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(72) Inventor; and
(71) Applicant : **SILVESTRINI, Bruno** [IT/IT]; Via Michelangelo Schipa, 15, 00179 Roma (IT).

(74) Agent: **IANNONE, Carlo Luigi**; Barzano' & Zanardo Roma S.p.A., Via Piemonte, 26, 00187 Roma (IT).

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(54) **Title**: A DOSAGE FORM COMPRISING A CALCIUM SALT, COLLAGEN AND A DRUG AND RELATED USE IN A METHOD OF CONTROLLED RELEASE ENDOWED WITH A REGULATORY MECHANISM OF DRUG RELEASE INSIDE THE COMPOSITION

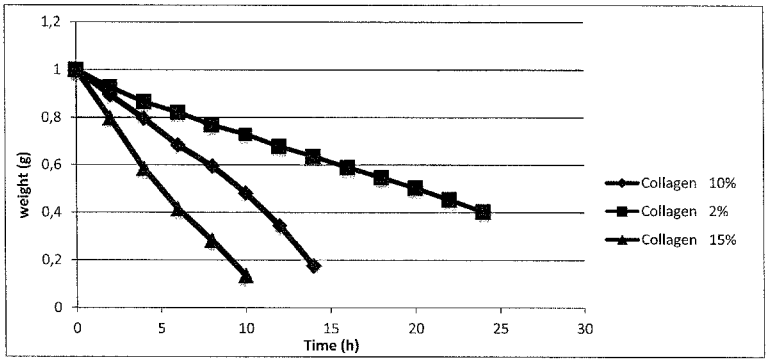

Fig. 1

(57) **Abstract**: The invention relates to the technical field of the science and technology of dosage forms with controlled release of a drug. The present invention regards a dosage form for the controlled release of a drug present therein comprising a calcium sulphate and/or calcium carbonate, preferably a calcium sulphate dihydrate, or a calcium salt with equivalent physical and chemical activity, a collagen and at least one drug. Said dosage form is advantageously used in a method of controlled release (also referred to as pro - longed or delayed, EMA, 2014) endowed with a regulatory mechanism inside the specific composition. In greater detail, the inven - tion relates to a dosage form consisting in a composition that comprises a mixture which comprises or, alternatively, consists of (i) a calcium sulphate and/or a calcium carbonate, preferably a calcium sulphate dihydrate, or a calcium salt with equivalent physical and chemical activity, (ii) a collagen and (iii) at least one drug or an active ingredient for pharmaceutical use. In the context of the present invention, the term drug is understood in the sense of active ingredient for pharmaceutical use. In the dosage form of the present invention, the release of the individual components, for example in a controlled or prolonged or delayed mode, takes place via a process of dissolution or solubilisation, the rate and kinetics of which are regulated by the ratio set between the collagen and the

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calcium salt present in the composition or in the dosage form. The drug is released thanks to the ratio set, at the time of preparation, between the collagen and the calcium salt. Advantageously, this regulatory mechanism simplifies the preparation, experimental study and industrial production of the dosage forms with controlled release. The present invention has been successfully applied to various drugs, as shown in the description that follows.

A DOSAGE FORM COMPRISING A CALCIUM SALT, COLLAGEN AND A DRUG AND RELATED USE IN A METHOD OF CONTROLLED RELEASE ENDOWED WITH A REGULATORY MECHANISM OF DRUG RELEASE INSIDE THE COMPOSITION

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FIELD OF APPLICATION

The invention relates to the technical field of the science and technology of dosage forms with controlled release of a drug. The present invention regards a dosage form for the controlled release of a drug present therein comprising a calcium sulphate and/or calcium carbonate, preferably a calcium sulphate dihydrate, or a calcium salt with equivalent physical and chemical activity, a collagen and at least one drug. Said dosage form is advantageously used in a method of controlled release (also referred to as prolonged or delayed, EMA, 2014) endowed with a regulatory mechanism inside the specific composition.

In greater detail, the invention relates to a dosage form consisting in a composition that comprises a mixture which comprises or, alternatively, consists of (i) a calcium sulphate and/or a calcium carbonate, preferably a calcium sulphate dihydrate, or a calcium salt with equivalent physical and chemical activity, (ii) a collagen and (iii) at least one drug or active ingredient for pharmaceutical use. In the context of the present invention, the term drug is understood in the sense of active ingredient for pharmaceutical use.

