MULTILAYERED PHARMACEUTICAL FORMULATION

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(54) Title: MULTILAYERED PHARMACEUTICAL FORMULATION

(57) Abstract: An oral trilayered formulation with multi-kinetic release in different sites of the gastro-intestinal tract, particularly suitable for the administration of combinations of active ingredients is described.

MULTILAYERED PHARMACEUTICAL FORMULATION

Description

The present invention relates to an oral trilayered formulation with multi-kinetic release in different sites of the gastro-intestinal tract, particularly suitable for the administration of combinations of active ingredients.

The trilayered technology has been already used in sustained release preparations for oral administration. In the patent literature there are several trilayered systems able to release one or more drugs from the different layers at different rates.

US 4,839,177 describes a controlled release system consisting of three layers wherein the external layers consist of an insoluble drug-free polymeric material, while the central layer is a swellable polymeric matrix containing the active ingredient. A linear release profile is obtained by coating the intermediate layer. In this case only one layer contains the drug while the other two layers are functional to the release modulation.

In other patent documents the layers contain one or more drugs and each layer is formulated in a different way; for example, in WO94/06416 a layer promptly releases one or more drugs, a second layer releases in a slow controlled way the same drug or the same drug combination present in the disintegrating layer and a third layer having barrier properties and with low permeability can be placed between the layers or over one of them. In this case the layers have only a time control on the release and cannot limit such release in the stomach for long time or limit the release in the intestine for one of the two drugs.

In WO95/01781 there are three layers containing the drug: the first layer releases a portion of the total dose of the drug, while the second one releases another portion of the drug in a controlled manner and the third layer releases the last portion of the drug more slowly than the second layer. Also in this case there is a time release control only and there is no spatial control as well as no control on the release position in the gastro-intestinal tract.

WO99/17745 describes a trilayered system consisting of a disintegrating layer (layer D), a layer consisting of an erodible matrix (layer E) and a controlled release swellable layer (layer R). Each layer contains one or more active ingredients which release rate changes depending from the relative position of the single layers in the trilayered tablet. In particular, when the erodible layer is the central layer (RED system), there is a fast initial release followed by a slower and almost linear release

of the active ingredients. When the swellable layer is the central layer (DRE system), an anomalous Fick kinetics with no biphasic release is achieved. When the central layer is the disintegrating layer (RDE system), a linear release of the active ingredients is achieved.

In the trilayered systems described in the literature the release rate is modulated but there is no spatial control, that is a control on the release site allowing also the modulation of the absorption of the active ingredients in different tracts of the gastro-intestinal system.

We have now found an oral trilayered formulation with multi-kinetic release and spatial control which allows to achieve different release kinetics and release sites for each active ingredient contained in it. This oral trilayered formulation is particularly advantageous for the administration of combinations of active ingredients with pharmacodynamic properties and/or dosage schedules different each other but with complementary therapeutic effect.

Therefore, object of the present invention is a trilayered tablet for oral administration comprising a rapid disintegrating central layer (layer B) interposed between a layer with a swellable floating sustained release hydrophilic matrix (layer A) and a layer with a gastro-resistant or sustained release or gastro-resistant sustained release hydrophilic matrix (layer C).

The tablet according to the invention, even if contains a trilayered system analogous to the RDE system described in WO99/17745, is completely different from it for the multi-kinetic release and for the specificity of the release sites.

Due to the specific combination of the layers ABC, the tablet according to the present invention shows the following spatial-time release pattern which is its characterizing and innovative aspect:

- layer A is formulated for a sustained release under floating conditions and consists of a hydrophilic matrix which swells and floats in an aqueous medium releasing the drug in a sustained way in the first tract of the gastro-intestinal apparatus, preferably in the stomach.;
- layer B is formulated to rapidly disintegrate so rapidly and immediately releasing the drug optionally contained in it in the stomach and causing the split of the multilayered tablet into the two portions corresponding to layers A and C, which continue their transit and the release of the drugs in the gastro-intestinal tract independently from each other;

- layer C is a gastro-resistant or a sustained release or a controlled release gastro-resistant formulation mainly releasing the drug in the intestine. Preferably layer C is a controlled release gastro-resistant formulation releasing the drug in the intestine for a period of some hours.

In the present contest, unless otherwise specified, drug contained in a layer of the tablet of the invention means the active ingredient or the combination of active ingredients present in the layer.

Each layer of the tablet according to the invention can contain the same active ingredient or the same combination of active ingredients with respect to one or both the other layers or can contain an active ingredient or a combination of active ingredients different from the other two layers.

Furthermore layer B can also be drug-free and exclusively act as disintegrating layer which allows the split of the tablet of the invention into the two portions corresponding to layers A and C.

Preferably, at least a layer of the tablet of the invention contains a drug different from the other two layers.

The tablet of the invention is particularly suitable for the administration of a combination of two active ingredients with pharmacokinetic characteristics and dosage schedule different from each other which usually are administered to the patient in different forms and at different times.

The tablet object of the present invention allows to administer the two active ingredients in a single pharmaceutical dosage form, achieving different profiles of modified release synchronized each other, so increasing the compliance of the patient and decreasing the risk of mistakes in the administration of the drugs.

Specific examples of active ingredients which can be used in combination in the tablets object of the present invention are those active ingredients having a higher absorption in the proximal intestinal tract, such as gabapentin (an A2d ligand), ACE-inhibitors (for example captopril, lisinopril, enalapril, ramipril), metformin, baclofen, or having their action site at gastric level, such as H2-inhibitors (for example ranitidine), antibiotics used for Helicobacter Pylori eradication (for example amoxicillin, clarithromycin, metronidazole) together with products which need gastroprotection, such as proton pump inhibitors or non steroidal anti-inflammatory agents (NSAIDs), or need a sustained release in the intestine, such as calcium antagonists.

Preferred combinations within the scope of the present invention are combinations of proton pump inhibitors (for example omeprazole, esomeprazole, lansoprazole, pantoprazole) and H2 receptor antagonists (cimetidine, ranitidine, famotidine); NSAIDs (for example flurbiprofen, ibuprofen, piroxicam, meloxicam, diclofenac, naproxen) and proton pump inhibitors or H2 receptor antagonists (for example cimetidine, ranitidine); ACE-inhibitors (for example captopril, enalapril, ramipril, lisinopril) and angiotensin II receptor antagonists (for example valsartan, losartan, eprosartan, candesartan, irbesartan, olmesartan, telmisartan); ACE-inhibitors and calcium antagonists (for example amlodipine, nifedipine, lercanidipine, felodipine, diltiazem, verapamil); angiotensin II receptor antagonists and calcium antagonists; antibiotics used for Helicobacter Pylori eradication (for example amoxicillin, clarythromycin, metronidazole) and proton pump inhibitors (for example omeprazole, esomeprazole, lansoprazole, pantoprazole); metformin and glicazide or glipizide or sitagliptin, baclofen and proton pump inhibitors.

Still more preferably the tablets of the invention contain a combination of a non steroidal anti-inflammatory agent with an A2d ligand as described in WO 2008/077599.

Particularly preferred is the combination of flurbiprofen and gabapentin.

The excipients used for the formulation of the layers of the tablet of the present invention are excipients conventionally used in pharmaceutical technique.

Layer A consists of a hydrophilic matrix containing a hydrophilic polymer able to swell in the presence of water and a substance able to develop gas in the gastric environment functional to the floating of the layer. The gas is entrapped into the gel which is formed following the swelling of the polymer of the hydrophilic matrix allowing layer A, once separated from the others layers, to float in the aqueous medium. In addition to the drug, to the hydrophilic polymer and to the gas developing substance, layer A generally contains also further excipients to allow the granulation of the active ingredient and then the tabletting.

The hydrophilic matrix generally consists of a swellable polymer of the class of cellulose derivatives such as hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose. Hydroxypropylmethylcellulose is particularly preferred. Also alginates, scleroglucans, carragenans or non ionic polymers such as polyethylenoxide can be used.

Among the commercially available polyethyleneoxides which can be used in the tablet object of the present invention, PolyoxWSR 303 (viscosity range 1% sol. 7500-10000 cP), PolyoxWSR N12K (viscosity range 2% sol. 400-800 cP) and PolyoxWSR 301 (viscosity range 1% sol. 1650-5500 cP) can be cited.

The substances able to develop gas are generally carbonates or bicarbonates, preferably of alkali or alkaline-earth metals such as, for example, sodium, potassium, calcium, magnesium carbonate or bicarbonates and the like.

It is particularly preferred sodium bicarbonate which is generally present in amounts from 5% to 10% by weight, preferably from 7% to 10% by weight.

Layer B contains a disintegrating agent, preferably a super-disintegrating agent, or mixtures thereof to achieve a rapid disintegration in contact with an aqueous medium. In addition to the optionally present drug and to the disintegrating agent, layer B generally contains also further excipients of conventional use to allow granulation and then tabletting.

Among these excipients particularly preferred is calcium hydrogen phosphate which is generally present in amounts from 30% to 60% by weight, preferably from 41% to 48% by weight.

