(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 2623096 B1**

(19) NO

NORGE

(51) Int Cl.

A61K 9/50 (2006.01)
A61K 31/495 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2019.09.02
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2019.04.03
(86)	Europeisk søknadsnr	13153638.5
(86)	Europeisk innleveringsdag	2013.02.01
(87)	Den europeiske søknadens Publiseringsdato	2013.08.07
(30)	Prioritet	2012.02.03, FR, 1200322
(84)	Utpekte stater	AL ; AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MK ; MT ; NL ; NO ; PL ; PT ; RO ; RS ; SE ; SI ; SK ; SM ; TR
	Utpekte samarbeidende stater	BA ; ME
(73)	Innehaver	Les Laboratoires Servier, 35, rue de Verdun, 92284 Suresnes Cedex, Frankrike
(72)	Oppfinner	Genty, Patrick, 2, rue des fleurs, 45100 ORLEANS, Frankrike Hermelin, Christophe, 62 rue de la Groue, 45380 CHAINGY, Frankrike Pean, Jean-Manuel, 2 bis rue Adolphe Crespin, 45000 ORLEANS, Frankrike
(74)	Fullmektig	OSLO PATENTKONTOR AS, Postboks 7007 M, 0306 OSLO, Norge

(54) Benevnelse **Pharmaceutical composition with slow release of trimetazidine**

(56) Anførte publikasjoner

EP-A1- 0 673 649
EP-A1- 1 108 424
WO-A1-2010/086868
US-A1- 2011 274 751
EP-A1- 1 195 160

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PHARMACEUTICAL COMPOSITION FOR THE PROLONGED RELEASE OF TRIMETAZIDINE

The invention relates to a pharmaceutical form for the prolonged release of trimetazidine and also to the use thereof in the treatment of angina.

Trimetazidine, or 1-(2,3,4-trimethoxybenzyl)piperazine, is a compound which, by maintaining the energy metabolism of a cell exposed to hypoxia or ischaemia, avoids the collapse of the intracellular level of adenosine triphosphate (ATP). It accordingly ensures functioning of the ion pumps and sodium-potassium trans-membrane flows and maintains cellular homeostasis.

Trimetazidine dihydrochloride is used therapeutically in the prophylactic treatment of angina pectoris attacks, in the course of chorioretinal disorders, and also for the treatment of vertigo of vascular origin (Meniere's vertigo, tinnitus).

The use of trimetazidine therapeutically has been described, in the form of an immediate-release pharmaceutical composition administered three times per day, especially in the patent specification FR 2 490 963.

The patent specification EP 1 108 424 describes a prolonged-release form which makes it possible to cover the entire 24-hour period on the basis of administration twice per day. That prolonged-release form makes it possible to obtain plasma levels in humans which are greater than 70 µg/l after each administration and to maintain a plasma level which is greater than or equal to 40 µg/l before the subsequent administration.

Reservoir-type pharmaceutical compositions for the prolonged release of trimetazidine which ensure release of the active ingredient over a period of 16 hours have been described in the patent specification EP 0 673 649. These reservoir-type forms for single daily administration have the advantage of reducing blood level peaks whilst ensuring regular and constant plasma levels of trimetazidine.

In the therapeutic arsenal available to patients, forms for the prolonged release of trimetazidine are proving necessary in order to ensure compliance and optimum therapeutic protection for the patient. The prolonged-release forms according to the present invention make possible, on the one hand, gradual and sustained release over 24 hours at a therapeutically efficacious plasma concentration of trimetazidine and, on the other hand, the availability of trimetazidine at a therapeutically efficacious plasma concentration a short time after administration. A therapeutically efficacious plasma concentration of trimetazidine is understood to be a plasma level greater than or equal to 40 µg/l, making possible efficacious myocardial protection. Furthermore, a short time is understood to be a period of less than 4 hours, preferably a period of less than 3 hours.

The pharmaceutical composition according to the invention is applied by oral administration once per day and releases trimetazidine throughout the 24-hour period whilst providing a high level of security with respect to any "burst"-type or discontinuous release.

The pharmaceutical composition according to the present invention is a composition for the prolonged release of trimetazidine in which the inner phase comprises a neutral core coated with trimetazidine and the outer layer comprises a retardant and an anti-agglomerant, in which the percentage of retardant is between 5.5 and 8 % inclusive of the total weight of the inner phase.

