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(54) **Title:** STABLE CONTROLLED-RELEASE PHARMACEUTICAL FORMULATION OF ELETRIPTAN

(57) **Abstract:** The invention provides a controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that an isolating protective layer comprising a hydrophobic substance is inserted between the ammonio methacrylate copolymer and the gelatine capsule. Such a formulation has improved stability on storage.

STABLE CONTROLLED-RELEASE PHARMACEUTICAL FORMULATION OF ELETRIPTAN

This application concerns a controlled release pharmaceutical formulation, in the form of a gelatine capsule, which shows improved stability. This application further concerns a process for preparing such a formulation and a method for improving the storage stability of a gelatin encapsulated controlled release formulation. In a preferred aspect, the application relates to a controlled release pharmaceutical formulation in the form of a gelatine capsule comprising eletriptan, or a salt thereof, which shows improved stability, and the use of such a formulation in the treatment of migraine and in the prevention of migraine recurrence.

It is desirable, in many cases, to provide a controlled release of a drug. Such a controlled release is often achieved by coating a multiparticulate composition comprising the active compound (e.g. beads, pellets, granulates, mini-tablets, mini- or microcapsules or caplets) with a commercially available aqueous dispersion such as an ammonio methacrylate copolymer, particularly a Eudragit® copolymer manufactured by Röhm Pharma GmbH. Such coated particulates are then usually dispensed into commercially available capsules, in most cases gelatine capsules, for ease of administration.

An example of such a gelatine-encapsulated controlled release formulation is described in WO-A-02/09675 in relation to the antimigraine drug eletriptan. This patent application describes a a pharmaceutical composition in particulate form, suitable for oral administration, including a core containing eletriptan or a pharmaceutically acceptable salt thereof, the core being coated with a water-insoluble, permeable coating including one or more acrylic copolymer(s) containing trimethylammoniumethylmethacrylate groups, said composition being capable of achieving a sigmoidal pattern of controlled drug release. The acrylic copolymer(s) is/are preferably selected from Eudragit RL® and Eudragit RS® and the particulate compositions described are preferably filled into hard gelatine capsules before administration.

In order to obtain a fast-acting initial dose, such a controlled release formulation comprising a drug core coated with ammonio methacrylate copolymers, may be

combined with a further portion of drug in immediate release form in the same capsule (see Example 7 of WO-A-02/09675). Alternatively, multiparticulate compositions with different controlled release profiles may be combined in one capsule. Such formulations are known as dual release formulations.

Such gelatine capsule preparations, once prepared, are usually stored for a period of time before use. The storage period may extend to months or even years and the conditions under which the preparations are stored may vary in terms of temperature and humidity. Clearly, the pattern of controlled release that an encapsulated preparation demonstrates when administered to a patient should not change during the storage period or the wrong dose of drug may be delivered to the patient at the wrong time.

Surprisingly, it has been found that gelatine capsule preparations manufactured in accordance with the teaching of WO-A-02/09675, containing a dual release formulation of eletriptan, are not stable on storage, particularly under stressing conditions (i.e. relatively high temperature and/or humidity). Such instability appears to be a general feature of gelatine capsules filled with multiparticulate compositions that are coated with aqueous dispersions of ammonio methacrylate copolymers such as Eudragit® RL 30 D (type A) or Eudragit® RS 30 D (type B) or with compositions that are produced from a solid ammonio methacrylate copolymer such as Eudragit® RL PO. It appears that the dissolution rate of the capsule shell changes over a period of time, leading to unexpected changes in the release profile of the immediate and/or controlled release particles contained in the capsule. In a dual release formulation such changes in programmed release occur unpredictably as either a delay in the initial release of drug from immediate release particles and/or, by interaction of formulation ingredients (e.g. by interaction of soluble, rapid-release anionic components with the ammonio methacrylate copolymers), as accelerated release of drug from controlled-release particles.

Such unpredictable changes in drug release profile from a gelatine-encapsulated formulation comprising ammonio methacrylate copolymers is quite unprecedented and the consequent unacceptable variability in drug release profile has been hitherto unrecognised. There therefore exists a need to provide means to stabilise such a

formulation, allowing long term storage at varying temperatures and levels of humidity without any change in the dissolution rate of the capsule shell and any consequent changes in the release profile of immediate or controlled-release particles contained therein.

We have now unexpectedly found that such means can be provided by an isolating protective layer, comprising a hydrophobic material, inserted between the ammonio methacrylate controlled release coating and the gelatine capsule.

The invention therefore provides a controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an anti-migraine drug and an ammonio methacrylate copolymer, characterised in that an isolating protective layer comprising a hydrophobic substance is inserted between the ammonio methacrylate copolymer and the gelatine capsule.

In one embodiment, the isolating protective layer is coated onto the drug-containing particles. In another embodiment, the protective layer is coated onto the inside of the gelatine capsule.

Thus, the invention also provides a multiparticulate composition, suitable for administration in a gelatine capsule, comprising an antimigraine drug-containing core, said core being coated with an inner controlled release coating and an outer isolating protective layer, wherein the inner coating comprises an ammonio methacrylate copolymer and the outer protective layer comprises a hydrophobic substance.

The invention further provides a method for improving the stability of a controlled release pharmaceutical formulation in the form of a gelatine capsule, said gelatine capsule containing one or more particles comprising an antimigraine drug and an ammonio methacrylate copolymer, by inserting an isolating protective layer comprising a hydrophobic substance between the ammonio methacrylate copolymer and the gelatine capsule.

The isolating protective layer comprises at least one hydrophobic substance. The isolating protective layer may thus comprise one or more other substances in addition

to a hydrophobic substance or may alternatively consist solely of one or more hydrophobic substances. Hydrophobic, in this context, means not soluble in water under acidic conditions, particularly at the pH of gastric juice which is normally from 1 to 3. The hydrophobic substance will most commonly be a hydrophobic polymer. It may also be a hydrophilic polymer which has been rendered hydrophobic by the addition of one or more additives (e.g. a lipid or wax). Equally, the hydrophobic substance may be a non-polymeric substance, such as a lipid or wax, which is capable of forming a continuous film around the drug-containing core.

Suitable hydrophobic polymers include a methacrylic acid–ethyl acrylate copolymer (e.g. a 1:1 copolymer such as Eudragit® L), ethylcellulose (e.g. Aquacoat® ECD 30), a copolymer of methacrylic acid and polyvinyl-acetate-phthalate and a modified natural polymer having an anionic character (e.g. cellulose-acetate-phthalate and hydroxypropyl-cellulose-methyl-cellulose-phthalate or cellulose-acetate-trimellitate and hydroxypropyl-cellulose-methyl-cellulose-phthalate). Examples of lipids that are appropriate for rendering a hydrophilic polymer hydrophobic, are glycerol monostearate, stearic acid and a natural or synthetic wax or wax-like substance. A typical isolating protective layer of this kind comprises Sepfilm LP 30 and 30% stearic acid. Glycerol monostearate is an example of a non-polymeric hydrophobic substance which can be used according to the invention.

Hydrophobic polymers containing carboxylic and/or sulfonic acid groups are particularly preferred. Polymers containing these groups have a particularly strong protective effect.

A preferred isolating protective layer comprising a hydrophobic polymer is an enteric coating. An enteric coating contains a polymer that is not soluble at acid pH (for instance, pH 1-3, as found in the stomach) but is soluble at neutral or alkaline pH (and therefore dissolves in the small intestine). A preferred example of an enteric coating is a methacrylic acid–ethyl acrylate copolymer, especially a 1:1 methacrylic acid–ethyl acrylate copolymer. Such an enteric coating preferably additionally comprises an emulsifier such as sodium lauryl sulphate or polysorbate (most preferably about 2% by weight). A coating comprising 1:1 methacrylic acid–ethyl acrylate copolymer, sodium lauryl sulphate and polysorbate, such as Eudragit® L 30 D-55, is particularly preferred.