Specific examples of disintegrating agents are: starch, microcrystalline cellulose, combinations of sodium bicarbonate and citric/tartaric acid.

Specific examples of super-disintegrating agents are: crospovidone, sodium croscarmellose, sodium carboxymethyl starch.

Layer C consists of a gastro-resistant or delayed release or, more preferably, gastro-resistant and delayed release hydrophilic matrix. After splitting from the other layers, layer C passes practically unchanged through the stomach and reaches the intestine where it releases the drug.

In its preferred embodiment, the matrix of layer C consists of excipients of conventional use suitably selected to obtain a gastro-resistant formulation which does not need any protective film coating. The possibility to obtain a gastro-resistant matrix can be achieved by combining an anionic polymer, with poor solubility in acid medium, with a non ionic polymer which remarkably gels also at acid pH values. In this way, the gelifying polymer rapidly builds a gel barrier which slows down the entry of acid within the matrix. This latter remains very compact because of the presence of a negatively charged polymer which does not jell in the acid medium. This polymer brings to the disintegration of the matrix when the pH of the external

environment moves to values above 5.0. Furthermore, the matrix contains an oligomer able to complex the drug molecules optionally dissolved during the jelling of the non-ionic polymer, preventing their diffusion to the external environment.

Preferred examples of said excipients, used alone or in combination, are methacrylic polymers soluble at basic pH, cellulose acetophthalate, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, sodium alginate, scleroglucan, carragenane or other anionic polymers.

Among the polymers which can be used in layer C of the trilayered tablet according to the present invention hydroxyproylmethylcellulose, sodium alginate and mixtures thereof are particularly preferred.

The amount of hydroxypropylmethylcellulose is generally from 18% to 40% by weight, preferably from 22% to 33% by weight.

The amount of sodium alginate is generally from 7% to 25% by weight, preferably from 11% to 22% by weight.

Among the complexing oligomers β-cyclodextrin in amounts generally from 7% to 25% by weight, preferably from 10% to 22% by weight, is preferably used.

For the gastro-resistant layer of the tablet object of the present invention, the combination sodium alginate, hydroxypropylmethylcellulose and β-cyclodextrin is particularly preferred.

The trilayered formulation object of the present invention is particularly suitable for the administration of combinations of active ingredients with different pharmaco-kinetic properties and/or dosage schedules.

In a particularly preferred embodiment, the trilayered tablet of the invention is used for the administration of a combination of gabapentin and flurbiprofenin a single oral pharmaceutical dosage form.

The gabapentin-flurbiprofen combination is particularly effective for the treatment of low urinary tract disorders with the following dosage regimen:

Gabapentin 375 mg, in two aliquots of 300 mg + 75 mg splitted among layer A and layer B respectively, and flurbiprofen 37.5 mg in layer C, twice a day.

The release kinetics of the two active ingredients from the pharmaceutical dosage form must be then able to cover a period of 6-12 hours between an administration and the subsequent one.

This is achieved by the trilayered tablet object of the present invention as follows:

layer A contains gabapentin (300 mg). After splitting from the other layers, this layer floats into the stomach and releases the second aliquot of gabapentin for a period of 6-8 hours;

layer B contains gabapentin (75 mg) and rapidly disintegrates into the stomach causing the splitting of the tablet into the two layers A and C and the immediate release of the first aliquot of gabapentin into the stomach;

layer C contains flurbiprofen (37.5 mg). The release of flurbiprofen starts in a significant way only when the layer reaches the intestine and continues for 6-8 hours.

In order to adapt the dosage regimen to different kinds of patients, it is also possible to prepare trilayered gabapentin/flurbiprofen tablets having a reduced dosage:

Gabapentin 250 mg, in two aliquots of 200 mg + 50 mg, splitted between layer A and layer B respectively, and flurbiprofen 25 mg in layer C.

As already described, the release kinetics of the two active ingredients from the pharmaceutical trilayered form must be able to cover a period of 6-12 hours between an administration and the subsequent one.

Layer A contains gabapentin (200 mg). After splitting from the other layers, this layer floats into the stomach and releases the second aliquot of gabapentin for a period of 6-8 hours.

Layer B contains gabapentin (50 mg) and rapidly disintegrates into the stomach causing the splitting of the tablet into the two layers A and C and the immediate release of the first aliquot of gabapentin into the stomach.

Layer C contains flurbiprofen (25 mg). The release of flurbiprofen starts only when the layer reaches the intestine and continues for 6-8 hours.

Another example of gabapentin/flurbiprofen trilayered tablets having a reduced dosage is:

Gabapentin 190 mg, in two aliquots of 150 mg + 40 mg, splitted between layer A and layer B respectively, and flurbiprofen 19 mg in layer C.

Also in this case, the release kinetics of the two active ingredients from the pharmaceutical trilayered form must be able to cover a period of 6-12 hours between an administration and the subsequent one.

Layer A contains gabapentin (150 mg). After splitting from the other layers, this layer floats into the stomach and releases the second aliquot of gabapentin for a period of 6-8 hours.

Layer B contains gabapentin (40 mg) and rapidly disintegrates into the stomach causing the splitting of the tablet into the two layers A and C and the immediate release of the first aliquot of gabapentin into the stomach.

Layer C contains flurbiprofen (19 mg). The release of flurbiprofen starts only when the layer reaches the intestine and continues for 6-8 hours.

Another dosage regimen which represents an help to the patient compliance is represented by the gabapentin/flurbiprofen trilayered tablets with increased dosage for the once-a-day administration:

Gabapentin 500 mg, in two aliquots of 450 mg + 50 mg, and flurbiprofen 50 mg in two aliquots of 45 mg and 5 mg.

Layer A contains gabapentin (450 mg). After splitting from the other layers, this layer floats into the stomach and releases the second aliquot of gabapentin.

Layer B contains gabapentin (50 mg) and flurbiprofen (5 mg) and rapidly disintegrates into the stomach causing the splitting of the tablet into the two layers A and C and the immediate release of the first aliquot of gabapentin and flurbiprofen into the stomach.

Layer C contains flurbiprofen (45 mg). The release of flurbiprofen starts only when the layer reaches the intestine.

The dissolution profile of the trilayered tablets according to the present invention has been evaluated by *in vitro* and *in vivo* experiments.

The *in vitro* experiments have been carried out in simulated gastric fluid also under conditions simulating unempty stomach. The resultant dissolution profiles did not show significant differences proving that the release of the drug from the tablets of the present invention was not affected by the content of the stomach.

The *in vivo* results confirm the release of gabapentin and flurbiprofen at different physiological sites, since the food prolonged the floating time of the gabapentin layer and it delayed the gastric transit time of the flurbiprofen layer, which releases the active ingredient at pH equal or greater than 4.5 when reaches duodenum.

Brief description of the figures

Figure 1 – dissolution profile of an oblong trilayered tablets containing gabapentin and flurbiprofen, prepared as described in example 1

Figure 2A – dissolution profile of an oblong trilayered tablets containing gabapentin and flurbiprofen, prepared as described in example 2

Figure 2B – dissolution profile of gabapentin in a tablet prepared as described in example 2 in simulated gastric fluid at pH 1.2, pH 1.6 (fasting condition) and pH 5.0 (fed condition)

Figure 3 – dissolution profile of an oblong trilayered tablets containing gabapentin and flurbiprofen, prepared as described in example 3

Figure 4 – dissolution profile of a cylindrical trilayered tablets containing gabapentin and flurbiprofen, prepared as described in example 6

Figure 5 – dissolution profile of a cylindrical trilayered tablets containing gabapentin and flurbiprofen, prepared as described in example 7

In order to better illustrate the present invention, without however limiting it, the following examples are now given.

Figure 6 – Mean plasma levels of gabapentin (±S.D.) in 24 healthy subjects in fasting and fed conditions.

Figure 7 – Mean plasma levels of flurbiprofen (±S.D.) in 24 healthy subjects in fasting and fed conditions.

Example 1

Oblong trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg.

Preparation of layer A

Hydroxypropylmethylcellulose and sodium bicarbonate were added to a granulate of gabapentin and glicerylbehenate, prepared by dry granulation. The powder was mixed in Turbula for 15 minutes. Subsequently talc, colloidal silica and magnesium stearate were added by mixing for further 5 minutes. The resultant mixture was compressed to obtain a layer weighing 458.33 mg.

The composition of layer A for each tablet is the following (within brackets percentage in weight):

Gabapentin	300 mg (65.46%)
Glicerylbehenate	15 mg (3.27%)
Hydroxypropylmethylcellulose (Methocel K15M, Colorcon)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.88%)
Colloidal silica (Aerosil 200NF, Evonik)	9.45 mg (2.06%)
Talc	6.3 mg (1.37%)

Magnesium stearate	1.58 mg (0.34%)

Preparation of layer B

Microcrystalline cellulose, calcium hydrogen phosphate dihydrate, crospovidone, starch, sodium croscarmellose and purple lake were added to a granulate of gabapentin and glicerylbehenate, prepared by dry granulation. The powder was mixed in Turbula for 15 minutes. Subsequently magnesium stearate and talc were added by mixing for further 5 minutes. The resultant mixture was compressed to obtain a layer weighing 236.06 mg.