In the dosage form of the present invention, the release of the individual components, for example in a controlled or prolonged or delayed mode, takes place via a process of dissolution or solubilisation, the rate and kinetics of which are regulated by the ratio set between the collagen and the calcium salt present in the composition or in the dosage form. The drug is released thanks to the ratio set, at the time of preparation, between the collagen and the calcium salt. Advantageously, this regulatory mechanism simplifies the preparation, experimental study and industrial production of the dosage forms with controlled release. The present invention has been successfully applied to various drugs, as shown in the description that follows.

STATE OF THE ART

Dosage forms with controlled release, also referred to as prolonged or delayed release (EMA, 2014), are known. The science and technology of controlled drug release developed starting from the ninety-forties, with practical applications ranging from medicine to cosmetics, from the food industry to agriculture (Bertrand and Leroux, 2011; Ravi Kuman, 2008). Current controlled release systems are generally based on a carrier, often consisting of a polymer (for example cellulose or derivatives thereof), which contains and gradually releases the active ingredient. The regulatory mechanisms and processes of release comprise diffusion, degradation, osmosis, pH, enzymatic digestion and the affinity between the carrier and active ingredient, as well as various forms of irradiation, including with light and sound (Chang *et al.*, 2011; Cheng *et al.*, 2013; Drulis *et al.*, 2010; Gopferich, 1999; He and Shi, 2011; Kim *et al.*, 2009; Langer *et al.*, 1981; Panyam and Labhasetwar, 2003; Malavia *et al.*, 2014; Stayton *et al.*, 2005; Wang and Recum, 2011; Wong-ekkabut and Karttunen, 2012; You *et al.*, 2010). The pharmaceutical forms currently used comprise tablets, capsules and microcapsules, liposomes, gels, creams, ointments and eye drops, transdermal patches and other fixed and mobile devices, such as vaginal rings (Allen and Cullis, 2010; Bonanomi and Silvestrini, 2008; Chang and Cheng, 2012; Engelberg and Kohn, 1991; Gopferich, 1999; Kawa and Dorotkiewicz-Jach, 2010; He and Shi, 2011; Langer and Peppas, 1981; Ranga Rao *et al.*, 1990; Ulrich *et al.*, 1999).

Dosage forms with controlled release bring three main advantages tied to the flattening of the absorption curve: a) they reduce the risk of potentially harmful absorption peaks responsible for acute side effects which have nothing to do with the therapeutic effect of the drug administered; b) they facilitate the stabilisation of therapeutic levels, ensuring the presence of the drug in the body over 24 hours; c) they enable daily administrations to be reduced to two, or possibly one.

TECHNICAL PROBLEM

Despite the variety of technological solutions that have been adopted to date, at present there is no system available which enables the rate of release to be easily and precisely regulated, so as to adapt it to the drug, dose and medical use envisaged in each instance. It follows that the need for a new technology which, by overcoming these disadvantages, facilitates the preparation, experimental study and industrial production of dosage forms with controlled release that are repeatable, easy to prepare and economical and also capable of administering drug doses with a constant profile over time and with accurate values.

Thus, there continues to be a demand on the part of experts in the field for a dosage form with controlled release capable of overcoming the limits and persisting drawbacks in the dosage forms present on the market.

The object of the present invention is to provide an adequate response to the aforementioned demands and provide a technical solution to the above-described technical problem.

SUMMARY OF THE INVENTION

After an intense activity of research and development, the Applicant has developed a new system of controlled release for oral use which is easy to prepare, repeatable and economical. The new system of release for oral use advantageously overcomes the aforesaid limits and advantages present in the prior art, thanks to a regulatory mechanism which may be likened to that of the osseous system and its role in controlling and maintaining the acid-base balance of blood. The new system of release is thus capable of providing the desired response to the above-described technical problem.

Therefore, the subject matter of the present invention relates to a carrier for dosing and releasing a drug with controlled release, said carrier consisting of a mixture which comprises or, alternatively, consists of a calcium salt selected between a calcium sulphate and/or a calcium carbonate (or a calcium salt with equivalent physical and chemical activity) and a collagen, having the features disclosed in the appended independent claim.

The subject matter of the present invention further relates to a pharmaceutical composition for medical use comprising said carrier consisting of a mixture which comprises or, alternatively, consists of a calcium salt selected between a calcium sulphate and/or a calcium carbonate (or a calcium salt with equivalent physical and chemical activity) and a collagen; and a drug or an active ingredient for pharmaceutical use, having the features disclosed in the appended independent claim.