However, the level of enteric coating needed to achieve a protective effect in accordance with the present invention is relatively low in comparison to the level needed to achieve an effective enteric effect and a substantial retarding effect of the coating is thus avoided. The isolating protective layer can therefore be relatively thin (5 to 50 μm, preferably 10 to 40 μm) in order to avoid undesired retarded release effects or other undesired influence on the controlled release profile of the capsule. Since the release of pharmaceutically active compounds from controlled release capsule preparations depends on many parameters, it is impossible to exactly predict the release profile of a capsule preparation when additional layers comprising inactive adjuvant material have been added or when existing layers have been modified. However, a person skilled in the art will, without any difficulties, be able to determine the appropriate amount and the thickness of a layer by simple in vitro testing using e.g. artificial gastric juice.

It is believed that the significant changes in the release characteristics of a gelatine encapsulated controlled release formulation comprising an ammonio methacrylate copolymer are brought about as a result of an interaction between the gelatine capsule and volatile impurities in the ammonio methacrylate copolymers which leads to cross-linking of the gelatine. Such impurities are thought to be low molecular weight aldehydes. This cross-linking process, which increases as a function of time and seems to be exacerbated by higher humidity and/or higher temperature, results in a markedly slower disintegration of the gelatine capsule when administered into an aqueous environment and a corresponding change in the release of active compounds contained therein.

This cross-linking effect is responsible for release delays of up to 12 minutes, especially if the capsule contains immediate release components, while the standard disintegration time of a freshly prepared capsule is only about 3 minutes. Strongly cross-linked gelatin capsules may be even totally resistant to gastric juice. In less cross-linked preparations the release time of the pharmacologically active particulate components is still delayed by 5 to 10 minutes. In the case of pharmaceuticals such as analgesics or antimigraine agents, where a rapid onset of action is required, such a delay in disintegration time is clearly unacceptable.

In the case of a dual release formulation, the longer disintegration time of the gelatine capsule seems to lead to unwanted, deleterious interactions between the particles programmed to have different release characteristics. This is because the capsule shell may partially leak relatively early e.g. as early as 3 minutes after being in contact with gastric juice, while maintaining its main structure and not allowing the release of particulate components for another 10 minutes before the complete breakup of the capsule-shell. In the "time-gap" of about 7 minutes, fast releasing components dissolve almost immediately inside the capsule-shell and form a highly concentrated solution of soluble ingredients which has sufficient time to interact with still intact slower releasing components. Osmotic influences and different ion-size, ion-charge and ion-hydration of e.g. phosphate, citrate, methansulfonate, bromide or sulphate anions in comparison to e.g. chloride ions may cause severe damage to the controlled release layer of the slower releasing components, and these undesired interactions change the release characteristics of the slower releasing components, often to an unacceptable degree.

In the case of the dual release formulation described in WO-A-02/09675, for instance, chloride anions from the ammonio methacrylate copolymers may exchange with sulphate anions from the immediate release portion of eletriptan hemisulphate, altering the properties of the controlled release coating and thus causing a significantly accelerated release of eletriptan from the controlled release particles. Such an interaction between chloride and sulphate anions takes place only if the capsule-shell is cross-linked and therefore hinders diffusion of sulphate anions from the immediate release portion out of the capsule during contact with gastric or intestinal juice.

It is believed that the isolating protective layer provided by the present invention isolates volatile impurities, such as low molecular weight aldehydes, emanating from ammonio methacrylate copolymers that would otherwise trigger or initiate the cross-linking of the gelatine capsule shell. The isolating protective layer can therefore alternatively be defined in functional terms as a layer (preferably a polymeric layer) which prevents the passage of volatile impurities such as low molecular weight aldehydes. It is also believed that the isolating protective layer provided by the present invention prevents, in the case of a dual release formulation, a rapid ingress of anions (e.g. sulphate anions) into the modified release coating, preventing a significant

amount of anion exchange in the ammonio methacrylate copolymers. The isolating protective layer can therefore alternatively be defined in functional terms as a layer (preferably a polymeric layer) which significantly impedes the passage of anions (especially sulphate anions).

The invention therefore further provides a controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that the formulation is provided with means to prevent capsule crosslinking on storage.

The invention further provides a dual release pharmaceutical formulation in the form of a gelatine capsule containing immediate release and delayed release particles, said delayed release particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that the delayed release particles are provided with means to prevent a significant amount of anion exchange in the ammonio methacrylate copolymer.

The amount of anion exchange is preferably less than 50%, more preferably less than 30%, most preferably less than 10%.

In order to further reduce cross-linking of the gelatin-shell, the level of volatile impurities in the formulation, especially in the ammonio methacrylate layer, should be kept to a minimum. As discussed above, the most important volatile impurities are thought to be aldehydes, especially lower aliphatic aldehydes with up to 6 carbon atoms, particularly formaldehyde and acetaldehyde. The aldehyde content of the particles contained within the gelatine capsule should therefore preferably be less than 10 ppm, more preferably less than 5 ppm and most preferably less than 2 ppm.

The level of volatile aldehyde impurities may be reduced by vacuum treatment of the ammonio methacrylate-containing particles (e.g. at less than 100 mbar, preferably 1-20 mbar), especially at raised temperatures (e.g. 25-50°C, preferably 35-45°C). Alternatively, the particles may be exposed to a stream of clean and dry air or nitrogen

at raised temperatures (30-50°C, preferably 35-45°C) in a fluidized bed unit. The air or nitrogen should have a relative humidity of less than 20%.

It is obvious to the person skilled in the pharmaceutical art, that the ingredients of the total capsule contents as well as the capsule forming gelatin must be as clean as possible before the capsule and/or its contents are finally prepared and composed.

Optionally, a formulation according to the invention may also comprise, either as part of the isolating protective layer or otherwise, a quenching agent. A quenching agent is a substance that is capable of chemically binding volatile impurities such as aldehydes. Such a quenching agent may be an amine, protein, amino-acid, oligo- or polypeptide, especially gelatin and/or an amino-acid. Particularly preferred quenching agents are cysteine, lysine, aspartic acid, asparagine, gelatine and glycine. Most preferred are glycine and aspartic acid. In one embodiment, the quenching agent is added to the isolating, protective layer. Equally, the quenching agent may be separately applied, for example as a part of a separate layer around the particles. This layer may also comprise a water soluble film forming material, for instance a hydrophilic polymer such as hydroxypropyl methylcellulose or hydroxypropyl cellulose. In such a later, the quenching agent will usually be present in an amount of from 1% to 60% by weight. Hydroxypropyl methyl cellulose is particularly suitable since it is highly soluble in water and body liquids and exerts a minimal influence on the desired profile of drug release. As a further alternative, the quenching agent may be integrated into the ammonio methacrylate copolymer.

A quenching agent layer may be added in a conventional manner using, for example, the method described in US-A-2002/0034545, paragraphs [005] to [007], for compositions where an inner core is coated first with a retarding water-insoluble permeable or semipermeable coating including one or more acrylic copolymer(s) containing trimethyl-ammonium-metacrylate groups, whereafter the coated core is provided with a second water soluble coating layer comprising the quenching agent as described above, e.g. gelatin or an amino-acid.

The term gelatine capsule or gelatine capsule preparation according to this invention refers to a capsule material with a gelatine content of about 20 to 100 weight %.

Capsule material containing less than 100% by weight gelatine comprise usual adjuvants known to a person skilled in the pharmaceutical capsule manufacturing art, such as water-soluble polymers.

In a preferred aspect of the invention, the ammonio methacrylate copolymer is a type A or a type B ammonio-methacrylate copolymer (e.g. the products marketed under the trade-marks Eudragit RL and Eudragit RS) or a mixture of the two. These copolymers contain chloride counter-ions.

If desired, a particulate composition according to the invention may be coated with a so-called top-coat (see, for instance, WO-A-02/09675) which conventionally has a hydrophilic character, consisting, for example, of hydroxypropylmethylcellulose. This is a usual measure in the field of gelatine capsule manufacture for improving the mechanical properties of the particulate composition with regard to its further processing (mixing, transport, filling into capsule-shells). Such a top-coat may be inserted between the drug-containing core and the controlled release layer, between the controlled release layer and the layer comprising a hydrophobic substance or as an outer layer. More than one such top-coat may be used.