The nature and the thickness of the excipients in the outer layer make it possible to control the release of the trimetazidine active ingredient as a function of time. More particularly, the retardant present in the outer layer, i.e. a retardant for the diffusion of the active ingredient, is involved in the process of prolonged release.

Among the retardants that may be used in the compositions according to the invention there may be mentioned, by way of non-limiting example, ethylcellulose (EC), ethylcellulose derivatives such as cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate and/or polymethacrylates. The retardants are placed in organic solution or in aqueous suspension in the course of their being

used in the process for manufacture of the pharmaceutical compositions according to the invention. Among the retardants there may be mentioned, more especially, ethylcellulose.

Among the anti-agglomerants according to the invention there may be mentioned talc, silicas and derivatives thereof, magnesium stearate, stearic acid and/or sodium fumaryl stearate. Preference is given to the anti-agglomerant being talc.

Besides the retardant and the anti-agglomerant, the outer layer of the pharmaceutical composition according to the invention comprises a plasticiser. Among the plasticisers which come into consideration according to the invention there may be mentioned acetyl tributyl citrate, glycerol triacetate, acetyl triethyl citrate, acetyl ethyl citrate, diethyl sebacate, dibutyl sebacate, ethyl phthalate, dibutyl phthalate, polyethylene glycol (PEG), glycerol and/or propylene glycol. Among the plasticisers there may be mentioned, more especially, acetyl tributyl citrate.

More particularly, the percentage of ethylcellulose is between 5.5 % and 8 % inclusive of the total weight of the inner phase. Specifically, the percentage of ethylcellulose is 6.5 % of the total weight of the inner phase.

The percentage of anti-agglomerant in the pharmaceutical composition is between 25 % and 200 % inclusive, preferably between 100 % and 200 % inclusive, of the weight of the retardant.

The percentage of talc as anti-agglomerant in the pharmaceutical composition is preferably between 100 % and 200 % inclusive of the weight of the retardant.

The percentage of plasticiser in the pharmaceutical composition is between 5 % and 50 % inclusive, preferably between 5 % and 30 % inclusive, of the weight of the retardant.

The percentage of acetyl tributyl citrate as plasticiser in the pharmaceutical composition is preferably between 5 % and 30 % inclusive of the weight of the retardant.

The inner phase of the pharmaceutical compositions according to the present invention comprises the active ingredient trimetazidine coated on a neutral core and a binder.

Among the binders according to the invention there may be mentioned hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), maltodextrin, polyvinylpyrrolidone (PVP) and/or microcrystalline cellulose.

Among the binders there may be mentioned, more especially, hydroxypropyl methylcellulose, which is customarily used in the field of the formulation of medicaments. More especially, the selected hydroxypropyl methylcellulose is of low viscosity. Preferably, the hydroxypropyl methylcellulose used is Pharmacoat™ 606.

The trimetazidine and the binder are deposited on a neutral core, the entirety thereof constituting the inner phase.

The cores or pellets conventionally used may be soluble or insoluble in water. These cores are spheres of sugar or spheres of sucrose/starch or of microcrystalline cellulose. The size of the cores varies from 100 to 1200 µm, preferably from 300 to 1000 µm and, even more preferably, from 710 to 850 µm; where appropriate, the size may be modified if it proves necessary.

Preference is given to the trimetazidine in the compositions according to the invention being in the form of the dihydrochloride of trimetazidine. The amount of trimetazidine dihydrochloride in the pharmaceutical composition is preferably 80 mg.

The percentage of binders in the pharmaceutical composition is between 1 % and 15 % inclusive of the total weight of the composition. The percentage of hydroxypropyl methylcellulose as binder in the pharmaceutical composition is between 1 % and 15 % inclusive of the total weight of the composition.

The percentage of neutral cores in the pharmaceutical composition is between 15 % and 40 % inclusive of the total weight of the composition. The percentage of cores of the sucrose/starch type is between 15 % and 40 % inclusive of the total weight of the composition.

The percentage of trimetazidine in the pharmaceutical composition is between 35 % and 70 % inclusive of the total weight of the composition.