The pharmaceutical composition of the present invention is for oral use and enables a drug to be dosed and released with a controlled release via a process of dissolution or solubilisation, the rate and kinetics of which are regulated by the ratio set between the collagen and the calcium salt present in said carrier and in the composition of the present invention. The drug is released thanks to the ratio set, at the time of preparation, between the collagen and the calcium salt.

The pharmaceutical composition of the present invention is for oral use and represents a dosage form with controlled release of a drug. The drug is distributed, or incorporated, or mixed inside the carrier together with a calcium salt selected between a calcium sulphate and/or a calcium carbonate (or a calcium salt with equivalent physical and chemical activity), and a collagen.

The carrier and the pharmaceutical composition according to the present invention can further comprise excipients or inert flavourings that do not affect the release performance of the drug, but are rather chosen, for example, to improve the industrial processing steps for the preparation of the carrier and of the pharmaceutical composition or to improve their acceptability by the consumer. Therefore, the carrier according to the present invention comprises or essentially consists of the calcium salt and collagen, as well as comprising the drug in a pharmaceutical composition, the rate of release of the drug increasing with increases in the percentage of collagen relative to the calcium salt.

The carrier and the pharmaceutical composition according to the present invention are in solid form for the oral administration.

Preferred embodiments of the present invention are disclosed in the appended dependent claims.

The preferred embodiments of the present invention described in the detailed description that follows are illustrated solely by way of example and in absolutely no way limit the broad scope of application of the present invention, which will become immediately clear to the person skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

The detailed description of the present invention is accompanied by the following drawings:

Figure 1 shows the patterns of dissolution and consequent release of an active ingredient with a carrier consisting, respectively, of 10%, 2% and 15% of partially hydrolysed collagen relative to calcium sulphate dihydrate.

DETAILED DESCRIPTION OF THE INVENTION

About 70 percent of the osseous system is made up of hydroxyapatite [$(Ca_5(PO_4)_3(OH)$], a substantially insoluble mineral, and the remainder of an organic matrix, composed principally of collagen.

Hydroxyapatite ensures the hardness and durability required to supporting the remaining part of the body, whilst collagen lends bone the ability not only to remodel itself incessantly (Guyton and Hall, 2006), but also to intervene in the acid-base balance of blood by releasing a calcium salt endowed with a buffer effect (Green and Kleeman, 1991; Lemann *et al.,* 1966).

Advantageously, the release of the drug present in the carrier and, therefore, in the composition of the present invention, takes place through a process of dissolution, the rate of which depends on the ratio between said calcium salt selected between a calcium sulphate and/or a calcium carbonate (or a calcium salt with equivalent physical and chemical activity), and said collagen.

The Applicant, both in order to produce said carrier for dosing and releasing a drug with a controlled release and to develop said dosage form with controlled release (pharmaceutical composition), together the subject

matter of the present invention, has intervened by adopting specific and selected adjustments after an intense research activity. Practically speaking, the following adjustments were made.

1. After multiple attempts were made, hydroxyapatite was replaced by a calcium sulphate, advantageously by calcium sulphate dihydrate ($CaSO_4$ $2H_2O$), a food additive present in many foods, which the FDA considers to be generally safe. Calcium sulphate dihydrate is easily workable and possesses good adhesive properties. Alternatively, other calcium salts, such as calcium carbonate, have been tested with favourable results.

2. After multiple attempts were made, the partially hydrolysed industrial derivative of collagen, known by the name of gelatine, was selected and used in the place of native collagen. It can be selected among mammal (e.g. bovine), chicken or fish collagen, with a Bloom degree comprised between 0 and 500, preferably from 30 to 300, even more preferably from 100 to 250, for example from 110 to 150. Collagen is considered a safe ingredient, widely used in the food and pharmaceutical industries, as such or in the form of an excipient, capsules and devices (Gareis and Schrieber, 2007).

3. After multiple attempts, the concentration of collagen, which in bone stands at around 30 percent, was calibrated and is here used in a range of values comprised from 1% to 20% by weight, relative to the weight of said calcium salt, according to the physicochemical properties of the drug, the dose and the duration of the release; preferably from 2% to 15%, and even more preferably from 5% to 10%. The complement to 100% being represented by said calcium sulphate.