The ammonio methacrylate coating applied to the particles of the invention may include one or more additional substances, such as a softening agent (e.g. an acetylated monoglyceride, triethyl citrate, acetyl-triethyl citrate, tributyl citrate, acetyltributyl citrate, another citrate ester, dibutyl phthalate, diethyl phthalate, another phthalate ester, diethyl sebacate, dibutyl sebacate, diethyl fumarate, diethyl succinate, a polyethylene glycol, glycerol, sesame oil, a lanolin alcohol or triacetin), an anti-tacking agent (e.g. talc, calcium stearate, colloidal silicon dioxide, glycerin, magnesium-stearate, mineral oil, a polyethylene glycol, zinc- stearate, aluminium-stearate or glycerol-monostearate), a wetting agent (e.g. sodium-lauryl-sulphate, stearyl alcohol, acacia, benzalkonium chloride, cetomacrogol emulsifying wax, cetostearyl alcohol, cetyl alcohol, cholesterol, diethanolamine, sodium stearate, glycerol monostearate, hydroxypropyl-cellulose, a lanolin alcohol, triethanolamine, lecithin, poloxamer, a polyoxyethylene alkyl ether, a sorbitan ester, a stearyl alcohol or simethicone) or a water insoluble polymer (e.g. ethyl-cellulose, cellulose-acetate or a poly-methacrylate copolymer). A preferred softening agent is triethyl-citrate, a

preferred anti-tacking agent is talc and a preferred wetting agent is sodium-lauryl-sulphate.

In principle, any drug that is to be formulated with an ammonio methacrylate copolymer and contained in a gelatine capsule may benefit from the technology of the present invention whereby an isolating protective layer comprising a hydrophobic substance is inserted between the ammonio methacrylate copolymer and the gelatine capsule. However, it is preferred that the drug is an antimigraine drug, particularly a 5-HT_{1B}, 5-HT_{1D} or 5-HT_{1F} agonist. Indole-containing antimigraine agents of the triptan class are particularly preferred. Examples are eletriptan, sumatriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, alnatriptan, almotriptan and avitriptan and their pharmaceutically acceptable salts. Eletriptan, or a pharmaceutically acceptable salt thereof, is most preferred, being effective in the treatment of migraine and the prevention of migraine recurrence. Preferred salts of eletriptan are the hydrobromide salt (especially the α-polymorph disclosed in WO-A-96/06842) and the hemisulphate salt (especially the form I polymorph disclosed in WO-A-01/23377). Eletriptan hemisulphate and its form I polymorph are particularly preferred.

When eletriptan, or a pharmaceutically acceptable salt thereof, is used according to the invention, it may be used alone or in combination with one or more further drugs, such as:

- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin or zomepirac;

- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone or cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid;
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amytriptiline or nortriptiline;
- an anticonvulsant, e.g. carbamazepine or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S,3S);
- a muscarinic antagonist, e.g oxybutin, tolterodine, propiverine, tropsium chloride or darifenacin;
- a selective COX-2 inhibitor, e.g. celecoxib, rofecoxib or valdecoxib;
- a non-selective COX inhibitor (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);

- a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol;
- a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- a corticosteriod such as dexamethasone
- a cholinergic (nicotinic) analgesic;
- Tramadol (trade mark);
- a PDEV inhibitor, such as sildenafil, vardenafil, taladafil, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, 1-{6-ethoxy-5-[3-ethyl-6,7-dihydro-2-(2-methoxyethyl)-7-oxo-2H-pyrazolo[4,3-d]pyrimidin-5-yl]-3-pyridylsulfonyl}-4-ethylpiperazine, or *N*-[1-(2-ethoxyethyl)-5-(*N*-ethyl-*N*-methylamino)-7-(4-methylpyridin-2-ylamino)-1H-pyrazolo[4,3-d]pyrimidine-3-carbonyl]methanesulfonamide;
- a canabinoid;
- a metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline;
- a noradrenaline reuptake inhibitor, especially a selective noradrenaline reuptake inhibitor such as (S,S)-reboxetine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine or (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid;
- an acetylcholine esterase inhibitor such as donepezil;
- a dopamine type 2 (D2) antagonist such as ziprazidone;
- an prostaglandin E_2 subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)carbonyl]-4-methylbenzenesulfonamide or 4-[(1*S*)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid;

or a pharmaceutically acceptable salt or solvate thereof. A combination of eletriptan, or a pharmaceutically acceptable salt thereof, and an NSAID (such as naproxen, or a pharmaceutically acceptable salt thereof) or a selective COX-2 inhibitor (such as celecoxib, valdecoxib, rofecoxib or a pharmaceutically acceptable salt thereof) is particularly advantageous.

A non-limiting example of a typical capsule preparation according to the present invention is as follows:

1. A core composition

The inner core composition contains an active compound in the form of crystals, granulates, pellets, spheric extrudates, spray dried products, minitablets, microcapsules or minicapsules in an amount of from 10 to 90% by weight.

2. A barrier coating

This optional layer contains a hydrophilic polymer such as hydroxypropyl methylcellulose in an amount of from 1 to 20% by weight.

3. A controlled release layer

This layer controls the release of the active compound or compounds and preferably contains

a. a water-insoluble polymer such as an ammonio methacrylate-copolymer, type A and/ or B (or a mixture thereof) in an amount of from 10 to 50% by weight,

b. a softening agent such as triethyl-citrate in an amount of from 1 to 15% by weight,

c. an anti-tacking agent such as talc in an amount of from 3 to 50% by weight.

4. A barrier coating

This optional layer, which is the same as layer (2) desribed above, contains a hydrophilic polymer such as hydroxypropyl methylcellulose in an amount of from 1 to 20% by weight.

5. A hydrophobic isolating protective layer

This layer contains, for example,

a. an isolating protective polymer such as ethyl-cellulose (e.g. Aquacoat® ECD 30) or a methacrylic acid–ethyl acrylate copolymer (e.g. a 1:1 copolymer such as Eudragit® L), in an amount of from 4 to 20% by weight,

b. a softening agent such as triethyl-citrate in an amount of from 0.25 to 4% by weight,

c. an anti-tacking agent such as talc in an amount of from 1 to 15% by weight.

6. A quenching protective layer

This optional layer contains for example gelatin, glycine, asparagine or cysteine in an amount of from 0.2 to 2% by weight.

7. A barrier coating

This optional layer, which is the same as layer (2) described above, is present in an amount of from 10 to 20% by weight.

8. The gelatine containing capsule-shell

The above example is only a typical formulation according to the invention. For example quenching layer 6 may - as an additional or alternative layer - also follow

layer 3. Preparations according to the present invention may also contain only the isolating protective layer and no quenching layer. Instead of having a separate quenching protective layer, a quenching agent may be incorporated in the hydrophobic isolating protective layer or the outer barrier coating and thus form a bifunctional or multifunctional layer. The preparation may also contain additional protective layers of both kinds and any practical number of top-coats or other useful layers known in the art.

The present invention thus provides a storage stable gelatin-capsule preparation which in a customary packaging may be stored over a long time even under the stressing conditions such as, for example, under relatively high temperatures of above 30° C and a high humidity of more than 50%. The invention is especially useful for capsule preparations for use in tropical regions. The capsules of the invention maintain a dissolution profile that is substantially identical to the initial product before storage.

The following examples only illustrate the present invention and may under no circumstances be seen as a limitation of the inventive concept:

Example 1

Changes to the release profile of a prior art dual release formulation on storage

A dual release formulation comprising eletriptan hemisulphate immediate release beads and eletriptan hemisulphate controlled release beads in a gelatine capsule was prepared using the procedures of WO-A-02/09675.

Eletriptan hemisulphate starter cores were coated first with the Eudragit polymers to create the controlled release coating and then with hydroxypropyl methylcellulose (Opadry) as a topcoat. The weight of the finished controlled release beads was 210.48mg.

Eletriptan hemisulphate controlled release beads		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00mg eletriptan base)	Core composition (including a barrier coat)	115.51 mg
Ammonio methacrylate copolymer Type B (Eudragit® RS)	Controlled release coating	40.62 mg
Ammonio methacrylate copolymer Type A (Eudragit® RL)		2.14 mg
Triethylcitrate NF		8.54 mg
Talc		21.37 mg
Opadry® Yellow YS-1-12570-A	Top coat	22.30 mg

The controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatine capsules (Size 1) using a Bosch GKF 400 capsule filling machine. The capsule fill weight was 325.99mg.