The composition of layer B for each tablet is the following (within brackets percentage in weight):

Gabapentin	75 mg (31.77%)
Glicerylbehenate (Compritol 888 ATO, Gattefossé)	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102, FMC)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.71%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)

Preparation of layer C

Sodium alginate, hydroxypropylmethylcellulose and β-cyclodextrin were added to a granulate of flurbiprofen, mannitol and polyvinylpyrrolidone, prepared by wet granulation. The powder was mixed in Turbula for 15 minutes. Subsequently magnesium stearate and yellow lake were added by mixing for further 5 minutes. The resultant mixture was compressed to obtain a layer weighing 200.2 mg.

The composition of layer C for each tablet is the following (within brackets

percentage in weight):

Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30, BASF)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	44.16 mg (22.06%)
Hydroxypropylmethylcellulose (Methocel K4M, Colorcon)	44.16 mg (22.06%)
Magnesium stearate	1 mg (0.5%)
Yellow lake	0.49 mg (0.24%)

Preparation of the trilayered tablets

The trilayered tablets were prepared by compressing in a single solid form layer A, layer B and layer C, prepared as above described, after having put them down in sequence into the die of a tabletting machine with oblong 9x19 mm punches.

The compression was carried out according to the following steps:

Step 1 – placing into the die the amount of mixture to be used for the preparation of layer A and pre-compressing up to a tap density value of about 1.43 g/ml.

Step 2 – placing the amount of mixture corresponding to layer B on the previous pre-compressed layer. The powder bed was pre-compressed again up to a tap density of about 1.26 g/ml for both layers.

Step 3 – placing layer C and final compression of the three layers to obtain a trilayered tablet having the following physical characterisitcs:

thickness: 6.35 ± 0.03 mm

hardness: 14.2 ± 0.8 Monsanto units

Example 2

Oblong trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg

By working in a way similar to that described in example 1, trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 1, the

composition of layer C was changed to obtain a slower delayed flurbiprofen release.

Composition of layer A	
Gabapentin	300 mg (65.46%)
Glicerylbehenate (Compritol 888 ATO)	15 mg (3.27%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.88%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.06%)
Talc	6.3 mg (1.37%)
Magnesium stearate	1.58 mg (0.34%)
Composition of layer B	
Gabapentin	75 mg (31.77%)
Glicerylbehenate (Compritol 888 ATO)	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.1%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)
Composition of layer C	
Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	22.08 mg (11.03%)
Hydroxypropylmethylcellulose (Methocel K4M)	66.24 mg (33.09%)

Magnesium stearate	1 mg (0.5%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 6.45 ± 0.03 mm

hardness: 11.5 ± 0.5 Monsanto units

Example 3

Oblong trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg

By working in a way similar to that described in example 1, trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 1, the composition of layer A was changed by replacing the hydrophilic polymer hydroxypropylmethylcellulose with polyethylenoxide.

Composition of layer A

Gabapentin	300 mg (65.46%)
Glycerylbehenate (Compritol 888 ATO)	15 mg (3.27%)
Polyethylenoxide (PolyoxWSR 303, Colorcon)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.88%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.06%)
Talc	6.3 mg (1.37%)
Magnesium stearate	1.58 mg (0.34%)

Composition of layer B

Gabapentin	75 mg (31.77%)
Glycerylbehenate (Compritol 888 ATO)	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.71%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)

Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)

Composition of layer C

Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	44.16 mg (22.06%)
Hydroxypropylmethylcellulose (Methocel K4M)	44.16 mg (22.06%)
Magnesium stearate	1 mg (0.5%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 6.99 ± 0.02 mm

hardness: 13.8 ± 0.5 Monsanto units

Example 4

Oblong trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg

By working in a way similar to that described in example 1, trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 3, the composition of layer C was changed to obtain a slower delayed flurbiprofen release.

Composition of layer A

Gabapentin	300 mg (65.46%)
Glycerylbehenate (Compritol 888 ATO)	15 mg (3.27%)
Polyethylenoxide (PolyoxWSR 303, Colorcon)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.88%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.06%)
Talc	6.3 mg (1.37%)

Magnesium stearate	1.58 mg (0.34%)

Composition of layer B

Gabapentin	75 mg (31.77%)
Glycerylbehenate (Compritol 888 ATO)	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.71%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)

Composition of layer C

Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	22.08 mg (11.03%)
Hydroxypropylmethylcellulose (Methocel K4M)	66.24 mg (33.09%)
Magnesium stearate	1 mg (0.5%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 6.55 ± 0.03 mm

hardness: 14.5 ± 0.5 Monsanto units

Example 5

Dissolution test

The dissolution profile of the trilayered tablets prepared as described in examples 1,

2 and 3 was determined by immersion into simulated gastric fluid (USP apparatus II for dissolution test).

After immersion, the tablets (n = 6) placed themselves on the bottom of the vessel and the development of CO_2 bubbles which remained entrapped into the hydroxypropylmethylcellulose gel formed in contact with the aqueous medium was observed from layer A. At the same time, layer B rapidly disintegrated in correspondence with the side surface of the layer exposed to the simulated gastric fluid.

The complete separation of the layers was observed after 54 seconds for the tablet prepared as described in example 1, after 57 seconds for the tablet prepared as described in example 2 and after 4 minutes for the tablet prepared as described in example 3.

The floating of layer A was observed about 24 seconds after the splitting of the layers for the tablet prepared as described in example 1; about simultaneously to the splitting of the layers for the tablet prepared as described in example 2 and about 2 minutes after the splitting of the layers for the tablet prepared as described in example 3.

The dissolution rate of trilayered tablets prepared as described in example 2, was evaluated also under simulated fasting and fed conditions. The evaluation was carried out under the following conditions: simulated gastric fluid at pH1.2 (SGF), simulated gastric fluid at pH 1.6 (FaSSGF) for fasting conditions and simulated gastric fluid at pH 5.0 (FeSSGFm) for fed conditions.

In Figure 1 the dissolution profile of gabapentin and flurbiprofen for the tablets of example 1 is graphically reported.

Gabapentin contained in layer B was released in the first 5 minutes while the remaining dose of gabapentin contained in layer A was slowly released in a prolonged way in about 8 hours. Flurbiprofen contained in layer C was not released in the first hour. After having raised the pH to 7.2 the release developed in a linear

way reaching 100% in 5 hours.

In Figure 2A the dissolution profile of gabapentin and flurbiprofen for the tablets of example 2 is graphically reported.

Gabapentin contained in layer B was released in the first 15 minutes while the remaining dose of gabapentin contained in layer A was slowly released in a prolonged way in about 9 hours. Flurbiprofen contained in layer C was not released at pH 1.2. After having raised the pH to 7.2 the release developed in a linear way reaching 90% in 6 hours.

In Figure 2B the dissolution profiles of gabapentin for the tablets of example 2 in SGF, FaSSGF and FeSSGFm are graphically reported.

The three profiles did not show significant differences. The f_2 factor, similarity index between SGF and FaSSGF release profiles (f_2 = 83), between SGF and FeSSGFm release profiles (f_2 = 65.8) and between FaSSFG and FeSSGFm release profiles (f_2 = 55.7), was always higher than 50, showing that the drug release rate was not affected by the simulated conditions of fast or fed stomach.

In Figure 3 the dissolution profile of gabapentin and flurbiprofen for the tablets of example 3 is graphically reported.

Gabapentin contained in layer B was released in the first 15 minutes while the remaining dose of gabapentin contained in layer A was slowly released in a prolonged way in about 9 hours. Flurbiprofen contained in layer C was not released at pH 1.2. After having raised the pH to 7.2 the release developed in a linear way reaching 90% in 6 hours.

Example 6

Cylindrical trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg

By working in a way similar to that described in example 1, cylindrical trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 1, the composition of layer A was changed by increasing the amount of

sodium bicarbonate to promote the floating of the layer.

Composition of layer A	
Gabapentin	300 mg (63.28%)
Glycerylbehenate (Compritol 888 ATO)	15 mg (3.16%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (19.93%)
Sodium bicarbonate	47.25 mg (9.97%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.0%)
Talc	6.3 mg (1.33%)
Magnesium stearate	1.58 mg (0.33%)
Composition of layer B	
Gabapentin	75 mg (31.77%)
Glycerylbehenate	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.71%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)
Composition of layer C	
Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	44.16 mg (22.06%)
Hydroxypropylcellulose (Methocel K4M)	44.16 mg (22.06%)
Magnesium stearate	1 mg (0.5%)

Yellow lake	0.49 mg (0.24%)

The compression was carried out with cylindrical 12 mm punches according to the following steps:

Step 1 – placing into the die the amount of mixture to be used for the preparation of layer A and pre-compressing up to a tap density value of about 1.1 g/ml.