The calcium sulphate and/or calcium carbonate (or a calcium salt having equivalent physical and chemical properties), and the collagen together, preferably also with the addition of other formulation components and additives (if required), represent the carrier for dosing and releasing a drug with controlled release, the subject matter of the present invention. However, said other formulation components and additives, like the properties of the drug, are irrelevant for the purposes of the regulatory

mechanism of drug release, which depends exclusively on the ratio between the percentages of calcium salt and collagen.

The calcium sulphate and/or calcium carbonate, or a calcium salt having equivalent physical and chemical properties, and the collagen mixed together with a drug form a solid composition (dosage form with controlled release consisting of a pharmaceutical composition for medical use), for example for oral use, wherein the rate of dissolution of the individual components present therein can be predetermined and calibrated to the desired values by varying the concentration of the collagen.

In one embodiment, said calcium sulphate is calcium sulphate dihydrate or calcium carbonate and said collagen is a gelatine of chicken or bovine origin having a Bloom strength comprised between 30 and 500, preferably from about 50 to 300, even more preferably from 100 to 250. Advantageously the collagen used, in powder, is chicken or bovine collagen and has a mesh size of about 10 to 100, preferably from 30 to 80, even more preferably from 40 to 60, for example 50, and has a Bloom degree of about 100 to 250, preferably 120.

According to particular embodiments, the drugs can be selected from among hypotensive, antiparkinson, antibiotic, anti-inflammatory, non-steroidal anti-inflammatory (NSAIDs) and antitumour drugs.

For example, the drugs can be selected from the group comprising or, alternatively, consisting of folic acid, thiamine, B complex, lithium carbonate, L-dopa, carbidopa, trazodone, lonidamine, ibuprofen, naproxene, ursodeoxycholic acid, carvedilol, dihydroergotamine and furosemide.

The carrier and the pharmaceutical composition according to the present invention can be prepared using techniques known to the person skilled in the art. For example, the process for preparing the pharmaceutical composition of the present invention can comprise a mixing step, in which said calcium salt in powder and said collagen in powder are mixed together to yield a homogeneous mixture, to which the drug in powder is added to obtain a second homogeneous mixture. One

then proceeds to add water at room temperature, for example at a temperature comprised from 18 °C to 25 °C, so as to obtain a homogeneous fluid paste. The amount of water added is comprised from 20 ml to 60 ml, relative to 100 grams of the mixture which comprises or, alternatively, consists of a calcium sulphate and/or a calcium carbonate, or a calcium salt with equivalent physical and chemical activity, a collagen and a drug or an active ingredient for pharmaceutical use; preferably, the water is comprised from 30 ml to 50 ml, even more preferably, it is comprised from 35 ml to 45 ml, for example 40 ml.

The final pharmaceutical form for oral use, such as, for example, a tablet or lozenges or granules, is prepared by percolation, followed by a drying step to remove the water present. As an alternative to a paste, the homogeneous mixture of the aforesaid components is granulated. The granulated mixture is converted into the final pharmaceutical form by compression. The aforesaid processes are of current use in pharmaceutical production.

The preparation process has been successfully implemented with various drugs, namely, folic acid, thiamine, B complex, lithium carbonate, L-dopa, carbidopa, trazodone, lonidamine, ibuprofen, naproxene, ursodeoxycholic acid, carvedilol, dihydroergotamine and furosemide.

Over a 24-hour period, corresponding to the average intestinal transit times, the concentrations of collagen needed in order to fix the required dissolution times range from 1% to 20%, according to the dose and the physicochemical characteristics of the individual drug; they are preferably comprised from 2% to 15%. Said dose and physicochemical characteristics of the individual drug are taken into consideration in order to fix the drug dissolution times, but they do not influence the regulatory mechanism of drug release, which depends solely on the percentages of calcium salt and collagen.

In practical terms, the invention relates to a dosage form, comprising calcium sulphate dihydrate, collagen and at least one drug, for use in a method of controlled release endowed with a regulatory mechanism inside in the composition, in terms of the amount by weight of

said calcium sulphate and said collagen. The release takes place via a dissolution process, which can be ascertained by determining the weight of the solid residue. The rate of release is regulated by the relative percentages of collagen and calcium salt.

The preparation, experimental study and industrial production of the dosage forms with controlled release are thereby simplified.