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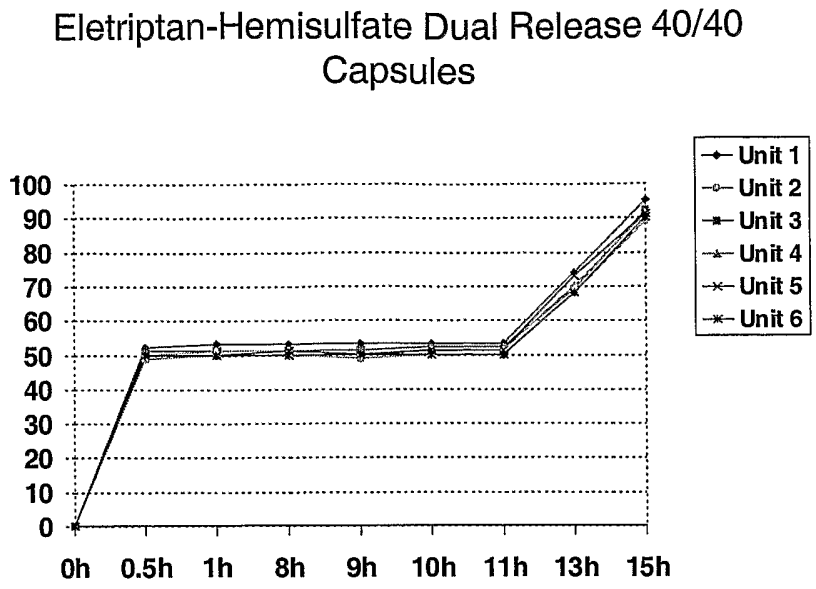
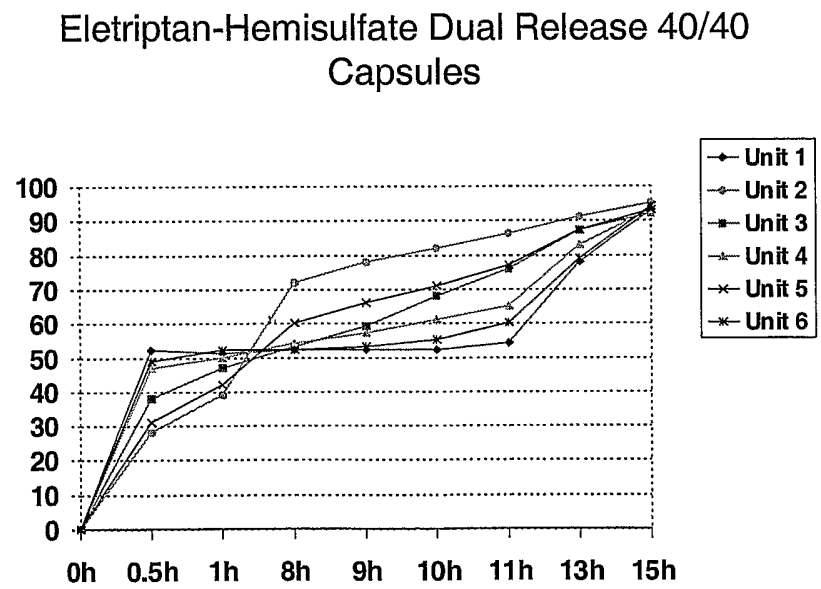
Eletriptan hemisulphate dual release capsule		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	115.51 mg
Eletriptan hemisulphate controlled release beads (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer and top coat	210.48 mg
Hard gelatine capsule shell size 1, two-tone grey	Capsule shell	76 mg

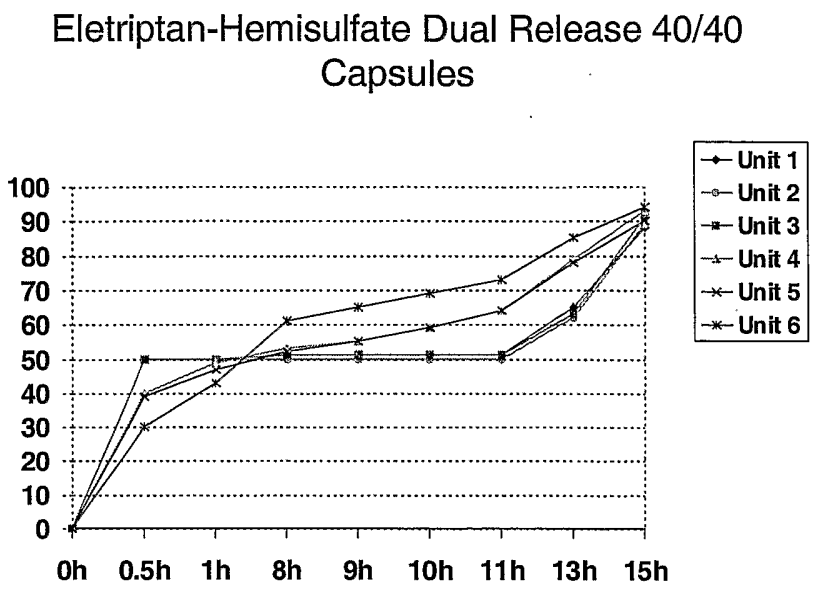
The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675:



After storage for 4 weeks at 40°C/75% relative humidity in HDPE (high density polyethylene) bottles the dissolution test was repeated and the following very different results were obtained:



Storage for 6 weeks at 30°C/60% relative humidity in HDPE bottles also resulted in very significant changes:



Thus, the dissolution profile of a gelatine-encapsulated dual release formulation of eletriptan, made in accordance with the procedures described in WO-A-02/09675, shows considerable variability when the formulation is stored in HDPE bottles under at least 2 different storage conditions (40°C/75% relative humidity and 30°C/60% relative humidity).

Example 2

Changes to the release profile of a prior art dual release formulation on storage

A further dual release formulation comprising eletriptan hemisulphate immediate release beads and eletriptan hemisulphate controlled release beads in a gelatine capsule was prepared using the procedures of WO-A-02/09675.

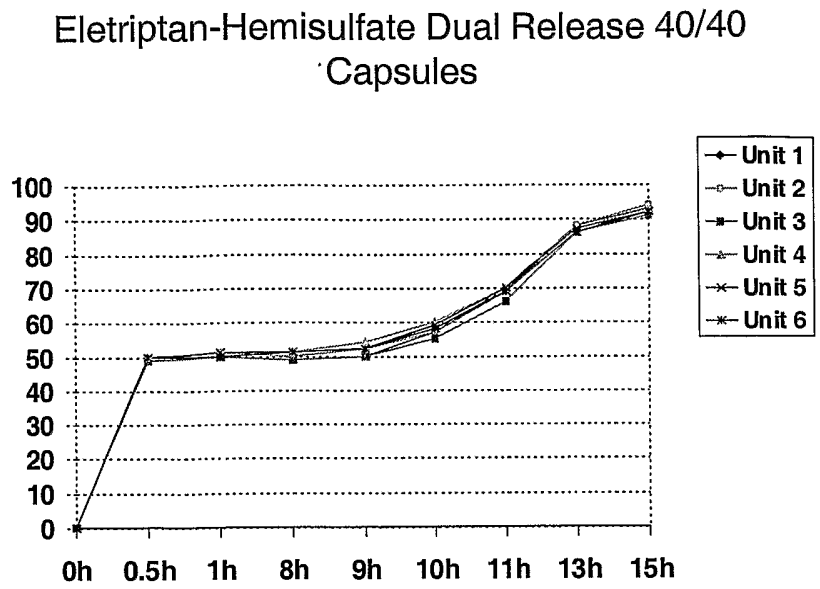
Eletriptan hemisulphate starter cores were coated first with the Eudragit® polymers to create the controlled release coating and then with hydroxypropyl methylcellulose (Opadry) as a topcoat. The weight of the finished beads was 175.40mg.