Step 2 – placing the amount of mixture corresponding to layer B on the previous pre-compressed layer. The powder bed was pre-compressed again up to a tap density of about 1.39 g/ml for both layers.

Step 3 – placing layer C and final compression of the three layers to obtain a trilayered tablet having the following physical characteristics:

thickness: 7.6 ± 0.08 mm

hardness: 9.6 ± 1.7 Monsanto units

Example 7

Cylindrical trilayered tablet containing gabapentin 375 mg and flurbiprofen 37.5 mg

By working in a way similar to that described in example 6, cylindrical trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 6, the composition of layer C was changed to obtain a slower flurbiprofen delayed release.

Composition of layer A

Gabapentin	300 mg (63.28%)
Glycerylbehenate (Compritol 888 ATO)	15 mg (3.16%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (19.93%)
Sodium bicarbonate	47.25 mg (9.97%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.0%)
Talc	6.3 mg (1.33%)
Magnesium stearate	1.58 mg (0.33%)

Composition of layer B

Gabapentin	75 mg (31.77%)
Glycerylbehenate (Compritol 888 ATO)	3.75 mg (1.59%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (10.01%)
Calcium hydrogen phosphate dihydrate	114.98 mg (48.71%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.88 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.16%)
Purple lake	0.19 mg (0.08%)

Composition of layer C

Flurbiprofen	37.5 mg (18.73%)
Mannitol	24.01 mg (12.0%)
Polyvinylpyrrolidone (PVPK30)	4.72 mg (2.36%)
β-cyclodextrin	44.16 mg (22.06%)
Sodium alginate	22.08 mg (11.03%)
Hydroxypropylmethylcellulose (Methocel K4M)	66.24 mg (33.09%)
Magnesium stearate	1 mg (0.5%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 7.6 ± 0.03 mm

hardness: 12.5 ± 0.5 Monsanto units

Example 8

Dissolution test

The dissolution profile of the trilayered tablets prepared as described in examples 6, and 7 was determined by immersion into simulated gastric fluid (USP apparatus II for dissolution test).

After immersion, the tablets (n = 6) placed themselves on the bottom of the vessel

and the development of CO_2 bubbles which remained entrapped into the hydroxypropylmethylcellulose gel formed in contact with the aqueous medium was observed from layer A. At the same time, layer B rapidly disintegrated in correspondence with the side surface of the layer exposed to the simulated gastric fluid.

The beginning of the floating of layer A was observed about 29±4 seconds for the tablet prepared as described in example 4, about simultaneously to the splitting of the layers. For the tablet prepared as described in example 5, the beginning of the floating of layer A was observed after 24±8 seconds, also in this case about simultaneously to the splitting of the layers.

In Figure 4 the dissolution profile of gabapentin and flurbiprofen for the tablets of example 6 is graphically reported.

Gabapentin contained in layer B was released in the first 15 minutes while the remaining dose of gabapentin contained in layer A was slowly released in a prolonged way reaching 90% in about 9 hours. Flurbiprofen contained in layer C was not released in the first hour. After having raised the pH to 7.2 the release reached 100% in 5 hours.

In Figure 5 the dissolution profile of gabapentin and flurbiprofen for the tablets of example 7 is graphically reported.

Gabapentin contained in layer B was released in the first 15 minutes while the remaining dose of gabapentin contained in layer A was slowly released in a prolonged way in about 9 hours. Flurbiprofen contained in layer C was not released at pH 1.2. After having raised the pH to 7.2 the release developed in a linear way reaching 90% in 7 hours.

Example 9

Oblong trilayered tablet containing gabapentin 250 mg and flurbiprofen 25 mg

By working in a way similar to that described in example 1, trilayered tablets with reduced dosage having the following composition of the layers for each tablet

(between brackets the weight percentage for each layer) were prepared. Compared with the formulations containing 375 and 37.5 mg, the removed amounts of active ingredients were replaced by mannitol. In case of the floating prolonged release gabapentin layer (Layer A), the amount of gabapentin was replaced by an equal amount of mannitol dry granulated with glycerylbehenate. In case of the delayed release flurbiprofen layer, the removed amount of drug was replaced by an equivalent amount of mannitol in the granulate.

Composition of layer A

Gabapentin	200 mg (43.64%)
Glycerylbehenate (Compritol 888 ATO)	10 mg (2.18%)
Mannitol (Pearlitol 160C, Roquette)	100 mg (21.82%)
Glycerylbehenate (Compritol 888 ATO)	5 mg (1.09%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.87%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.06%)
Talc	3.15 mg (1.37%)
Magnesium stearate	1.58 mg (0.35%)

Composition of layer B

Gabapentin	50 mg (21.18%)
Glycerylbehenate (Compritol 888 ATO)	2.5 mg (1.06%)
Microcrystalline cellulose (Avicel PH102)	29.02 mg (12.99%)
Calcium hydrogen phosphate dihydrate	135.83 mg (57.54%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.86 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.17%)
Purple lake	0.19 mg (0.08%)

Composition of layer C

Flurbiprofen	25 mg (12.15%)
Mannitol (Pearlitol 160C)	16 mg (7.77%)
Polyvinylpyrrolidone (PVPK30)	4.4 mg (2.14%)
β-cyclodextrin	45.4 mg (22.06%)
Sodium alginate	45.4 mg (22.06%)
Hydroxypropylmethylcellulose (MethocelK4M)	45.4 mg (22.06%)
Mannitol (Pearlitol SD200, Roquette)	22.7 mg (11.03%)
Magnesium stearate	1 mg (0.49%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 6.29 ± 0.03 mm

hardness: 14.6 ± 0.7 Monsanto units

Example 10

Oblong trilayered tablet containing gabapentin 250 mg and flurbiprofen 25 mg

By working in a way similar to that described in example 9, trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 9, the composition of layer C was changed to obtain a slower flurbiprofen delayed release.

Composition of layer A

Gabapentin	200 mg (43.64%)
Glycerylbehenate (Compritol 888 ATO)	10 mg (2.18%)
Mannitol (Pearlitol 160C)	100 mg (21.82%)
Glycerylbehenate (Compritol 888 ATO)	5 mg (1.09%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (20.62%)
Sodium bicarbonate	31.5 mg (6.87%)
Colloidal silica (Aerosil 200NF)	9.45 mg (2.06%)
Talc	3.15 mg (1.37%)

Magnesium stearate	1.58 mg (0.35%)
Composition of layer B	
Gabapentin	50 mg (21.18%)
Glycerylbehenate (Compritol 888 ATO)	2.5 mg (1.06%)
Microcrystalline cellulose (Avicel PH102)	29.02 mg (12.99%)
Calcium hydrogen phosphate dihydrate	135.83 mg (57.54%)
Crospovidone	3.15 mg (1.33%)
Maize starch	7.86 mg (3.34%)
Sodium croscarmellose	3.94 mg (1.67%)
Talc	3.15 mg (1.33%)
Magnesium stearate	0.39 mg (0.17%)
Purple lake	0.19 mg (0.08%)
Composition of layer C	
Flurbiprofen	25 mg (12.15%)
Mannitol (Pearlitol 160C)	16 mg (7.77%)
Polyvinylpyrrolidone (PVPK30)	4.4 mg (2.14%)
β-cyclodextrin	45.4 mg (22.06%)
Sodium alginate	22.7 mg (11.03%)
Hydroxypropylmethylcellulose (MethocelK4M)	68.1 mg (33.09%)
Mannitol (Pearlitol SD200)	22.7 mg (11.03%)
Magnesium stearate	1 mg (0.49%)
Yellow lake	0.49 mg (0.24%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 6.34 ± 0.09 mm

hardness: 16.0 ± 0.8 Monsanto units

Example 11

Oblong trilayered tablet containing gabapentin 190 mg and flurbiprofen 19 mg

By working in a way similar to that described in example 1, trilayered tablets with

reduced dosage having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with the formulations containing 375 and 37.5 mg, the removed amounts of active ingredients were replaced by mannitol. In case of the floating prolonged release gabapentin layer (Layer A), the amount of gabapentin was replaced by an equal amount of mannitol dry granulated with glycerylbehenate. Also in the other two layers, the removed amount of drug was replaced by an equivalent amount of mannitol in the granulate.