Water-soluble vitamins, like folic acid, are rapidly eliminated through urine. To remedy this drawback, the WHO recommends at least 5 portions a day of foods rich in water-soluble vitamins. However, this recommendation does not cover the hours of sleep, during which a foetus can be in a condition of deficiency.

Advantageously, the carrier and the composition of the present invention solve this problem.

The subject matter of the present invention relates to a pharmaceutical composition, in tablet form based on folic acid (which has a breakdown time of 24 hours) or in granulated form, for medical use comprising:

Folic acid .....5.00 mg
Calcium sulphate dihydrate .....465.00 mg
Partially hydrolysed collagen ..... 15.00 mg
Excipients .....15.00 mg

The collagen used (in powder) is chicken or bovine collagen and has a mesh size of about 50 and a Bloom degree of about 120.

Taking into account, on the one hand, the pharmacokinetic profile of folic acid and, on the other hand, the dissolution time of the tablets, it is easy to calculate that the physiological needs of a pregnant woman can be assured by a single daily administration of the aforesaid pharmaceutical form.

With reference to lithium carbonate, the peak in plasma concentrations is reached after 1-2 hours in the case of forms with

immediate release, and after 4-5 hours in the majority of the dosage forms with controlled release available today.

With the carrier and the composition of the present invention, there is a reduction in the potentially toxic absorption peaks, with a flattening and lengthening of the absorption curve, whose area below the curve remains substantially unchanged: the result is an advantage in terms of reducing the daily dose by approximately 25-50 percent. The carrier and the composition of the present invention thus enable the release and absorption curves to be further flattened and lengthened over time, with a reduction in the daily therapeutic dose and an increase in the safety of use of the lithium.

The subject matter of the present invention relates to a pharmaceutical composition for oral use in tablet form or in granules based on lithium carbonate, having a breakdown time of 24 hours, said composition comprising:

Lithium carbonate ..... 300.00 mg
Calcium sulphate dihydrate ,..... 700.00 mg
Partially hydrolysed collagen .....20.00 mg
Excipients .....40.00 mg

The collagen used (in powder) is chicken or bovine collagen and has a mesh size of about 50 and a Bloom degree of about 120.

The dose of lithium takes into account, on the one hand, its pharmacokinetic profile and, on the other hand, the dissolution time of the tablets: on the basis of these two elements it is reasonable to expect that the daily administration of 300 mg will be able to maintain the plasma concentrations within the therapeutic window. The risk of accumulation can be avoided, where necessary, by providing for a temporary suspension of the treatment guided by the usual monitoring of the lithaemia.

The subject matter of the present invention relates to a pharmaceutical composition for oral use in tablet form or in granules

based on trazodone, having a breakdown/dissolution time of 4 hours; said composition comprises:

Trazodone	50.00 mg
Calcium sulphate dihydrate	450.00 mg
Partially hydrolysed collagen	45.00 mg
Excipients	15.00 mg

The collagen used (in powder) is chicken or bovine collagen and has a mesh size of about 50 and a Bloom degree of about 120.

The carrier and pharmaceutical composition of the present invention all use food grade compounds or edible substances; no use is made of cellulose, or cellulose derivatives (as occurs in the case of the other carriers present on the market), which are difficult to digest and, therefore, are entrained in faeces together with the drug.

The carrier and pharmaceutical composition of the present invention employ natural substances for food use, which do not entail safety problems.

The drug, understood in the sense of active ingredient for pharmaceutical use, can consist of any substance or association of substances, which, irrespective of their pharmacological properties, do not alter the ability of the carrier to dissolve in the times predetermined by the ratio between calcium salt and collagen. In this regard, the performances have been successfully tested using drugs belonging to various pharmacological categories: folic acid, thiamine, B complex, lithium carbonate, L-dopa, carbidopa, trazodone, lonidamine, ibuprofen, naproxene, ursodeoxycholic acid, carvedilol, dihydroergotamine and furosemide.

In the examples that follow, the collagen used (in powder) is chicken or bovine collagen and has a mesh size of about 50 and a Bloom degree of about 120.