Eletriptan hemisulphate controlled release beads		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat	105.54 mg
Ammonio methacrylate copolymer type B (Eudragit® RS)	Controlled release layer	36.66 mg
Ammonio methacrylate copolymer type A (Eudragit® RL)		1.93 mg
Triethylcitrate NF		7.71 mg
Talc		19.29 mg
Opadry® Blue OY-LS-20925	Top coat	4.27 mg

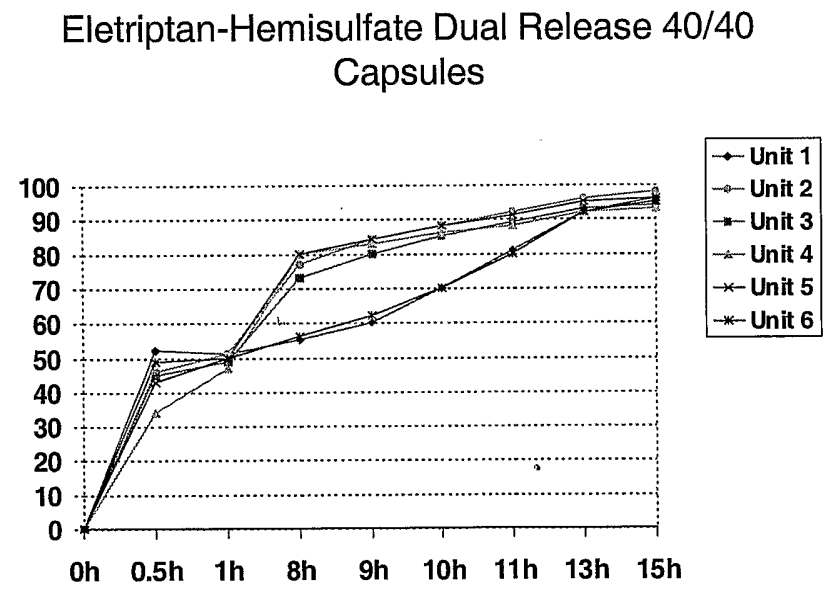
The controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatin capsules (size 1) using a Bosch GKF 400 capsule filling machine. The capsule fill weight was 280.94mg.

Eletriptan hemisulphate dual release capsule		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	105.54 mg
Eletriptan hemisulphate controlled release beads (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer and top coat	175.40 mg
Hard gelatine capsule shell (Size 1), two-tone grey	Capsule shell	76 mg

The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675:



After storage for 3 months at 25°C/60% relative humidity in aluminium/aluminium foil/foil blisters the dissolution test was repeated and the following very different results were obtained:



Similarly, 3-month storage at 40°C/30% relative humidity in PVC/Aclar white opaque blisters, 3-month storage at 25°C/60% relative humidity in HDPE bottles, 6-week storage at 40°C/30% relative humidity in HDPE bottle and 6-week storage at

30°C/60% relative humidity in HDPE bottles all resulted in significant changes to the release profile.

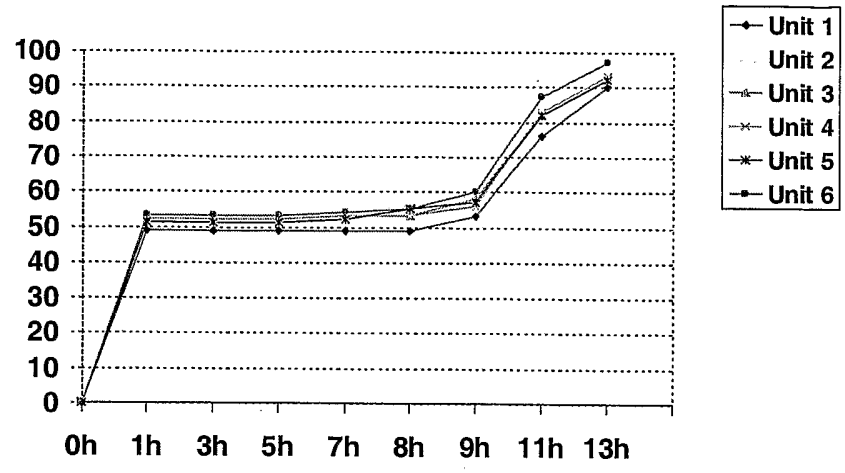
These experiments show that the dissolution profile of a gelatine-encapsulated dual release formulation made in accordance with the procedures described in WO-A-02/09675 shows considerable variability when stored under different storage conditions (i.e. 25°C/60% relative humidity, 30°C/60% relative humidity, 40°C/30% relative humidity and 40°C/75% relative humidity) and in different packaging materials (i.e. aluminium/aluminium foil/foil blisters, PVC/Aclar white opaque blisters and HDPE bottles).

Example 3

Experiment to determine whether changes in stability relate to changes in the gelatine capsule or the drug-containing beads

Dual release gelatine capsules made according to Example 2 were tested for dissolution, as described in Example 2, and found to give the expected release profile. They were then stored at 40°C/75% relative humidity in PVC/Aclar White Opaque blisters and retested. The expected significant changes in dissolution profile were observed.

Capsules stored for the same time under the same conditions were opened and the beads were removed from the capsule shells and tested for dissolution. The following release profile was observed:



Without capsule shells, bead dissolution was substantially unaffected after storage, showing that changes in dissolution profile are linked to changes in the capsule shell and not the beads themselves.

Example 4

Changes in the release profile of gelatine capsules containing drugs other than eletriptan or no drug at all

Minipress® retard 1mg capsules (Pfizer) containing prazosin hydrochloride, medium-chain triglycerides, lactose monohydrate, talc, maize starch, saccharose, ammonio methacrylate copolymer, indigo carmine (E 132), erythrosin (E127), iron oxides (E 172), and titanium dioxide (E 171) were stored for 6 weeks at 40°C/75% relative humidity in HDPE bottles. The capsule shells were opened, emptied and filled with eletriptan immediate release beads (corresponding to 40 mg eletriptan) and eletriptan controlled release beads (corresponding to 40 mg eletriptan). A non-uniform release pattern of drug release was observed.

In a separate experiment, glass beads were coated with ammonio methacrylate copolymers type A and B and talc and filled into hard gelatine capsule shells (size 1). After 4-week storage of this placebo formulation (without any active ingredient) at

40°C/75% relative humidity in induction-sealed HDPE bottles, the capsule shells were opened, emptied and filled with eletriptan immediate release beads (corresponding to 40 mg eletriptan) and eletriptan controlled release beads (corresponding to 40 mg eletriptan). The capsule shells were closed again and subjected to a dissolution test. A non-uniform pattern of drug release was observed.

In a further experiment, hard gelatine capsule shells (size 1) were filled with 282 mg of ammonio methacrylate copolymer Type A as a powder (Eudragit® RL PO) without any other ingredient. After storage for 3 weeks at 40°C/75% relative humidity in induction-sealed HDPE bottles, the capsule shells were opened, emptied and filled with eletriptan immediate release beads (corresponding to 40 mg eletriptan) and eletriptan controlled release beads (corresponding to 40 mg eletriptan. The capsule shells were closed again and subjected to a dissolution test. A non-uniform pattern of drug release was observed.

These experiments show that crosslinking of capsule shells does not only happen specifically with an eletriptan dual release formulation but generally with all formulations containing ammonio methacrylate copolymers, independently of the active ingredient used and even if no active is present.

Example 5

Stabilisation of an eletriptan hemisulphate dual release formulation with a hydrophobic isolating protective layer comprising methacrylic acid–ethyl acrylate copolymer 1:1

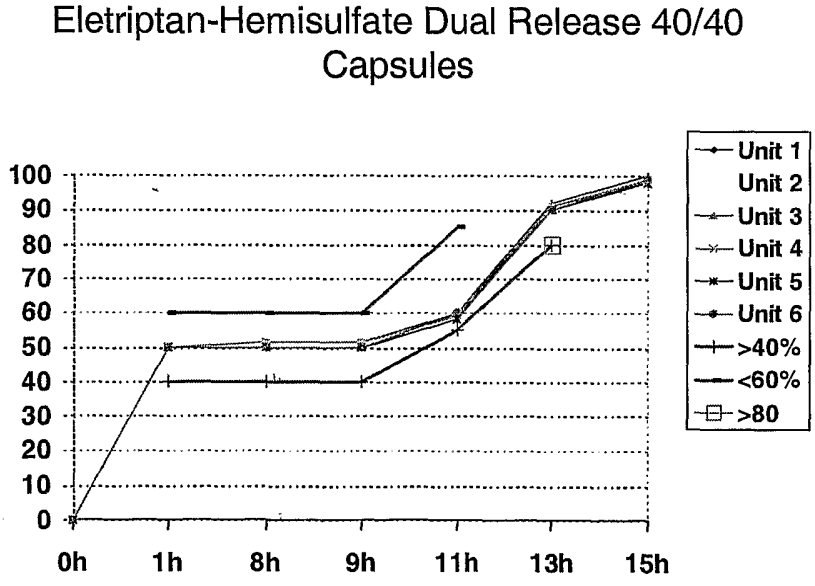
Eletriptan hemisulphate cores were prepared and coated with ammonio methacrylate copolymers Type A and B according to the disclosure of WO-A-02/09675. A further coating of methacrylic acid–ethyl acrylate copolymer (Eudragit® L) was applied by dispersing 1 part of talc in 5 parts of purified water using an Ultra-Turrax® rotor-stator stirrer, dissolving triethylcitrate in a 30% aqueous dispersion of Eudragit® L (as Eudragit® L 30 D-55) using a blade stirrer, combining 6 parts of the aqueous talc dispersion and 7 parts of the aqueous Eudragit® L/triethyl citrate dispersion, stirring the combined dispersion using a blade stirrer and spraying onto the controlled release beads using a 6-inch Wurster coating device in a Glatt GPCG-1 fluid bed unit. Final batch size was 1.5 kg. The bead weight was 184.70mg.