Preferably, the outer layer of the pharmaceutical compositions according to the invention comprises from 5.5 % to 8 % of ethylcellulose relative to the total weight of the inner phase, from 5 % to 30 % of acetyl tributyl citrate relative to the weight of the retardant and from 100 % to 200 % of talc relative to the weight of the retardant.
Likewise preferably, the inner phase of the pharmaceutical compositions according to the invention comprises from 15 % to 40 % of neutral core, from 35 % to 70 % of trimetazidine and from 1 % to 15 % of hydroxypropyl methylcellulose relative to the total weight of the composition.

The amount of components of the pharmaceutical composition is 80 mg of trimetazidine dihydrochloride, 36.677 mg of neutral minigranules, 6.40 mg of hydroxypropyl methylcellulose, 1.2 mg of acetyl tributyl citrate, 8 mg of ethylcellulose and 12 mg of talc.

Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral administration, especially in capsule form.

The *in vitro* dissolution rate of the composition according to the invention is from 8 to 28 % of the trimetazidine released by 4 hours and from 37 to 57 % of the trimetazidine released by 8 hours and more than 75 % of the trimetazidine released by 24 hours. These dissolution kinetics are selected so that the therapeutically efficacious plasma concentration of trimetazidine obtained *in vivo* is

prolonged over 24 hours following administration of the pharmaceutical composition.

In accordance with the process for manufacture of the pharmaceutical compositions according to the invention, neutral cores are coated with successive layers of active ingredient using a coating pan, with or without perforations, or fluidised-bed apparatus. The active ingredient in the form of a solution or suspension, which is aqueous or organic, is sprayed onto the neutral cores and then dried.

The minigranules, prepared by one or other of the processes, are subsequently coated, either in a coating pan, with or without perforations, or in a fluidised-bed type apparatus. The minigranules are coated using a solution or suspension of the retardant which is involved in the diffusion of the active ingredient and thereby controls the release kinetics.

The coated minigranules are placed in capsules.

By way of example, the following manufacturing process may be mentioned:

Neutral cores composed of sucrose/starch are coated with successive layers of trimetazidine hydrochloride solution associated with hydroxypropyl methylcellulose in a fluidised-bed system.

Coating of the minigranules thereby prepared is carried out in a fluidised-bed apparatus using a suspension composed of ethylcellulose, acetyl tributyl citrate and talc.

The coated minigranules are filled into capsules in the presence of magnesium stearate.

The present invention relates also to the pharmaceutical compositions according to the invention for use in the prophylactic treatment of angina pectoris, in the course of chorioretinal disorders and also for the treatment of vertigo of vascular origin.

The Examples hereinbelow illustrate, but do not limit, the invention.

Example 1: Pharmaceutical composition for a capsule containing 80 mg of trimetazidine

The trimetazidine minigranules are coated with a film containing 6.5 % ethylcellulose.

Figure 1 illustrates the structure and formulation of the pharmaceutical composition described below.

Table 1:

Compounds	Amount (mg)
Active ingredient minigranules	
Trimetazidine dihydrochloride	80.00
Neutral minigranules	36.677
Hydroxypropyl methylcellulose	6.40
Coating (6.5 % EC)	
Acetyl tributyl citrate	1.20
Ethylcellulose	8.00
Talc	12.00
Capsule	
Coated minigranules	144.277
Magnesium stearate	0.434

Example 2: Macroscopic appearance of the minigranules

In the absence of anti-agglomerant in the outer phase of the pharmaceutical compositions there are found, on an industrial scale, irregular minigranules (Figure 2), numerous cracks in the minigranules' coating and even amalgamations between the minigranules. These coating defects cause major modifications to the *in vitro* dissolution kinetics, especially profiles of accelerated dissolution.

If the anti-agglomerant is in excess, then the minigranules obtained on an industrial scale have an irregular and flaky surface (Figure 2) due to the presence of excessive talc sticking to the surface of the minigranules. These minigranules have dissolution kinetics that are greatly accelerated and even immediate-release kinetics.

