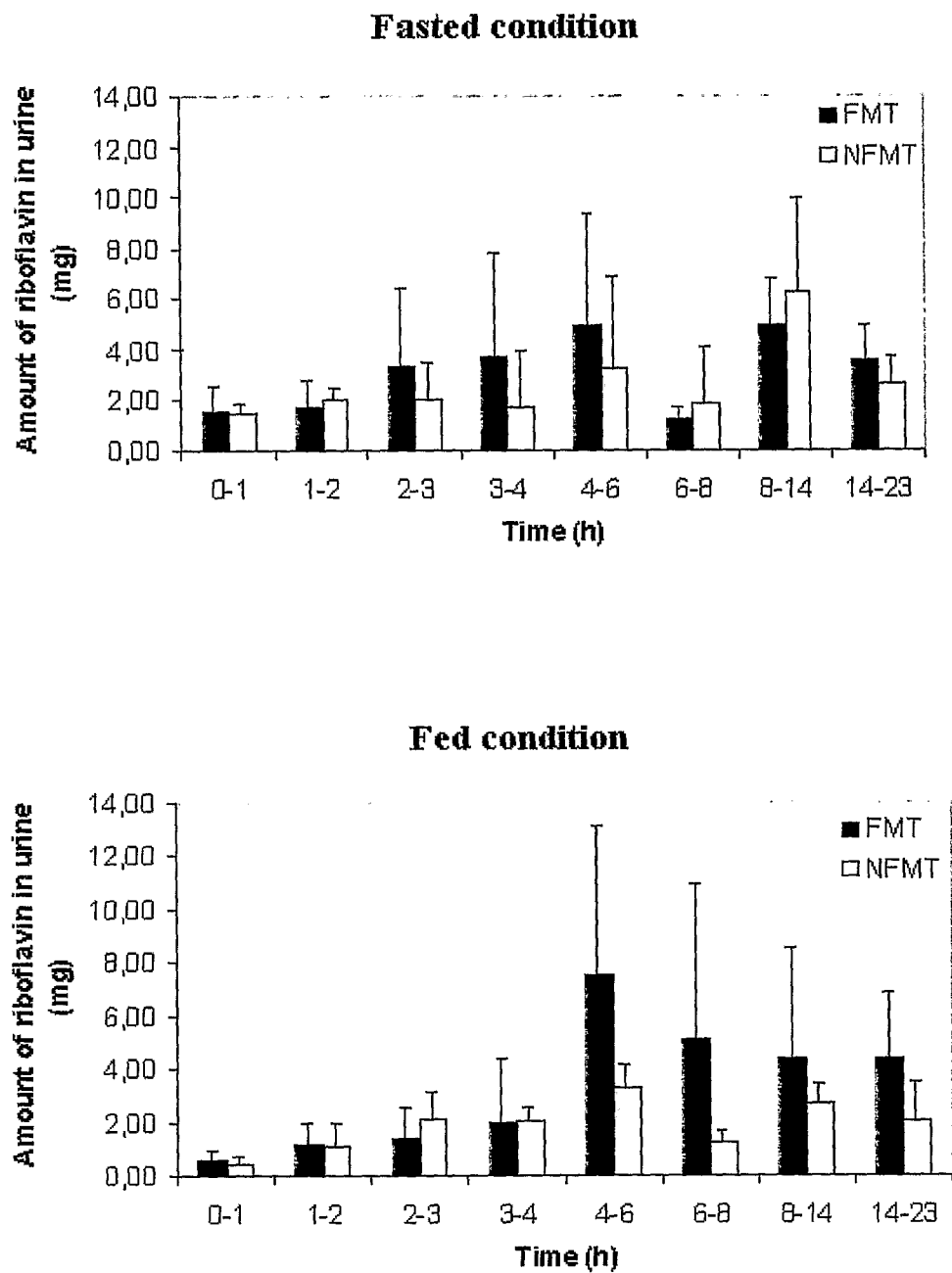
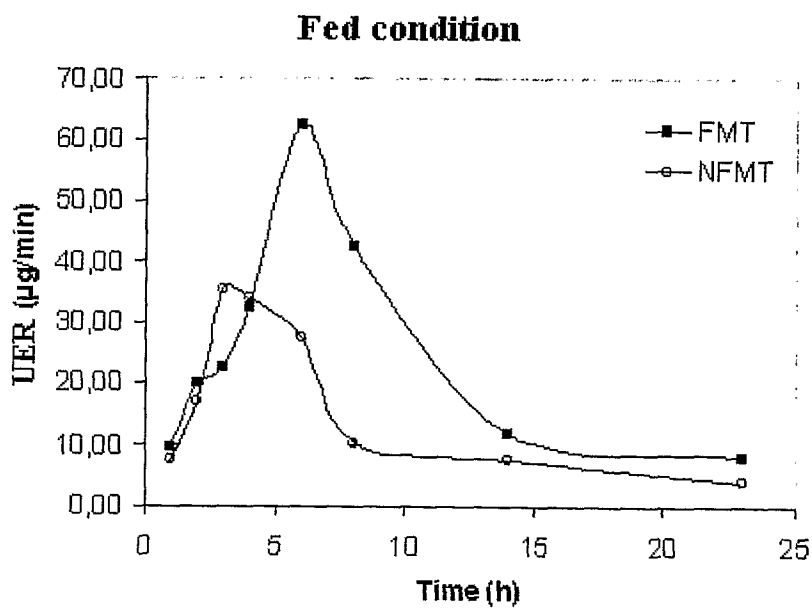
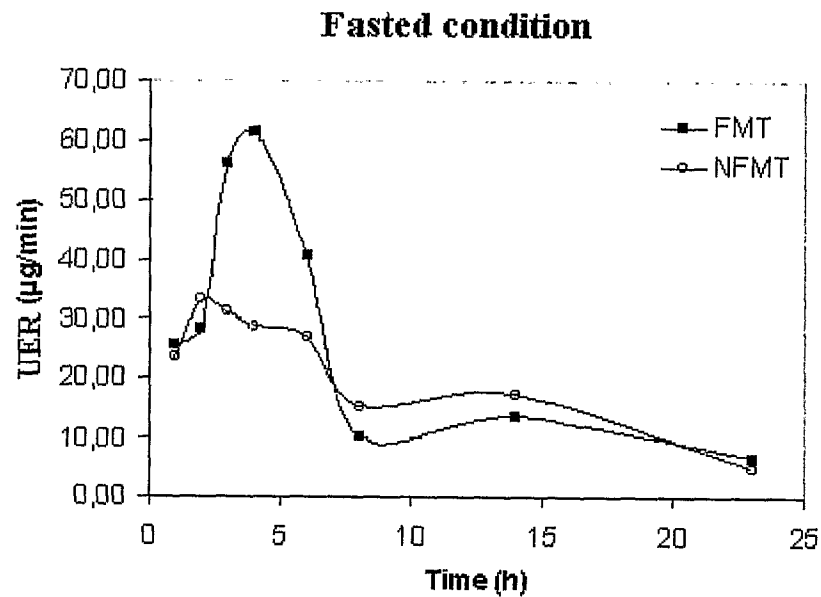
Figure 7**Figure 8**