Composition of layer A

Gabapentin	150 mg (32.75%)
Mannitol (Pearlitol 160C)	150 mg (32.75%)
Glycerylbehenate (Compritol 888 ATO)	15 mg (3.28%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (20.63%)
Sodium bicarbonate	31.5 mg (6.88%)
Colloidal silica (Aerosil 200NF)	9.12 mg (1.99%)
Talc	6.3 mg (1.37%)
Magnesium stearate	1.58 mg (0.35%)

Composition of layer B

Gabapentin	40 mg (14.29%)
Mannitol (Pearlitol 160C)	40 mg (14.29%)
Glycerylbehenate (Compritol 888 ATO)	4 mg (1.43%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (8.44%)
Calcium hydrogen phosphate dihydrate	114.98 mg (41.06%)
Crospovidone	3.15 mg (1.12%)
Maize starch	7.88 mg (2.81%)
Sodium croscarmellose	3.94 mg (1.41%)
Mannitol (Pearlitol SD200, Roquette)	37.04 mg (13.23%)
Colloidal silica (Aerosil 200NF)	0.70 mg (0.25%)

Talc	3.15 mg (1.12%)
Magnesium stearate	1.40 mg (0.50%)
Purple lake	0.13 mg (0.05%)

Composition of layer C

Flurbiprofen	19 mg (6.19%)
Mannitol (Pearlitol 160C)	13.22 mg (4.3%)
Polyvinylpyrrolidone (PVPK30)	1.34 mg (0.44%)
β-cyclodextrin	68.09 mg (22.18%)
Sodium alginate	68.09 mg (22.18%)
Hydroxypropylmethylcellulose (MethocelK4M)	68.09 mg (22.18%)
Mannitol (Pearlitol SD200)	67.26 mg (21.91%)
Magnesium stearate	1.51 mg (0.49%)
Yellow lake	0.40 mg (0.13%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 7.43 ± 0.07 mm

hardness: 12.4 ± 1.5 Monsanto units

Example 12

Oblong trilayered tablet containing gabapentin 190 mg and flurbiprofen 19 mg

By working in a way similar to that described in example 11, trilayered tablets having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with example 11, the composition of layer C was changed to obtain a slower flurbiprofen delayed release.

Composition of layer A

Gabapentin	150 mg (32.75%)
Mannitol (Pearlitol 160C)	150 mg (32.75%)
Glycerylbehenate	15 mg (3.28%)
Hydroxypropylmethylcellulose (Methocel K15M)	94.5 mg (20.63%)
Sodium bicarbonate	31.5 mg (6.88%)

Colloidal silica (Aerosil 200NF)	9.12 mg (1.99%)
Talc	6.3 mg (1.37%)
Magnesium stearate	1.58 mg (0.35%)
Composition of layer B	
Gabapentin	40 mg (14.29%)
Mannitol (Pearlitol 160C)	40 mg (14.29%)
Glycerylbehenate (Compritol 888 ATO)	4 mg (1.43%)
Microcrystalline cellulose (Avicel PH102)	23.63 mg (8.44%)
Calcium hydrogen phosphate dihydrate	114.98 mg (41.06%)
Crospovidone	3.15 mg (1.12%)
Maize starch	7.88 mg (2.81%)
Sodium croscarmellose	3.94 mg (1.41%)
Colloidal silica (Aerosil 200NF)	0.70 mg (0.25%)
Mannitol (Pearlitol SD200)	37.04 mg (13.23%)
Talc	3.15 mg (1.12%)
Magnesium stearate	1.40 mg (0.50%)
Purple lake	0.13 mg (0.05%)
Composition of layer C	
Flurbiprofen	19 mg (6.19%)
Mannitol (Pearlitol 160C)	13.22 mg (4.3%)
Polyvinylpyrrolidone (PVPK30)	1.34 mg (0.44%)
β-cyclodextrin	68.09 mg (22.18%)
Sodium alginate	34.05 mg (11.09%)
Hydroxypropylmethylcellulose (MethocelK4M)	102.13 mg (32.27%)
Mannitol (Pearlitol SD200)	67.26 mg (21.91%)
Magnesium stearate	1.51 mg (0.49%)
Yellow lake	0.40 mg (0.13%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 7.46 ± 0.06 mm

hardness: 11.8 ± 0.9 Monsanto units

Example 13

Oblong trilayered tablet containing gabapentin 500 mg and flurbiprofen 50 mg

By working in a way similar to that described in example 1, trilayered tablets with increased once-a-day dosage having the following composition of the layers for each tablet (between brackets the weight percentage for each layer) were prepared. Compared with the previous formulations the intermediate immediate release layer was prepared by mixing the two previously prepared granulates of gabapentin and flurbiprofen and by adding further excipients among which there is also β-cyclodextrin, needed to solubilize flurbiprofen in acid medium where the drug is very low soluble.

The fraction of flurbiprofen in the immediate release layer corresponds to 10% of the total dose.

Composition of layer A	
Gabapentin	450 mg (65.46%)
Glycerylbehenate (Compritol 888 ATO)	22.48 mg (3.27%)
Hydroxypropylmethylcellulose (Methocel K15M)	141.75 mg (20.62%)
Sodium bicarbonate	47.3 mg (6.88%)
Colloidal silica (Aerosil 200NF)	14.16 mg (2.06%)
Talc	9.42 mg (1.37%)
Magnesium stearate	2.34 mg (0.34%)
Composition of layer B	
Gabapentin	50 mg (18.50%)
Flurbiprofen	5 mg (1.85%)
Glycerylbehenate (Compritol 888 ATO)	2.5 mg (0.92%)

Mannitol (Pearlitol 160C)	3 mg (1.11%)
Polyvinylpyrrolidone (PVP K30)	0.35 mg (0.13%)
β-cyclodextrin	5 mg (1.85%)
Microcrystalline cellulose (Avicel PH102)	26.63 mg (9.85%)
Calcium hydrogen phosphate dihydrate	114.98 mg (42.54%)
Crospovidone	3.15 mg (1.17%)
Maize starch	7.88 mg (2.92%)
Sodium croscarmellose	3.94 mg (1.46%)
Mannitol (Pearlitol SD200)	42.49 mg (15.72%)
Colloidal silica (Aerosil 200NF)	0.70 mg (0.26%)
Talc	3.15 mg (1.17%)
Magnesium stearate	1.40 mg (0.52%)
Purple lake	0.13 mg (0.05%)

Composition of layer C

Flurbiprofen	45 mg (21.73%)
Mannitol (Pearlitol 160C)	27 mg (13.04%)
Polyvinylpyrrolidone (PVPK30)	3.15 mg (1.52%)
Mannitol (Pearlitol SD200)	20 mg (9.66%)
β-cyclodextrin	20 mg (9.66%)
Sodium alginate	22.63 mg (10.93%)
Hydroxypropylmethylcellulose (MethocelK4M)	67.89 mg (32.78%)
Magnesium stearate	0.96 mg (0.46%)
Yellow lake	0.48 mg (0.23%)

The physical characteristics of the resultant trilayered tablets were the following:

thickness: 7.84 ± 0.07 mm

hardness: 12.5 ± 1.3 Monsanto units

Example 14

In vivo studies

A three layer tablet of gabapentin 375 mg and flurbiprofen 37.5 mg, prepared as described in example 4, was administered to 24 healthy male and female subjects, 18-55 years old, in fasting conditions and after a high fat meal in single dose according to a randomized cross-over design. The treatment periods were separated by a wash out interval of at least 5 days.

Each dose was taken with 240 mL of water in fasting conditions from at least 10 hours or 30 minutes after a standardized meal, which was high-caloric (approximately 1000 Kcal) and high-fat (approximately 50 percent of total caloric content of the meal).

Gabapentin and flurbiprofen plasma levels were determined by a validated HPLC/MS/MS analytical method at the following times: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24 and 32 h post-dose.

Results show that release of gabapentin from floating layer is prolonged by presence of food compared to the administration in fasting conditions; both Cmax and AUC were significantly increased (Tables 1 and 2). As shown in Figure 6 plasma gabapentin levels were maintained at plateau over 8 hours in fed conditions compared to about 4 hours in fasting conditions.

Table 1

Main PK parameters (arithmetic mean ± s.d.) of gabapentin (n=24)

	Fasting conditions	Fed conditions
Cmax (ng/mL)	2340 ± 748	3080 ± 727
Tmax (hr)^	4 (2 – 7)	5 (2 – 10)
AUCinf (hr*ng/mL)	24126 ± 8150	39181 ± 9074

^median (min - max)

Table 2

Statistical analysis on gabapentin

Treament comparison		Ratio of geometric means	
	Parameter	Ratio (%)	90% CI
Test / Reference (Fed / fasting)	Cmax	136 %	119 – 155 %
	AUCinf	167 %	150 – 187 %

While results of flurbiprofen show that release was very low up to 2 hours after intake in fasting conditions and it was delayed up to 4 hours post dose in fed conditions, in agreement with a prolonged transit time through the stomach (Fig. 7). Plasma levels reached a plateau around 4 hour post dose in fasting conditions and around 6 hours in fed conditions, afterward levels were maintained constant up to 12 hours post dose. The high fat meal increased the Cmax compared to the fasting administration, however the AUC was not affected by food (Tables 3 and 4).