Example 3: Dissolution kinetics compared as a function of the percentage of ethylcellulose in the coating, knowing that only composition E110055 corresponds to the claims

Table 2:

Batch	E110055	E110118	E110120	E110121	E110124
EC % Coating ratio %	6.5 14.7	10 20.9	4.5 10.7	9 19.3	5 11.7
Composition					
Trimetazidine Neutral cores HPMC	80 36.677 6.4	80 36.677 6.4	80 36.677 6.4	80 36.677 6.4	80 36.677 6.4
Ethylcellulose Acetyl tributyl citrate Talc	8 1.2 12	12.3 1.8 18.5	5.5 0.8 8.3	11.1 1.7 16.7	6.2 0.9 9.3
Mg stearate	0.4	0.4	0.4	0.4	0.4
Total weight	144.711	156	138	152.9	139.8
Dissolution					
4 hrs	20.9	2.1	46.3	4.9	36.6
8 hrs	48.5	26.9	69.1	31.7	62.9
12 hrs	62.0	44.1	80	48.1	75.7
16 hrs	72.6	54.5	86.5	58.3	83.4

It is to be noted that the coating ratio was calculated as follows: weight of outer phase / total weight.

Furthermore, the above dissolution profiles were obtained starting from minigranules which had not been distributed into capsules. The dissolution profiles of the batches on an industrial scale (minigranules encapsulated in capsules) are

slowed down by 4, 3, 2 and 1 % at the 4, 8, 12 and 16 hour points, respectively, relative to the dissolution profiles described above (not filled).

The *in vitro* dissolution kinetics of the pharmaceutical compositions E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %) (Figure 4) were compared to the *in vitro* release kinetics of the reference pharmaceutical composition E110055 (EC 6.5 %). The dissolution profiles are compared with the aid of the similarity factor (f_2).

The dissolution kinetics of the compositions E110118 (EC 10 %) and E110121 (EC 9 %), on the one hand, and E110120 (EC 4.5 %) and E110124 (EC 5 %), on the other hand, are not similar to the dissolution kinetics of the reference pharmaceutical composition E110055 (EC 6.5 %). Consequently, the percentage of retardant in the pharmaceutical composition is, on the one hand, strictly less than 9 % and, on the other hand, strictly greater than 5 %.

Two dissolution profiles are considered to be similar when the value (f_2) is greater than or equal to 50. Calculation of the similarity factor (f_2) is advised by the directives of the EMA and the FDA in order to compare two dissolution profiles and to make it possible to decide if said dissolution profiles are the same.

The similarity factor (f_2) has the following formula:

$$f_2 = 50 \bullet \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} \left[\overline{R}(t) - \overline{T}(t)\right]^2}{n}}} \right]$$

wherein f_2 is the similarity factor, n is the number of normalised points, R(t) is the percentage mean of active ingredient dissolved from the reference pharmaceutical composition E110055 and T(t) is the percentage mean of active ingredient dissolved from a pharmaceutical composition E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %). The normalised points are at least at t = 8 hours, t = 12 hours and t = 16 hours.

The evaluated minigranules filled into capsules have different formulations; these formulations vary especially as a function of the amount of ethylcellulose and anti-agglomerant.

The observed *in vitro* dissolution profiles of the pharmaceutical compositions E110118 (EC 10 %), E110120 (EC 4.5 %), E110121 (EC 9 %), and E110124 (EC 5 %) (Figure 3) were modelled by applying Weibull's law to each of them (Figure 4). Weibull's law constitutes an especially valuable approximation which makes it possible to predict continuous *in vitro* dissolution profiles from observed *in vitro* dissolution profiles.

A *vitro-vivo* correlation equal to 1 was put forward as the hypothesis; consequently the profiles of the fractions absorbed *in vivo* (Figure 4) correspond exactly to the modelled *in vitro* dissolution profiles. A convolution step was then carried out in order to predict the pharmacokinetic profiles of the various pharmaceutical compositions. The convolution step (function Cp(t)) is defined as follows: Cp(t) = I(t)*P(t)

wherein I(t) is an input function and P(t) is a disposition function.

The input function represents the fractions absorbed *in vivo* as a function of time and the disposition function is a polyexponential equation of the pharmacokinetics of a pharmaceutical composition for the prolonged release of trimetazidine obtained in the study SKH-6790-005-FRA. The predicted mean pharmacokinetic profiles are shown in Figure 5.

Starting from said plasma profiles obtained by convolution, the pharmacokinetic parameters AUC and Cmax were calculated where AUC represents the exposure to the medicament and Cmax the maximum concentration.