Figure 9

5 Figure 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/BE2006/000021

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K9/00 A61K9/20

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 practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 514 524 B1 (SASLAWSKI OLIVIER [FR] ET AL) 4 February 2003 (2003-02-04) column 1, lines 11-16 column 2, lines 1-7 column 12, line 61 - column 13, line 3 examples 7, 11, 19	1-14, 16-18, 22-25
X	WO 03/097018 A (RANBAXY LAB LTD [IN]; KUMAR MANOJ [IN]; TALWAR NARESH [IN]; RAGHUVANSH) 27 November 2003 (2003-11-27) page 1, lines 5-13 page 7, lines 10-28 page 8, lines 6-16 page 23, lines 3-12 claims 1, 13, 14; example 1 ----- --/--	1, 2, 4-6, 8-13, 16-19, 22

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Date of the actual completion of the international search

1 November 2006

Date of mailing of the international search report

09/11/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/BE2006/000021

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2005/063203 A2 (VECTURA LTD [GB]; MORTON DAVID [GB]; SIMPSON DAVID [GB]; STANIFORTH JO) 14 July 2005 (2005-07-14) page 1, lines 4-11; examples 1-7 -----	1-7, 11-14, 17,22,25
P,X	HAMDANI ET AL: "Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization" INTERNATIONAL JOURNAL OF PHARMACEUTICS, AMSTERDAM, NL, vol. 322, no. 1-2, 28 September 2006 (2006-09-28), pages 96-103, XP005637138 ISSN: 0378-5173 the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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