Table 3

Main PK parameters (arithmetic mean ± s.d.) of flurbiprofen (n=24)

	Fasting conditions	Fed conditions
Cmax (ng/mL)	1714 ± 380	2782 ± 943
Tmax (hr)^	12 (4 – 24)	10 (4 – 24)
AUCinf (hr*ng/mL)	35725 ± 13162	36201 ± 14711

^median (min - max)

Table 4

Statistical analysis on flurbiprofen data

Treament comparison		Ratio of geometric means	
	Parameter	Ratio (%)	90% CI
Test / Reference (Fed / fasting)	Cmax	157 %	136 – 181 %
	AUCinf	98 %	94 – 103 %

CLAIMS

1) A trilayered tablet for oral administration comprising a central rapidly disintegrating layer (layer B) placed between a swelling floating layer having a sustained release hydrophilic matrix (layer A) and a layer having a gastro-resistant or delayed release or gastro-resistant controlled release hydrophilic matrix (layer C).

2) A tablet according to claim 1 wherein layer A consists of a hydrophilic matrix swelling and floating in an aqueous medium and releasing the drug in a sustained way in the first tract of the gastro-intestinal apparatus.

3) A tablet according to claim 2 wherein the hydrophilic matrix contains a swelling polymer selected among cellulose derivatives, such as hydroxypropylmethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose, alginates, scleroglucans, carrageenans and non ionic polymers, such as polyethylenoxide, and a substance able to develop gas selected among alkaline and alkaline earth metal carbonates and bicarbonates.

4) A tablet according to claim 3 wherein the substance able to develop gas is sodium bicarbonate in an amount from 5% to 10% by weight.

5) A tablet according to claim 1 wherein layer B is formulated to rapidly disintegrate so rapidly and immediately releasing the drug optionally contained therein into the stomach and causing the separation of the trilayered tablet into the two parts corresponding to layers A and C.

6) A tablet according to claim 5 wherein layer B contains a disintegrant selected among starch, microcrystalline cellulose, combinations of sodium bicarbonate and citric/tartaric acid, or a super-disintegrant selected among crospovidone, sodium croscarmellose, sodium carboxymethyl starch, or mixtures thereof.

7) A tablet according to claim 1 wherein layer C is a gastro-resistant controlled release formulation mainly releasing the drug in the intestine for a period of some hour.

8) A tablet according to claim 7 wherein the gastro-resistant formulation contains an

excipient selected among methacrylic polymers soluble at basic pH, cellulose acetophthalate, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate, sodium alginate, scleroglucan, carrageenan and other anionic polymers.

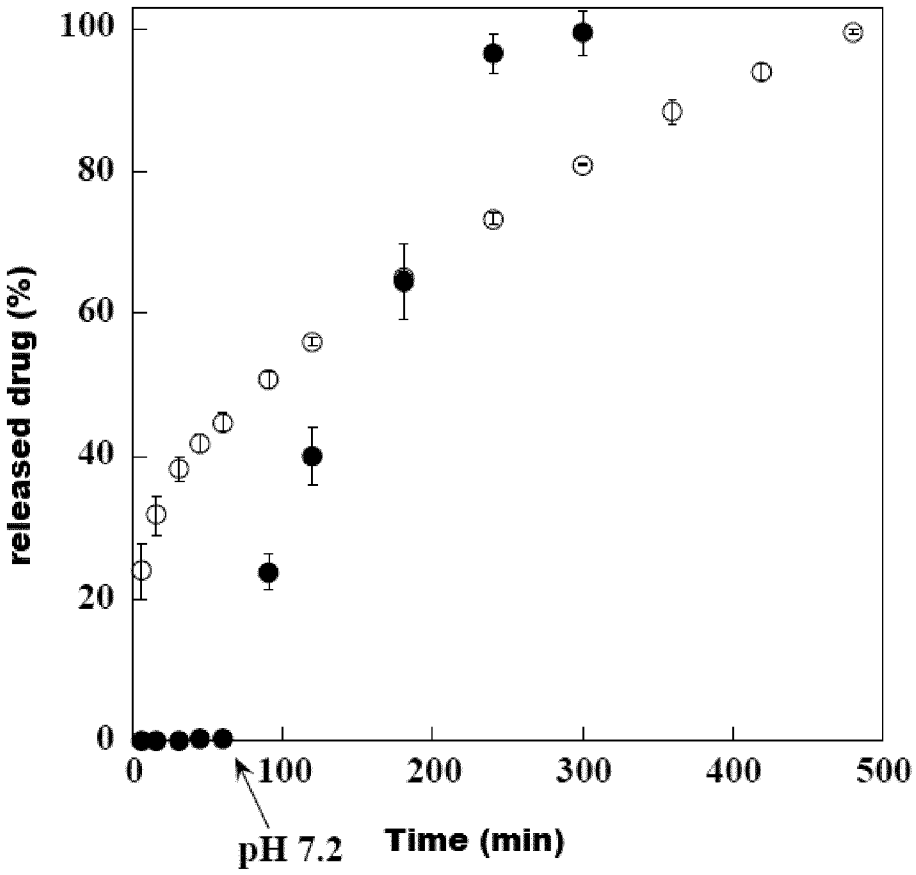
9) A tablet according to claim 7 wherein the gastro-resistant formulate contains a complexing oligomer.

10) A tablet according to claim 1 for the administration of a combination of two active ingredients selected among gabapentin, ACE-inhibitors, angiotensin II receptor antagonists, metformin, baclofen, H2-inhibitors, antibiotics for Helicobacter Pylori eradication, proton pump inhibitors, non steroidal anti-inflammatory agents, calcium antagonists.

11) A tablet according to claim 10 for the administration of a combination selected among combinations of proton pump inhibitors and H2 receptor antagonists, combinations of non steroidal anti-inflammatory agents and proton pump inhibitors or H2 receptor antagonists, combinations of ACE-inhibitors and calcium antagonists, combinations of angiotensin II receptor antagonists and calcium antagonists, combinations of ACE-inhibitors and angiotensin II receptor antagonists, combinations of antibiotics for Helicobacter Pylori eradication and proton pump inhibitors, combinations of metformin and glicazide or glipizide or sitagliptin, combinations of baclofen and proton pump inhibitors.

12) A tablet according to claim 11 for the administration of a combination of flurbiprofen and gabapentin.