Table 3:

	AUC (ng.h/mL)	Cmax (ng/mL)
E110124	1620	83.6
E110120	1678	85.6
E110055	**1776**	**67.8**
E110121	1501	57.0
E110118	1418	54.2

The AUC of the pharmaceutical composition E110055 (EC 6.5 %) is the highest of the pharmaceutical compositions evaluated above and the exposure of the patient to the trimetazidine is significantly improved.

Furthermore, the pharmacokinetic profiles make it possible to measure the efficacious myocardial protection time of the treated patient, or the time during which said patient is covered by a therapeutically efficacious plasma concentration (40 µg/l). This therapeutic protection time is at least 22 hours for the composition E110155 (EC 6.5 %) whereas it is only 16 hours for the composition E110118 (EC 10 %). The therapeutic protection time is improved even when the percentage of retardant, which is responsible for the prolonged release in the therapeutic composition, is reduced from 10 % to 6.5 %.

Patentkrav

1. Farmasøytisk sammensetning med langvarig frigivelse av trimetazidin med:
   - en indre fase omfattende en nøytral trimetazidin-belagt kjerne;
   - et ytre lag omfattende et forsinkelsesmiddel og et anti-agglomereringsmiddel

karakterisert ved at prosentandel av forsinkelsesmidlet er mellom 5,5 og 8% av den totale massen av den indre fasen.

2. Sammensetning ifølge krav 1, hvor forsinkelsesmidlet er valgt fra etylcellulose, celluloseacetat, celluloseacetatbutyrat, celluloseacetatpropionat, celluloseacetatftalat, hydroksypropylmetylcellulose succinatacetat og / eller polymetakrylater.

3. Sammensetning ifølge krav 1 eller 2, hvor anti-agglomereringsmidlet er valgt fra talkum, kolloidalt silisiumdioksid, magnesiumstearat, stearinsyre og/eller natrium fumaryl stearat.

4. Sammensetning ifølge et hvilket som helst av kravene 1 til 3, hvor det ytre laget omfatter et mykgjørende middel.

5. Sammensetning ifølge krav 4, karakterisert ved at mykgjørende midlet er valgt fra acetyltributylcitrat, glyceroltriacetat, acetyltrietylcitrat, etyl-acetylcitrat, dietylsebacat, dibutylsebacat, etyldibutylftalat, polyetylenglykol, glyserol og / eller propylenglykol.

6. Sammensetning ifølge krav 4 eller 5, hvor prosentandelen av det mykgjørende midlet er mellom 5 og 50% av massen av forsinkelsesmidlet.

7. Sammensetning ifølge et hvilket som helst av kravene 1 til 6, hvor prosentandelen av anti-agglomereringsmidlet er mellom 25% og 200% av massen av forsinkelsesmidlet.

8. Sammensetning ifølge et hvilket som helst av kravene 1 til 7, hvor den indre fasen omfatter et bindemiddel.

9. Sammensetning ifølge krav 8, hvor bindemidlet er valgt fra hydroksypropylmetylcellulose, hydroksypropylcellulose, maltodextrin, polyvinylpyrrolidon og/eller mikrokrystallinsk cellulose.

10. Sammensetning ifølge et hvilket som helst av kravene 1 til 9, hvor den nøytrale kjernen består av sukrose, sukrose og stivelse eller mikrokrystallinsk cellulose.

11. Sammensetning ifølge et hvilket som helst av kravene 1 til 10, hvor det ytre laget omfatter:

- fra 5% til 30% acetyltributylcitrat av massen av forsinkelsesmidlet;
- fra 5,5% til 8% etylcellulose av den totale massen av den interne fasen;
- fra 100% til 200% talkum av massen av forsinkelsesmidlet.

12. Sammensetning ifølge et hvilket som helst av kravene 1 til 11, hvor den indre fasen omfatter:

- fra 15% til 40% av den nøytrale kjernen av den totale masse av sammensetningen;
- fra 35% til 70% trimetazidin av den totale masse av sammensetningen;
- fra 1% til 15% av hydroksypropylmetylcellulose av den totale masse av sammensetningen.