Example 1

Folic acid, also known as vitamin B9, is essential for DNA and protein synthesis, for the formation of haemoglobin and for tissues undergoing processes of proliferation and differentiation, especially during embryonic and foetal development. A deficiency thereof in the early stages of pregnancy increases the risk both of foetal malformations, such as spina bifida and anencephaly, and of intrauterine growth retardation, premature birth and placental lesions. The generally recommended daily dose is 0.4 mg of folic acid, which in pregnant women should be raised to 5 mg (Wald *et al.*, 2001). Since a normal diet does not always satisfy physiological folic acid requirements, experts recommend taking action on three fronts: a) a diet rich in folic acid; b) reliance on strongly fortified, or folic acid-enriched, foods; c) a daily intake of food supplements containing folic acid. Various foods are rich in folic acid, e.g. spinach, broccoli, asparagus, lettuce, oranges and legumes, but the cooking process destroys most of the folic acid present in food. In 1998 the FDA (Food and Drug Administration) provided for the addition of folic acid to 'fortified' cereals, in an amount of 0.14 mg per 100 grams of product. Like the majority of water-soluble vitamins, folic acid is rapidly eliminated through urine (Kokue *et al.*, 1994; Nguyen *et al.*, 2008). To remedy this drawback, the WHO recommends at least 5 portions a day of foods rich in water-soluble vitamins. However, this recommendation does not cover the hours of sleep, during which a foetus can be in a condition of deficiency.

The carrier and the composition of the present invention solve this problem. One embodiment is given by the following pharmaceutical form of folic acid in tablets, with a breakdown time of 24 hours, and having a composition which comprises:

Folic acid .....5.00 mg
Calcium sulphate dihydrate .....465.00 mg
Partially hydrolysed collagen .....15.00 mg
Excipients ..... 15.00 mg

The ratio between said collagen and said calcium sulphate is 15:465=X:100, X=3.22%.

Taking into account, on the one hand, the pharmacokinetic profile of folic acid and, on the other hand, the dissolution time of the tablets, it is easy to calculate that the physiological needs of a pregnant woman can be assured by a single daily administration of the aforesaid pharmaceutical form.

Example 2

Lithium carbonate is probably the best mood stabiliser currently available (Cipriani *et al.*, 2013; Grandjean and Aubry, 2009; Hajek *et al.*, 2012 and 2014; Kovacsics *et al.*, 2009; Müller-*et al*, 2003). Its therapeutic action is manifested in plasma concentrations comprised between 0.6–0.8 and 1.2–1.5 mmol/L, above which it becomes toxic (Johnson *et al.*, 1982; Perlis *et al.*, 2002; Solomon *et al.*, 1996). The peak in plasma concentrations is reached after 1-2 hours in the case of forms with immediate release, and after 4-5 hours in the majority of the dosage forms with controlled release available today. With the carrier and the composition of the present invention, there is a reduction in the potentially toxic absorption peaks, with a flattening and lengthening of the absorption curve, whose area below the curve remains substantially unchanged: the result is an advantage in terms of reducing the daily dose by approximately 25 - 50 percent. The carrier and the composition of the present invention enable the release and absorption curves to be further flattened and lengthened over time, with a reduction in the daily therapeutic dose and an increase in the safety of use of the lithium. One embodiment of the present invention is given by the following pharmaceutical form of lithium carbonate in tablets, with a breakdown time of 24 hours, and having a composition which comprises:

Lithium carbonate .....300.00 mg
Calcium sulphate dihydrate.,.....700.00 mg
Partially hydrolysed collagen .....20.00 mg
Excipients .....40.00 mg

The ratio between said collagen and said calcium sulphate is 20:700=X:100, X=2.26%.

The dose of lithium takes into account, on the one hand, its pharmacokinetic profile and, on the other hand, the dissolution time of the tablets: on the basis of these two elements it is reasonable to expect that the daily administration of 300 mg will be able to maintain the plasma concentrations within the therapeutic window. The risk of accumulation can be avoided, where necessary, by providing for a temporary suspension of the treatment guided by the usual monitoring of the lithaemia.

Example 3

Trazodone is an antidepressant originally synthesised and discovered in Italy (Palazzo and Silvestrini, 1968; Silvestrini *et al.*, 1968). It was developed based on the hypothesis of mental pain, according to which the greatest depression is associated with a reduction in the pain threshold (Silvestrini, 1986, 1989; Valeri *et al.*, 1988). Trazodone belongs to the class of serotonin antagonist and reuptake *inhibitor*s (SARI). Unlike other antidepressants, it manifests a powerful blocking of α1-adrenergic receptors, associated with orthostatic hypotension. This side effect depends on the peaks in blood concentration, which occur about an hour after the administration of a conventional form (Nilsen and Dale, 1992). The following form in tablets has been adjusted to a dissolution time of 4 hours, which avoids the aforesaid dangerous peaks, and has a composition which comprises:

Trazodone..... 50.00 mg
Calcium sulphate dihydrate..... 450.00 mg
Partially hydrolysed collagen .....45.00 mg
Excipients ..... 15.00 mg

The ratio between said collagen and said calcium sulphate is 45:450=X:100, X=10%.