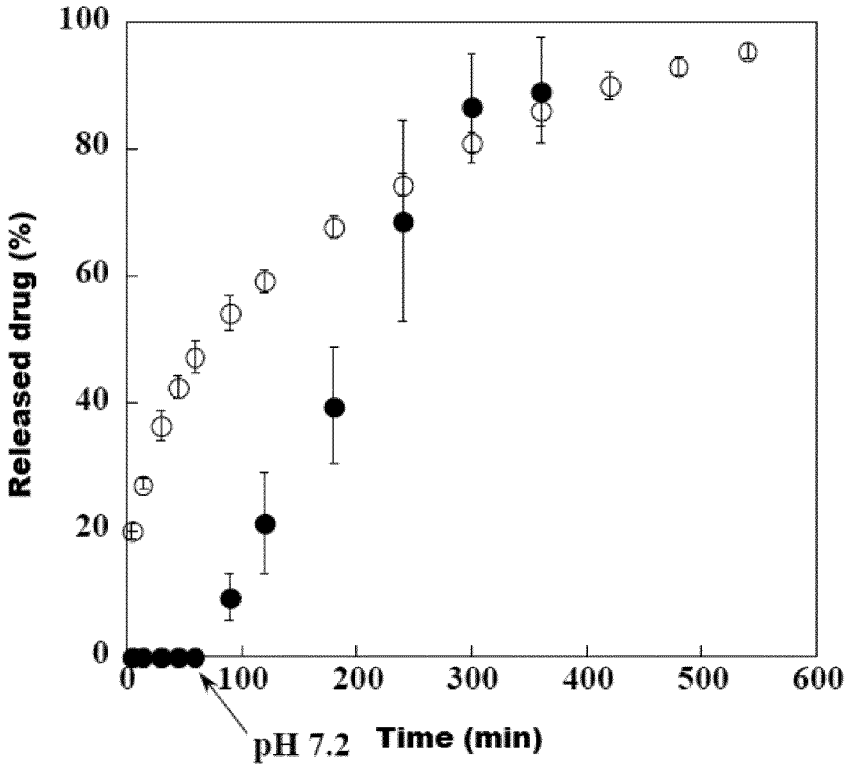
FIGURE 1



●flurbiprofen

○gabapentin

FIGURE 2A



●flurbiprofen

○gabapentin

FIGURE 2B

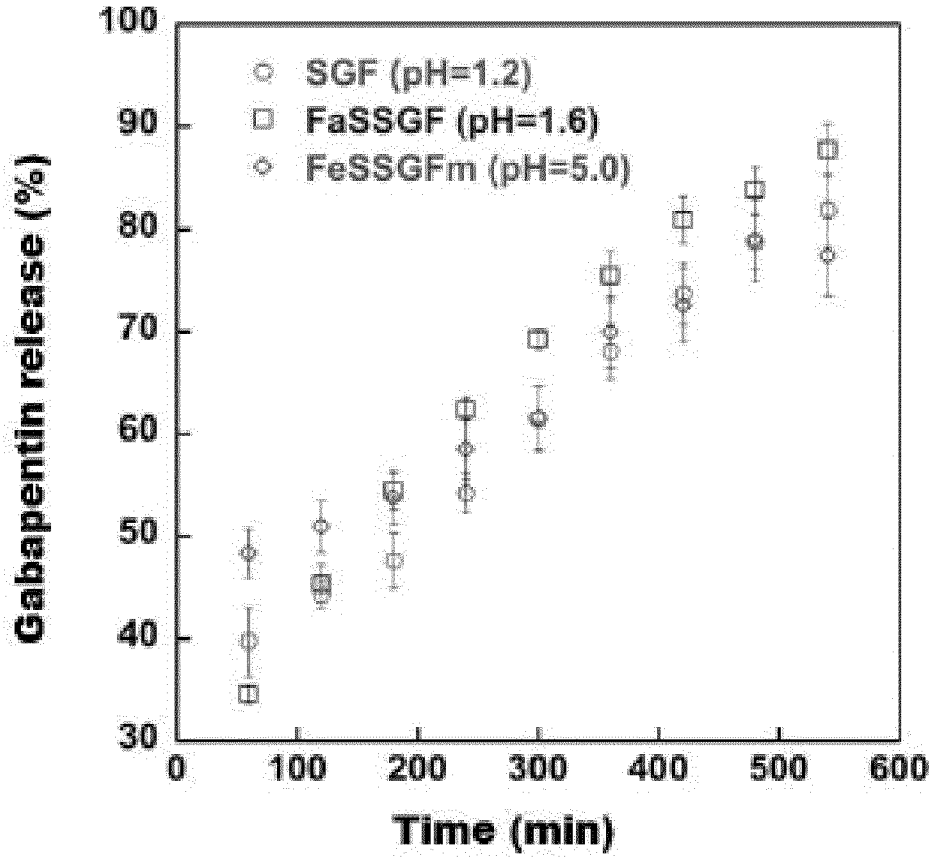
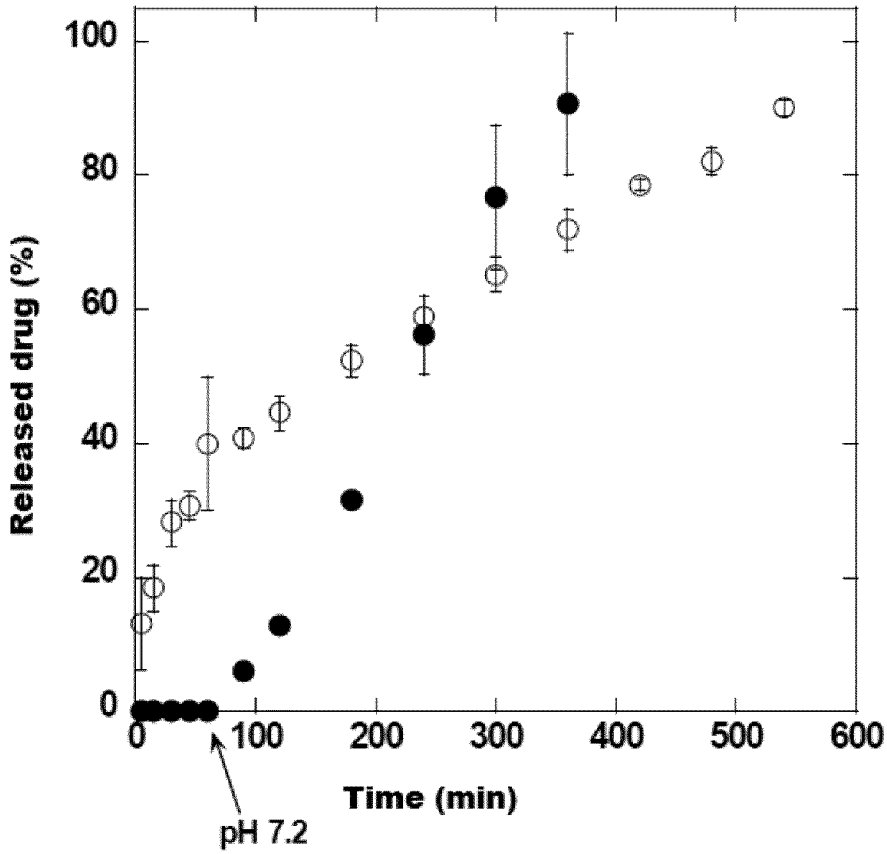

SGF (pH=1.2)
FaSSGF (pH=1.6)
FeSSGFm (pH=5.0)
Gabapentin release (%)
Time (min)
100
90
80
70
60
50
40
30
0
100
200
300
400
500
600

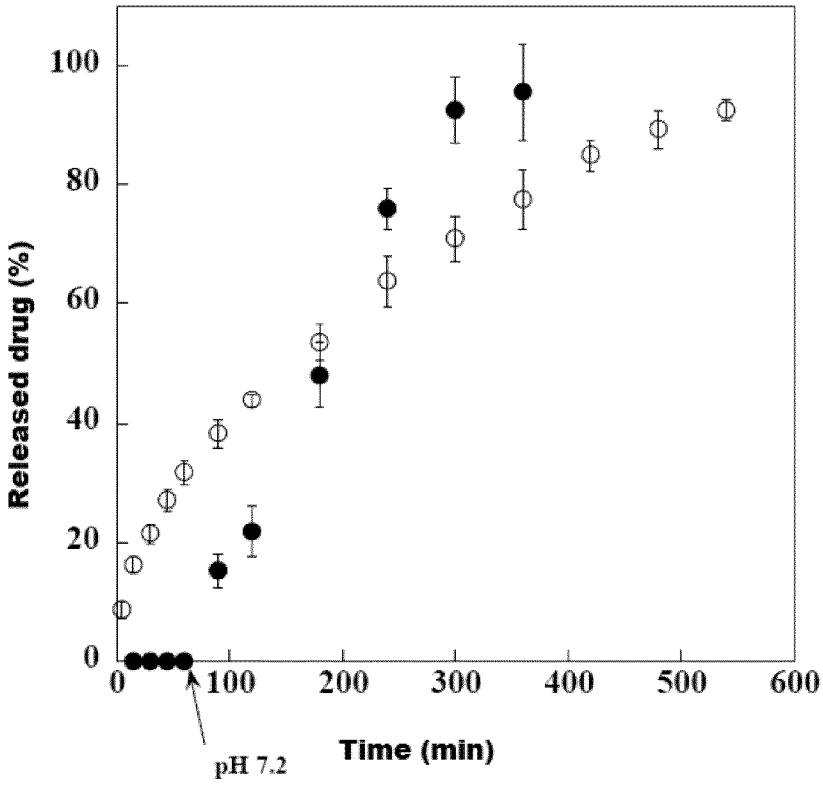
FIGURE 3



●flurbiprofen

○gabapentin

FIGURE 4



●flurbiprofen

○gabapentin

FIGURE 5

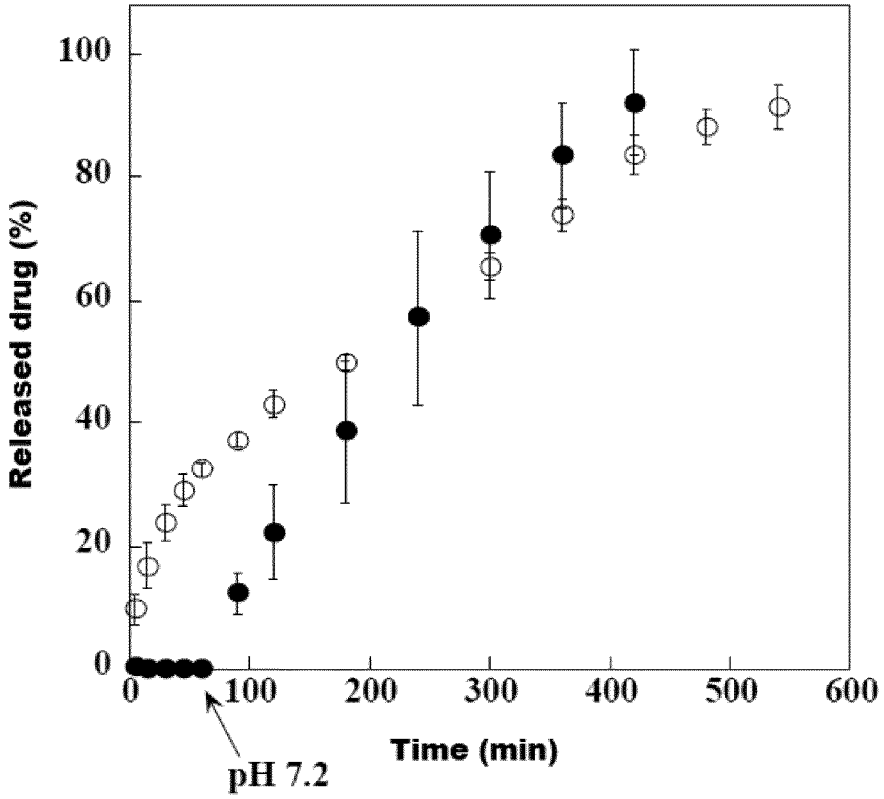

Released drug (%)
100
80
60
40
20
0
0
100
200
300
400
500
600
Time (min)
pH 7.2
●flurbiprofen
○gabapentin