13. Sammensetning ifølge et hvilket som helst av kravene 1 til 12, hvor trimetazidin er i form av dihydroklorid.

14. Sammensetning ifølge et hvilket som helst av kravene 1 til 13, som inneholder 80 mg trimetazidindihydroklorid.

15. Sammensetning ifølge krav 1, som inneholder 80 mg trimetazidindihydroklorid, 36,677 mg nøytrale minigranuler, 6,40 mg hydroksypropylmetylcellulose, 1,2 mg acetyltributylcitrat, 8 mg etylcellulose og 12 mg talkum.

16. Farmasøytisk sammensetning ifølge et hvilket som helst av kravene 1 til 15, hvor *in vitro*-oppløsningshastigheten av sammensetningen er 8 til 28% trimetazidin frigjort etter 4 timer og 37 til 57% trimetazidin frigjort etter 8 timer, og mer enn 75% trimetazidin frigjort etter 24 timer og valgt slik at den terapeutisk effektive

plasmakonsentrasjon av trimetazidin oppnådd *in vivo* forlenges med 24 timer etter administrering av den farmasøytiske sammensetningen.

17. Fremgangsmåte for fremstilling av en sammensetning ifølge et hvilket som helst av kravene 1 til 16, som omfatter følgende trinn:

a) å belegge de nøytrale kjernene med trimetazidin og et bindingsmiddel;
b) å belegge med et forsinkelsesmiddel, et mykgjørende middel og et anti-agglomereringsmiddel, minigranulene oppnådd i a);
c) kondisjonering av de belagte minigranulene oppnådd i b) og smøring.

18. Farmasøytisk sammensetning ifølge et hvilket som helst av kravene 1 til 16 til anvendelse for profylaktisk behandling av angina pectoris, for chorioretinale lidelser og for behandling av svimmelhet av vaskulær opprinnelse.