EXAMPLE 4:

The dissolution patterns and consequent release of an active ingredient with the carrier according to the present invention were determined with a "dissolution test". The test apparatus consists of a vessel typically covered with glass, a motor, an agitator and a cylindrical basket. The vessel is partially immersed in a temperature-controlled bath, which enables a T of 37 +/- 0.5 °C to be maintained throughout the duration of the test, while ensuring a constant and regular movement of the dissolution medium. The environment is buffered with a phosphate buffer. The weight-bearing structure of the apparatus is totally fixed; the only movements are the ones allowed by the regular movement of the agitator. The vessel has a flange on which it is possible to apply a specific lid in order to delay the evaporation process (*Official Pharmacopeia 12th edition*). At the beginning of the test, the preparation being tested is placed inside a dry basket located about 25 mm from the bottom of the vessel. A sample is taken at regular time intervals, the aliquot removed being replaced with an equal volume of the dissolution medium at 37 °C, after which an analysis is performed on the test sample with a suitable assay method.

This example refers to a 1 g percolate containing partially hydrolysed collagen, calcium sulphate dihydrate and 1mg of lithium carbonate, wherein the carrier consists, respectively, of 10%, 2% and 15% of partially hydrolysed collagen relative to the calcium sulphate dihydrate. Figure 1 shows the dissolution patterns and consequent release of an active ingredient, which increases with increases in the percentage of collagen.

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CLAIMS

1. A carrier for dosing and releasing a drug with a controlled release, said carrier consisting of a mixture which comprises or, alternatively, consists of a calcium salt selected between a calcium sulphate and/or a calcium carbonate and a collagen, wherein the ratio between the percentages of the calcium salt and the collagen regulates the controlled release of the drug, said ratio being able to determine the dissolution rate of the carrier and with it the release rate of the drug.

2. The carrier according to claim 1, wherein said collagen is present in an amount comprised from 1% to 20% by weight, relative to the weight of said calcium salt; preferably from 2% to 15%.

3. The carrier according to claim 1 or 2, wherein said collagen is a partially hydrolysed collagen, for example a mammal, chicken or fish collagen, also called gelatine.

4. A pharmaceutical composition for medical use comprising said carrier according to any one of the preceding claims, and at least one drug or an active principle for pharmaceutical use.

5. The pharmaceutical composition for medical use according to claim 4, wherein said drug is released with a controlled release regulated by the ratio between the percentages of the calcium salt and of the collagen, said ratio being able to determine the dissolution rate of the carrier and with it the release rate of the drug.

6. The pharmaceutical composition for medical use according to claim 5, wherein said drug is selected from the group comprising hypotensive, antiparkinson, antibiotic, anti-inflammatory, non-steroidal anti-inflammatory (NSAIDs) and antitumour drugs.

7. The pharmaceutical composition for medical use according to claim 6, wherein said drug is selected from the group comprising folic acid, thiamine, B complex, lithium carbonate, L-dopa, carbidopa, trazodone, lonidamine, ibuprofen, naproxene, ursodeoxycholic acid, carvedilol, dihydroergotamine and furosemide.

8. The pharmaceutical composition for medical use according to one of claims 4-7, wherein said composition is for oral use and is in solid form, such as, for example, in the form of a tablet or lozenges or granules.