FIGURE 6

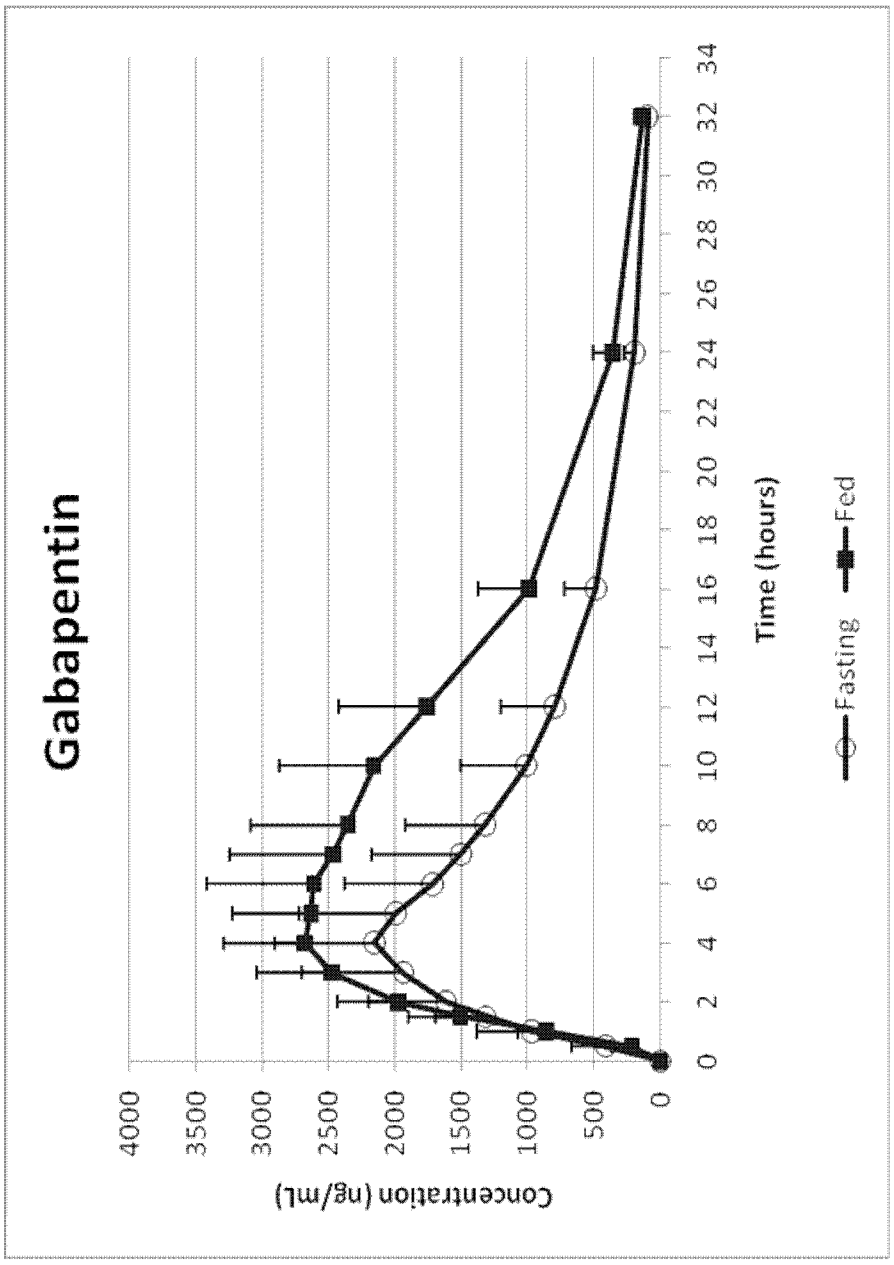
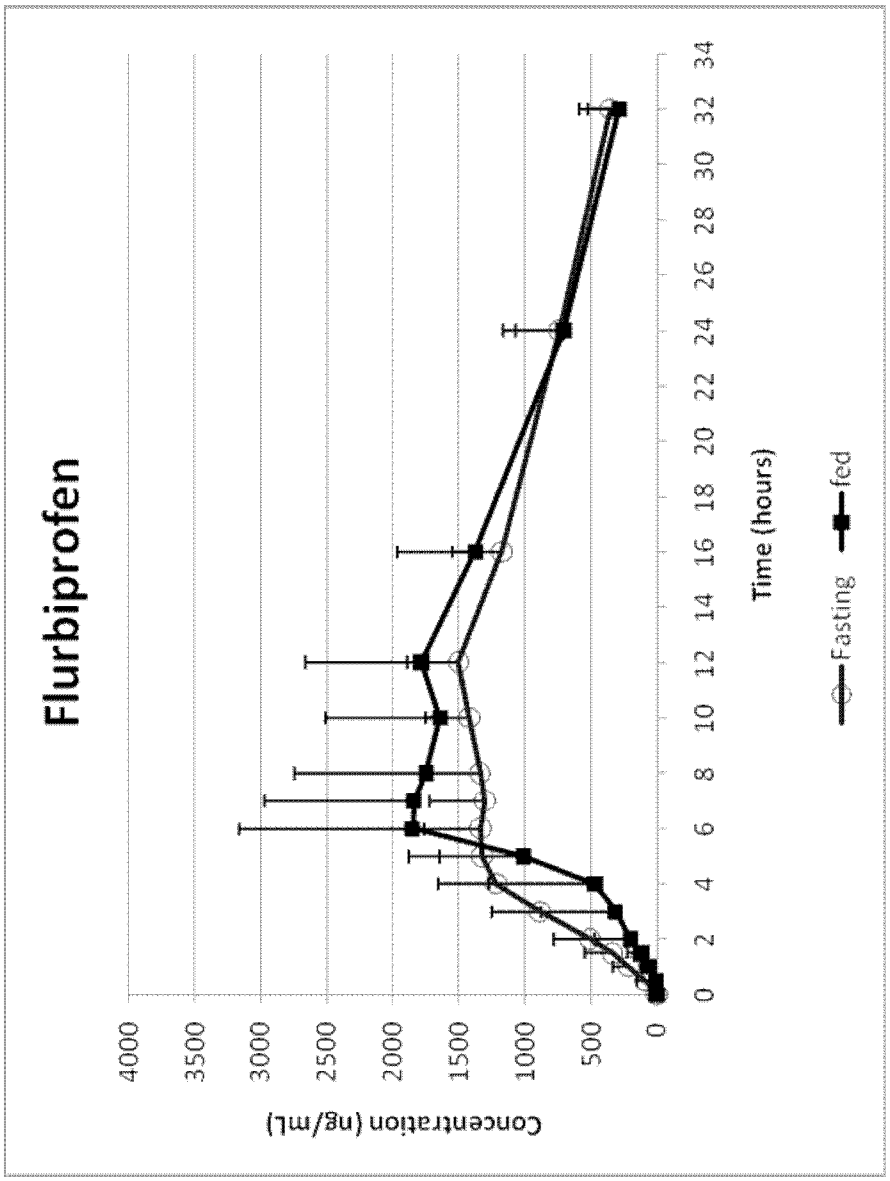

Gabapentin
Concentration (ng/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
Time (hours)
Fasting
Fed

FIGURE 7


Flurbiprofen
Concentration (ng/mL)
4000
3500
3000
2500
2000
1500
1000
500
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34
Time (hours)
Fasting
fed

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065167

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/00 A61K9/24
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/17745 A1 (CHIESI FARMA SPA [IT]; CHIESI PAOLO [IT]; VENTURA PAOLO [IT]; ACERBI D) 15 April 1999 (1999-04-15) cited in the application page 2, line 29 - line 31 page 3, line 11 - line 18 page 5, line 10 - line 25 page 6, line 7 - line 12 -----	1,2,4-7, 9-12
X	WO 2011/124953 A2 (LUPIN LTD [IN]; DESHMUKH ASHISH ASHOKRAO [IN]; BHUTADA PRAVIN MEGHRAJJ) 13 October 2011 (2011-10-13) page 12, line 19 - line 24 page 13, line 25 - line 29 page 14, line 1 - line 18 page 15, line 24 page 21 -----	1-3,5-12

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

[X] See patent family annex.

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2013	18/09/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Laurent, Antoine

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/065167

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/01781 A1 (APPLIED PHARMA RES [CH]; CONTE UBALDO [IT]; MAGGI LAURETTA [IT]; GIUNC) 19 January 1995 (1995-01-19) cited in the application page 3, paragraph 4 - paragraph 6 -----	1-12
A	WO 2011/077239 A2 (LUPIN LTD [IN]; BHUTADA PRAVIN MEGHRAJJI [IN]; CHANDRAN SAJEEV [IN]; D) 30 June 2011 (2011-06-30) page 18, line 3 - line 9 -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/065167

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