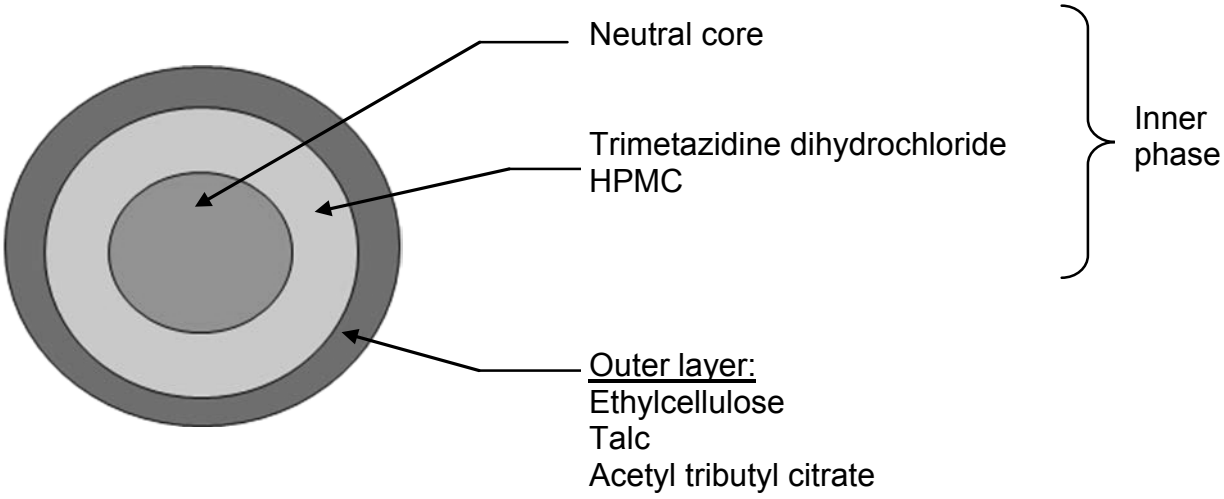

Figure 1: Structure and formulation of the pharmaceutical compositions

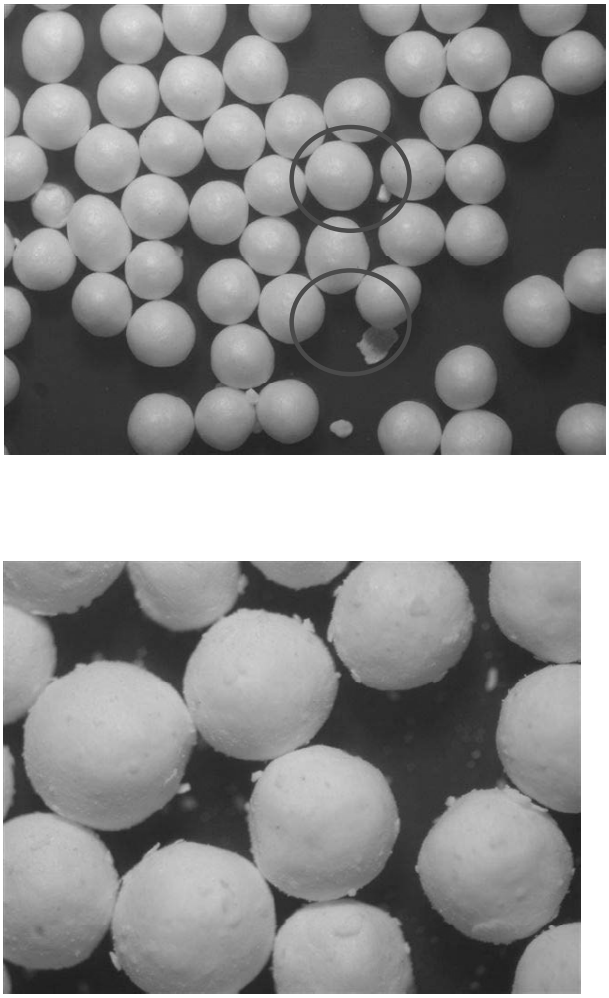

Figure 2: Comparative appearance of minigranules without anti-agglomerant (top) and with an excess of anti-agglomerant (bottom)