Eletriptan hemisulphate controlled release beads coated with Eudragit® L 30 D-55		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat	108.04 mg
Ammonio methacrylate copolymer Type B (Eudragit® RS)	Controlled release layer	36.40 mg
Ammonio methacrylate copolymer Type A (Eudragit® RL)		1.92 mg
Triethylcitrate NF		7.66 mg
Talc		19.15 mg
Methacrylic acid–ethyl acrylate Copolymer 1:1 (used as 30% aqueous dispersion, Eudragit® L 30 D-55)	Hydrophobic isolating protective layer	7.21 mg
Talc		3.60 mg
Triethylcitrate NF		0.72 mg

The coated controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatine capsules (Size 1). The capsule fill weight was 301.66mg.

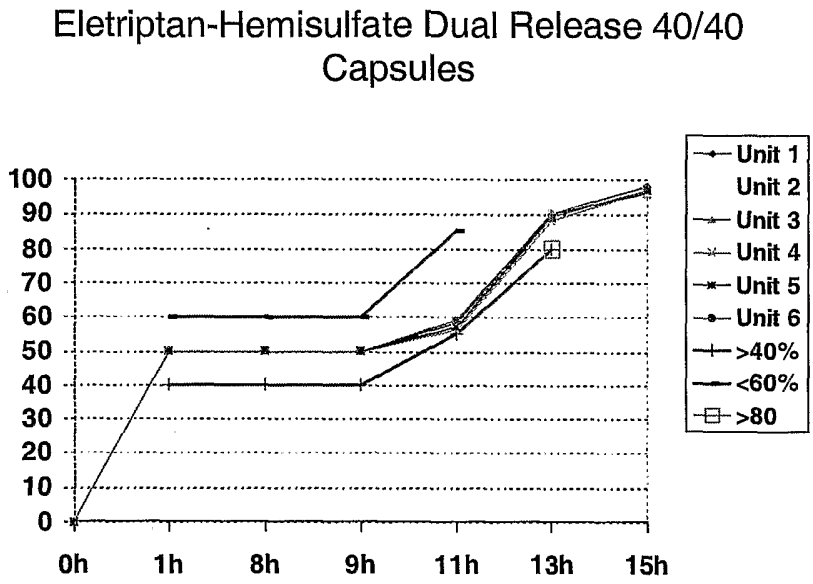
Eletriptan hemisulphate dual release capsule with Eudragit® L		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	116.96 mg
Eletriptan hemisulphate controlled release beads coated with Eudragit L (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer, and hydrophobic isolating protective layer	184.70 mg
Hard gelatine capsule shell (Size 1), two-tone grey	Capsule shell	76 mg

The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675 (pH 7.5):



Eudragit® L 30 D-55 is used as an enteric coating material to prevent the release of drugs in the stomach. The coating level used in this Example is 5.4%, significantly lower than the level of Eudragit® L 30 D-55 recommended for enteric coating (10-30%). Thus, under acidic conditions (pH 2), drug release is not prevented completely but the dissolution lag time is shifted upward by about 2 hours (from 9 to 11 h).

The dual release capsules were stored for 6 weeks at 40°C/75% relative humidity in induction-sealed HDPE bottles. No change of the dissolution profile was seen under this these conditions:



This experiment demonstrates that a hydrophobic isolating protective layer comprising methacrylic acid–ethyl acrylate copolymer 1:1 prevents any deleterious interaction between ammonio methacrylate-containing controlled release beads and the gelatine capsule and provides a formulation which is stable upon storage.

Example 6

Stabilisation of an eletriptan hemisulphate dual release formulation with a hydrophobic isolating protective layer comprising Sepifilm LP 30 with 30% stearic acid

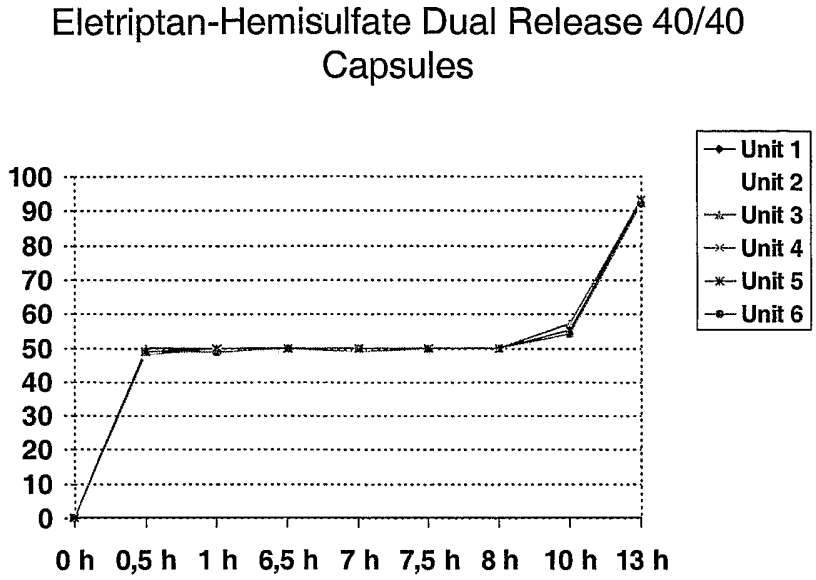
Eletriptan hemisulphate cores were prepared and coated with ammonio methacrylate copolymers Type A and B according to the procedures of WO 02/09675. A further coating of Sepifilm LP 30 was applied using a 10% aqueous dispersion of Sepifilm LP 30 with 30% stearic acid at a final batch size of 1.3 kg in a Glatt GPCG-1 fluidized-bed unit with a 6-inch Wurster coating insert. The bead weight was 174.90mg.

Eletriptan hemisulphate controlled release beads coated with Sepifilm LP 30		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat	108.04 mg
Ammonio methacrylate copolymer type B (Eudragit® RS)	Controlled release layer	24.91 mg
Ammonio methacrylate copolymer type A (Eudragit® RL)		1.31 mg
Triethylcitrate NF		5.24 mg
Talc		13.10 mg
Sepifilm LP 30 with 30% stearic acid	Hydrophobic isolating protective layer	22.30 mg

The controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatine capsules Size 1. The capsule fill weight was 291.86mg.

Eletriptan Hemisulphate Dual release Capsule with Sepifilm LP 30		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	116.96 mg
Eletriptan hemisulphate controlled release beads coated with Sepifilm LP 30 (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer, and hydrophobic isolating protective layer	174.90 mg
Hard gelatine capsule shell (size 1), two-tone grey	Capsule shell	76 mg

The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675 (pH 7.5):



The capsule product proved to be stable (as judged by dissolution profile) for at least two weeks at 40°C/75% in induction-sealed HDPE bottles.

This experiment demonstrates that a hydrophobic isolating protective layer comprising Sepifilm LP 30 with 30% stearic acid prevents any deleterious interaction between ammonio methacrylate-containing controlled release beads and the gelatine capsule and provides a formulation which is stable upon storage.