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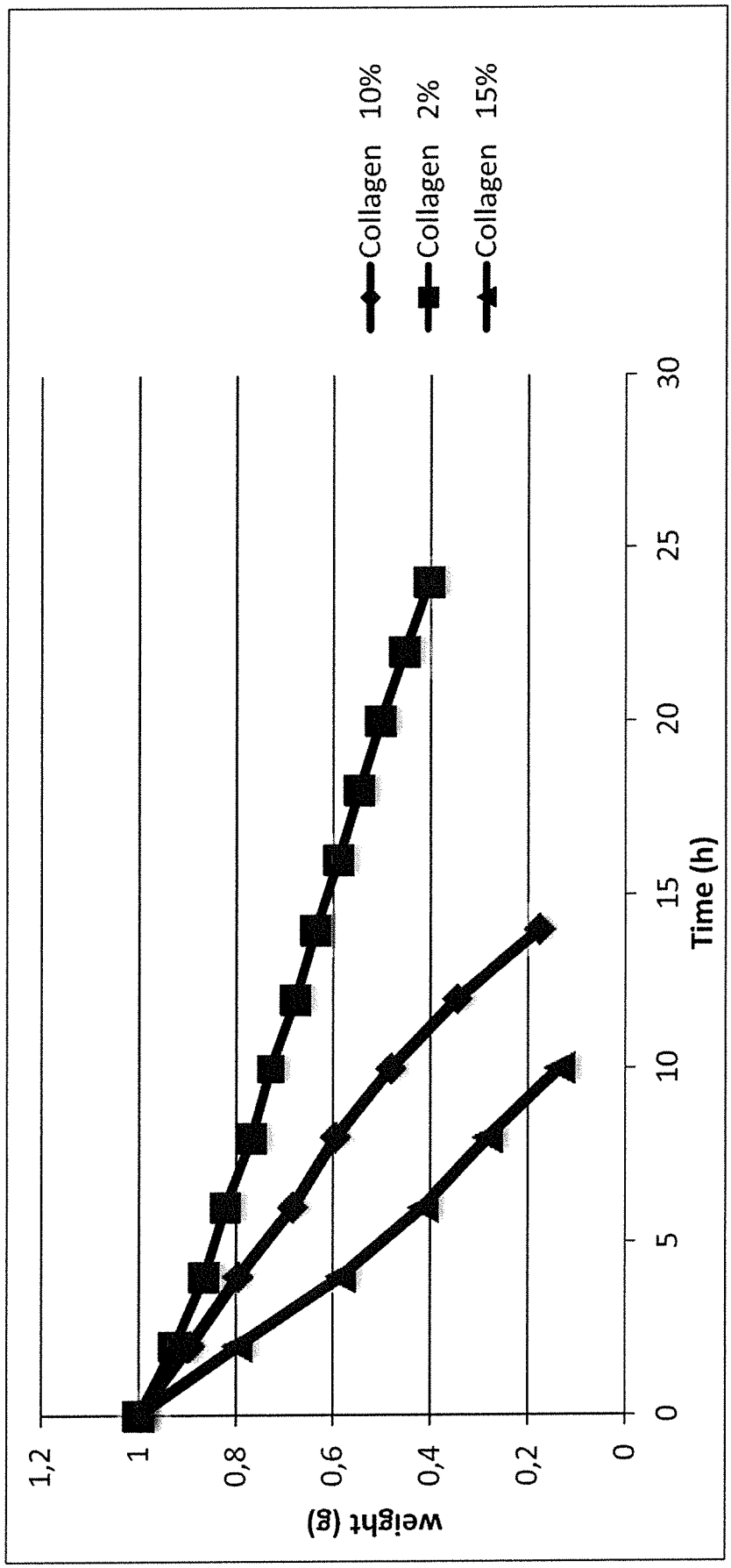
Collagen 10%
Collagen 2%
Collagen 15%
weight (g)
1,2
1
0,8
0,6
0,4
0,2
0
0
5
10
15
20
25
30
Time (h)

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2017/000029

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/519 A61K33/00
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, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 717 713 A (ZATZ JOEL L [US] ET AL) 5 January 1988 (1988-01-05) tables XI, XXXII-XXXIV column 23, line 62 - line 68	1-8
X	US 3 507 952 A (REDNICK ALVIN B ET AL) 21 April 1970 (1970-04-21) example 5 claims	1-8
X	US 4 163 777 A (MITRA ARUN K [US]) 7 August 1979 (1979-08-07) column 1, line 5 - line 7 examples 1,7	1-8

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

[X] See patent family annex.

* Special categories of cited documents :

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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
30 May 2017	16/06/2017

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	Giró, Annalisa

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IT2017/000029

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 425 769 A (SNYDERS JR ROBERT V [US]) 20 June 1995 (1995-06-20) column 4, line 4 - line 21 examples 1,2 column 8, line 48 - line 54 -----	1-8
X,P	WO 2016/068228 A1 (KOKEN KK [JP]) 6 May 2016 (2016-05-06) the whole document -----	1-8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IT2017/000029

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 3507952 A	21-04-1970	NONE	
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		WO 2016068228 A1	06-05-2016