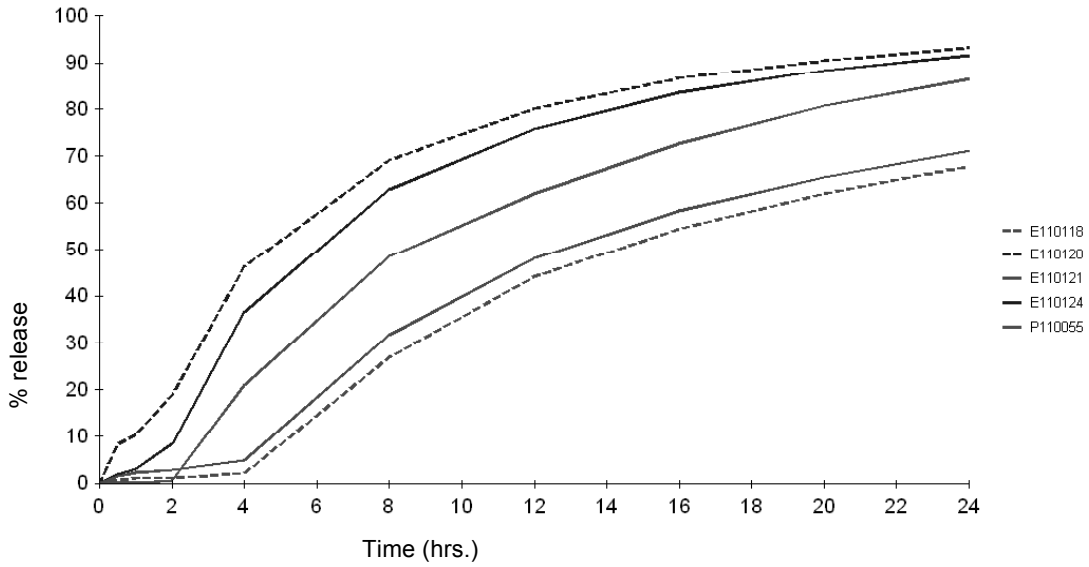

Figure 3: *In vitro* dissolution profiles

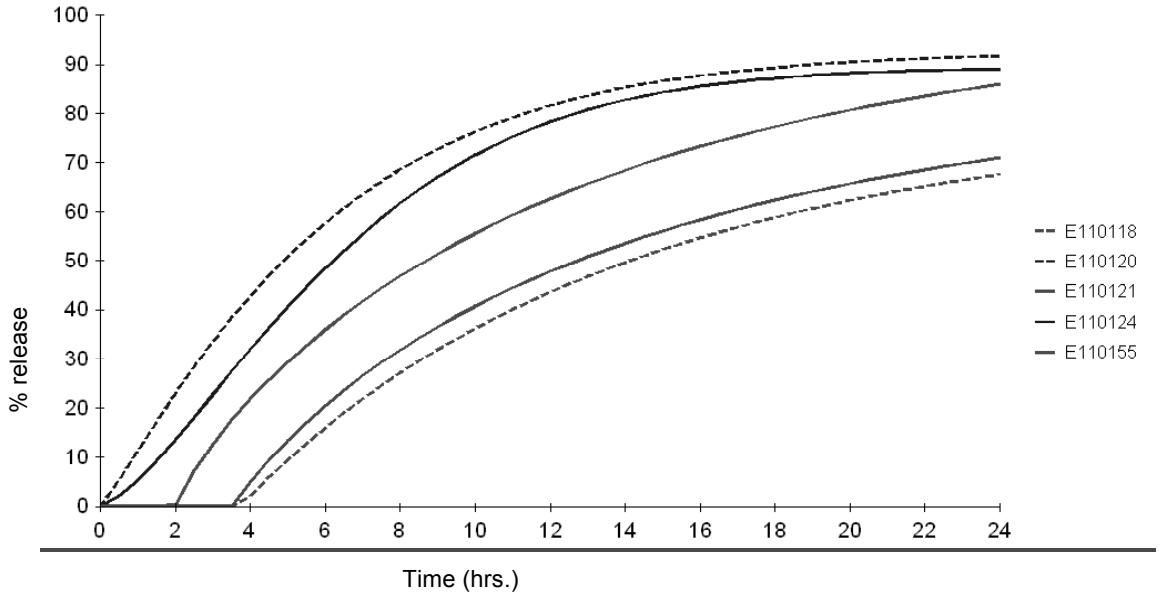

Figure 4: Modelled *in vitro* dissolution profiles

= profiles of fractions absorbed *in vivo*

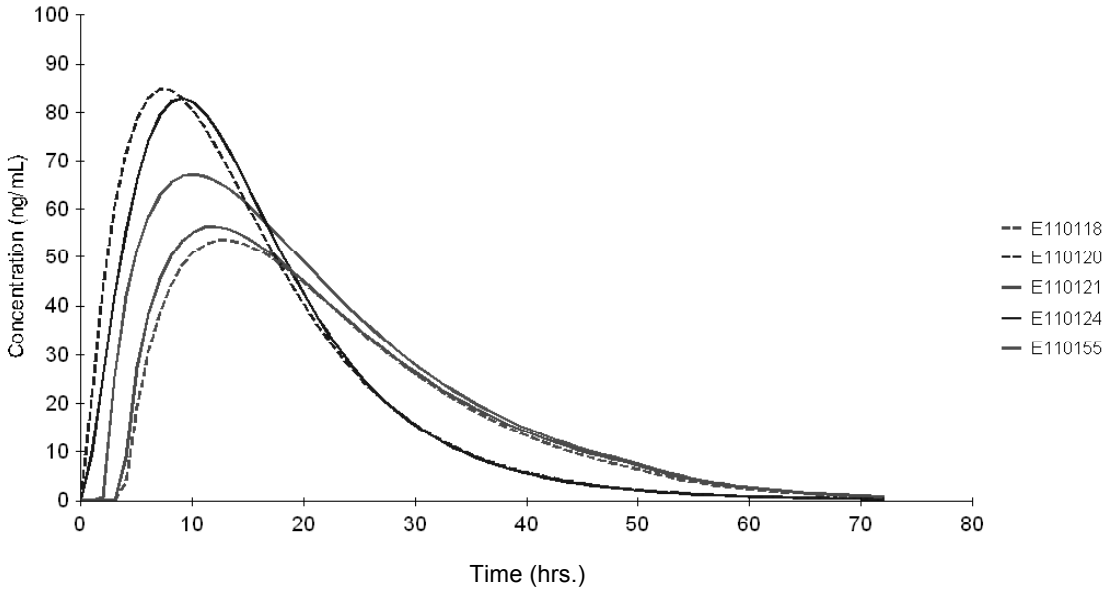

Figure 5: Predicted plasma concentrations obtained by convolution