Example 7

Stabilisation of an eletriptan hemisulphate dual release formulation with a hydrophobic isolating protective layer comprising ethylcellulose (Aquacoat® ECD 30)

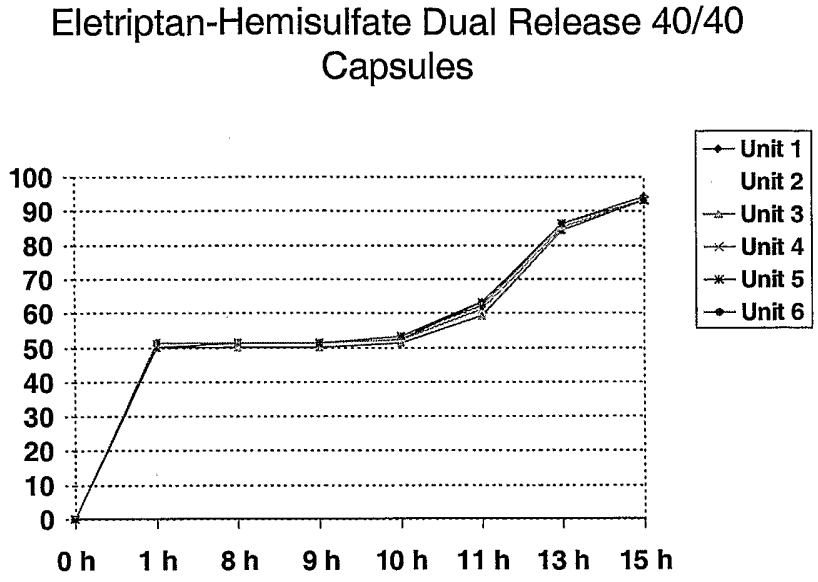
Eletriptan hemisulphate cores were prepared and coated with ammonio methacrylate copolymers Type A and B according to the procedures of WO-A-02/09675. A further coating of ethylcellulose was applied by dissolving triethylcitrate in a 30% aqueous dispersion of ethylcellulose (Aquacoat® ECD 30) using a blade stirrer, diluting 5 parts of this dispersion with 1 part of purified water and spraying this final coating dispersion under continuous stirring with a blade stirrer onto the modified release beads using a Glatt GPCG-1 fluidized-bed unit with a 6-inch Wurster coating insert. The final batch size was 1.5 kg. The bead weight was 182.17mg.

Eletriptan hemisulphate controlled release beads coated with ethylcellulose		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat	108.04 mg
Ammonio methacrylate copolymer type B (Eudragit® RS)	Controlled release layer	36.40 mg
Ammonio methacrylate copolymer type A (Eudragit® RL)		1.92 mg
Triethylcitrate NF		7.66 mg
Talc		19.15 mg
Ethylcellulose (as 30% aqueous dispersion Aquacoat® ECD 30)	Hydrophobic isolating protective layer	7.21 mg
Triethylcitrate NF		1.79 mg

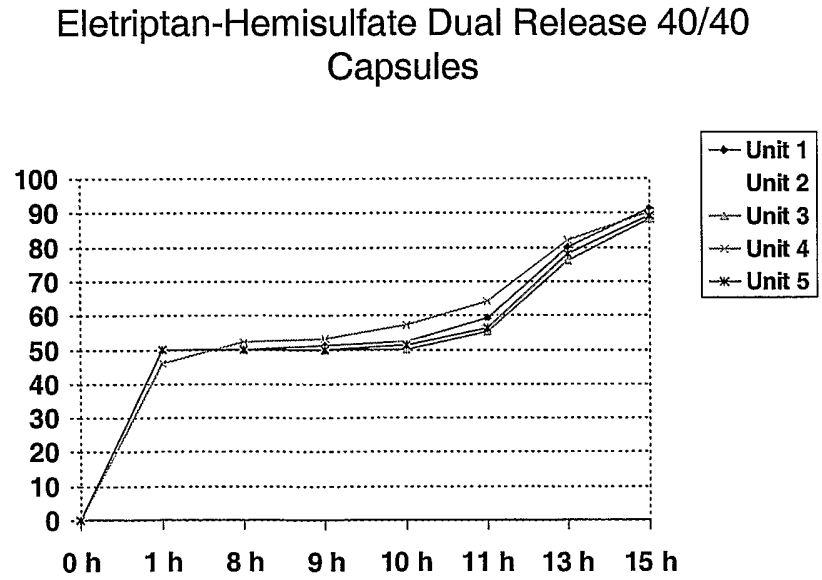
The coated controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatine capsules (size 1). The capsule fill weight was 299.13mg.

Eletriptan hemisulphate dual release capsule with ethylcellulose		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	116.96 mg
Eletriptan hemisulphate controlled release beads coated with ethylcellulose (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer, and hydrophobic isolating protective layer	182.17 mg
Hard gelatine capsule shell (size 1), two-tone grey	Capsule shell	76 mg

The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675 (pH 7.5):



The dual release capsules were stored for 2 weeks at 40°C/75% relative humidity in induction-sealed HDPE bottles. The dissolution profile proved to be stable under these storage conditions and no significant change in drug release profile was observed:



This experiment demonstrates that a hydrophobic isolating protective layer comprising ethylcellulose prevents any deleterious interaction between ammonio methacrylate-containing controlled release beads and the gelatine capsule and provides a formulation which is stable upon storage.

Example 8

Stabilisation of an eletriptan hemisulphate dual release formulation with a hydrophobic isolating protective layer comprising methacrylic acid–ethyl acrylate copolymer (Eudragit® L) and additionally incorporating glycine as a quenching agent

An aqueous dispersion of talc was prepared using a rotor-stator stirrer (Ultra-Turrax®). Triethylcitrate was dissolved in purified water using a blade stirrer and 30% aqueous dispersions of ammonio methacrylate copolymer dispersions type A (Eudragit® RL) and B (Eudragit® RS) were added and dispersed. The aqueous talc dispersion and the aqueous ammonio methacrylate copolymer dispersion were combined and sprayed onto eletriptan hemisulphate starter cores using a Glatt GPCG-1 fluid-bed equipment with a 6-inch Wurster insert at a 1.3-kg batch size.

Glycine was dissolved in 1 part of water and triethylcitrate and talc were dispersed in another part of water using a rotor-stator stirrer (Ultra-Turrax®). The glycine solution and the triethylcitrate/talc dispersion were added to two parts of a 30% aqueous dispersion of methacrylic acid–ethyl acrylate copolymer (Eudragit® L) and sieved through a sieve with 500 μm mesh size. The combined dispersion was sprayed onto the controlled release beads using the same Wurster coating equipment at a temperature between 25 and 30°C. The bead weight was 164.63mg.

Eletriptan hemisulphate controlled release beads		
Component	**Description**	**Amount**
Eletriptan hemisulphate starter cores (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat	108.04 mg
Ammonio methacrylate copolymer type B (Eudragit® RS)	Controlled release Layer	24.91 mg
Ammonio methacrylate copolymer type A (Eudragit® RL)		1.31 mg
Triethylcitrate NF		5.24 mg
Talc		13.10 mg
Methacrylic acid–ethyl acrylate copolymer 1:1 (used as 30% aqueous dispersion, Eudragit® L 30 D-55)	Hydrophobic isolating protective layer including quenching agent	7.21 mg
Talc		3.60 mg
Triethylcitrate		0.72 mg
Glycine		0.50 mg

The coated controlled release beads were cured in a tray oven at 40°C for 24 hours and then filled together with immediate release beads into hard gelatin capsules (size 1). The capsule fill weight was 280.14mg.

Eletriptan hemisulphate dual release capsule		
Component	**Description**	**Amount**
Eletriptan hemisulphate immediate release beads (corresponding to 40.00 mg eletriptan base)	Core composition including top coat	115.51 mg
Eletriptan hemisulphate controlled release beads (corresponding to 40.00 mg eletriptan base)	Core composition including barrier coat, controlled release layer and hydrophobic isolating layer including a quenching agent	164.63 mg
Hard gelatine capsule shell (size 1), two-tone grey	Capsule shell	76 mg

Capsules were filled using a Bosch GKF 400 capsule filling machine with two pellet filling stations. Batch size was 5,245 capsules, machine speed 13,500 capsules/hour. Standard deviation of total fill weights was 0.8%.

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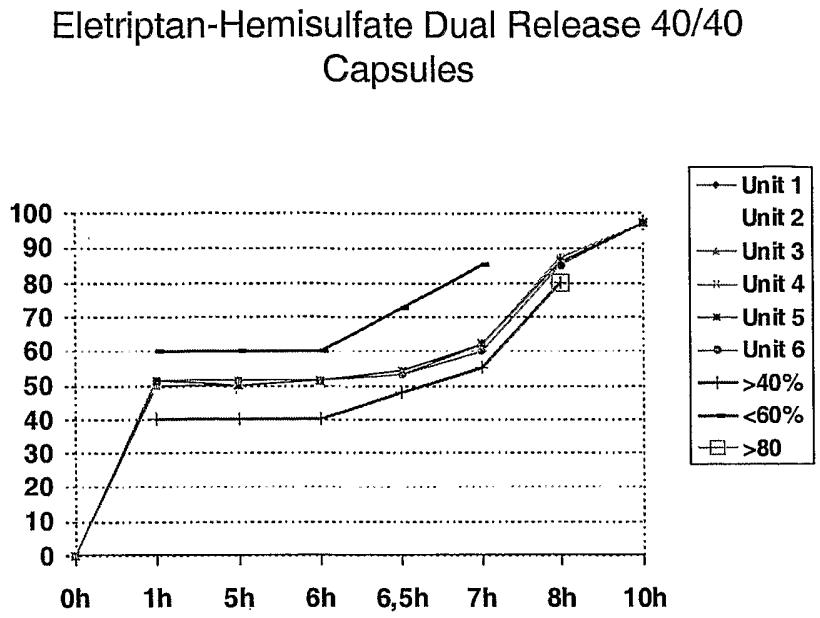
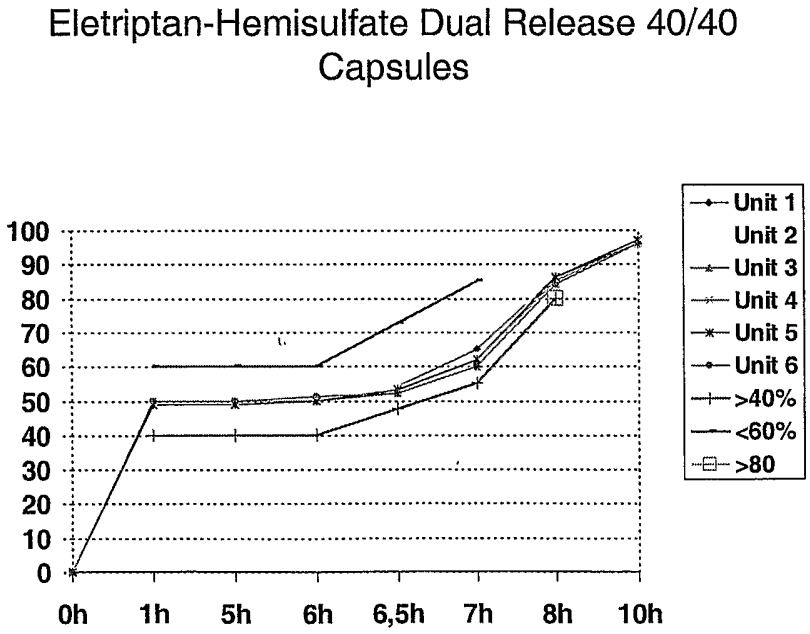
The following release profile was obtained using the dissolution test described in Example 6 of WO-A-02/09675 (pH 7.5):



No changes in dissolution were seen after storage for 6 weeks at 40°C/75% relative humidity in induction-sealed HDPE bottles:



This experiment demonstrates that a hydrophobic isolating protective layer comprising methacrylic acid–ethyl acrylate copolymer in combination with glycine as a quenching agent prevents any deleterious interaction between ammonio methacrylate-containing

controlled release beads and the gelatine capsule and provides a formulation which is stable upon storage.

Claims

1. A controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that an isolating protective layer comprising a hydrophobic substance is inserted between the ammonio methacrylate copolymer and the gelatine capsule.

2. A controlled release pharmaceutical formulation as claimed in claim 1 wherein the isolating protective layer comprises a hydrophobic polymer.

3. A controlled release pharmaceutical formulation as claimed in claim 2 wherein the hydrophobic polymer is ethyl-cellulose or a methacrylic acid–ethyl acrylate copolymer.

4. A controlled release pharmaceutical formulation as claimed in claim 1 wherein the isolating protective layer comprises a methacrylic acid–ethyl acrylate copolymer and an emulsifier.

5. A controlled release pharmaceutical formulation as claimed in claim 2 wherein the hydrophobic polymer contains carboxylic and/or sulfonic acid groups.

6. A controlled release pharmaceutical formulation as claimed in any one of claims 1 to 5, further comprising a quenching agent.

7. A controlled release pharmaceutical formulation as claimed in claim 6, wherein the quenching agent is cysteine, lysine, aspartic acid, asparagine, gelatine or glycine.

8. A controlled release pharmaceutical formulation as claimed in any one of claims 1 to 7 wherein the capsule contains a dual release formulation comprising immediate release particles and controlled release particles.

9. A controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that a layer which prevents the passage of volatile impurities, such as low molecular weight aldehydes, is inserted between the ammonio methacrylate copolymer and the gelatine capsule.

10. A controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that a layer which significantly impedes the passage of anions is inserted between the ammonio methacrylate copolymer and the gelatine capsule.

11. A controlled release pharmaceutical formulation in the form of a gelatine capsule containing one or more particles, said particles comprising an antimigraine drug and an ammonio methacrylate copolymer, characterised in that the formulation is provided with means to prevent capsule crosslinking on storage.

12. A multiparticulate composition, suitable for administration in a gelatine capsule, comprising an antimigraine drug-containing core, said core being coated with an inner controlled release coating and an outer isolating protective layer, wherein the inner coating comprises an ammonio methacrylate copolymer and the outer protective layer comprises a hydrophobic substance.

13. A controlled release pharmaceutical formulation as claimed in any one of claims 1 to 11 or a multiparticulate composition as claimed in claim 12 wherein the drug is eletriptan or a pharmaceutically acceptable salt thereof.

14. A controlled release pharmaceutical formulation or a multiparticulate composition as claimed in claim 13 wherein the drug is eletriptan hemisulphate.

15. The use of a controlled release pharmaceutical formulation or a multiparticulate composition as claimed in claim 13 or claim 14 for the manufacture of a

medicament for the treatment of migraine or the prevention of migraine recurrence.

16. A method of treating migraine or preventing migraine recurrence in a mammal, including a human, comprising administration to said mammal of a therapeutically effective amount of a controlled release pharmaceutical formulation or a multiparticulate composition as claimed in claim 13 or claim 14.

17. A process for the preparation of a controlled release pharmaceutical formulation as claimed in claim 1 comprising the steps of

(a) coating one or more antimigraine drug-containing particles with a controlled release coating comprising an ammonio methacrylate copolymer;
(b) coating the controlled release particles from step (a) with an isolating protective layer comprising a hydrophobic substance; and
(c) filling the particles into a gelatine capsule.

18. A method of improving the stability of a controlled release pharmaceutical formulation in the form of a gelatine capsule, said gelatine capsule containing one or more particles comprising an antimigraine drug and an ammonio methacrylate copolymer, by inserting an isolating protective layer comprising a hydrophobic substance between the ammonio methacrylate copolymer and the gelatine capsule.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/EP2005/002191

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/18 A61K31/635

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/09675 A (PFIZER LIMITED; PFIZER, INC; DE RASPIDE, MANAUD, PIERRE, FREDERICK; MA) 7 February 2002 (2002-02-07) cited in the application page 6, line 1 - line 10 claims 1-3,13-15	1-18
Y	US 2002/058050 A1 (SACKLER RICHARD S ET AL) 16 May 2002 (2002-05-16) paragraph '0069! table 2 examples 1-7	1-18

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 October 2005	28/10/2005

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/198673 A1 (OSHLACK BENJAMIN ET AL) 23 October 2003 (2003-10-23) paragraph '0091! examples 1-7 paragraph '0143!	1-18
Y	US 2002/182253 A1 (DEBREGEAS PATRICE ET AL) 5 December 2002 (2002-12-05) example 5	1-18

INTERNATIONAL SEARCH REPORT

ınal application No.
:T/IB2005/002191

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB2005/002191

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