Oral pharmaceutical formulation in the form of an aqueous suspension of microcapsules for the modified release of active principle(s)

The invention relates to the field of the modified release of pharmaceutical active principles, excluding amoxicillin. In the present disclosure, the expression "modified release" arbitrarily denotes release of the active principle(s) which starts as soon as the galenical form is brought into contact with its dissolution medium (in vivo or in vitro) or release of the active principle(s) which does not start until after a predetermined period ranging e.g. from 0.5 to several hours. In terms of the invention, the time taken to release 50% of the active principle(s) is typically several hours and can extend e.g. from 0.5 to 30 hours.

More precisely, the invention relates to liquid pharmaceutical formulations for oral administration with the modified release of active principle(s), excluding amoxicillin. These formulations consist of suspensions or dispersions of microcapsules, each of which is formed of a core comprising amoxicillin and of a coating enveloping said core. According to the invention, the microcapsules constituting the disperse phase of the suspension are designed to allow the modified release of the active principle(s), excluding amoxicillin.

Even more particularly, the invention relates especially to "multimicrocapsular" aqueous suspensions of active principle(s) for oral administration, excluding amoxicillin, said suspensions being stable throughout the treatment and allowing the modified release of the active principle (excluding amoxicillin). These suspensions are of particular value in the case of:

- forms for the modified release of active principles in high therapeutic doses (for example of 500 to 1000 milligrams or more);
- liquid paediatric or geriatric forms for the modified release of active principles (for example sachets or reconstitutable oral suspensions in bottles);
- taste masking and/or protection of sensitive active principles.

The invention further relates to a specific process for the preparation of the microcapsules to be suspended in water.

Oral pharmaceutical formulations for the modified release of active principle(s) are well known.

Some of these formulations consist of tablets comprising a therapeutically active core covered with various thicknesses of non-digestible materials.

Microcapsules or microspheres comprising a core of active principle(s) coated with layers of different permeability or solubility have appeared more recently. These microcapsules/microspheres are placed e.g. in gelatin capsules to form galenical systems for the modified release of active principle(s).

The majority of modified-release pharmaceutical forms that comprise a coated core of active ingredient(s) are presented in solid form: tablets, gelatin capsules, microspheres or microcapsules.

By way of illustration of microcapsules in the dry form, particular mention may be made of patent EP-B-0 709 087, ... describes a (pharmaceutical or dietetic) galenical system, preferably in the form of a tablet, advantageously a disintegrating tablet, or in the form of a powder or gelatin capsule, characterized in that it comprises microcapsules of the reservoir type containing at least one medicinal and/or nutritional active principle (AP) selected especially from antibiotics, and intended for oral administration, characterized in that:

- they consist of particles of AP each covered with a film coating of the following composition:
  1 - at least one film-forming polymer (P1) insoluble in the tract fluids, present in an amount of 50 to 90% by dry weight, based on the total weight of the coating composition, and consisting of at least one water-insoluble cellulose derivative, ethyl cellulose and/or cellulose acetate being particularly preferred;
  2 - at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25% by dry weight, based on the total weight of the coating composition, and consisting of at least one polyacrylamide and/or poly-N-vinylamide and/or poly-N-vinyllactam, polyacrylamide and/or polyvinylpyrrolidone being particularly preferred;
  3 - at least one plasticizer present in an amount of 2 to 20% by dry weight, based on the total weight of the coating composition, and consisting of at least one of the following compounds: glycerol esters, phthalates, citrates, sebacates, cetyl alcohol esters, castor oil, salicylic acid and cutin, castor oil being particularly preferred;
  4 - and at least one surfactant and/or lubricant present in an amount of 2 to 20% by dry weight, based on the total weight of the coating composition, and selected from anionic surfactants, preferably alkali metal or alkaline earth metal salts of fatty acids, stearic and/or oleic acid being preferred, and/or from non-ionic surfactants, preferably polyethoxylated sorbitan esters and/or polyethoxylated castor oil derivatives, and/or from lubricants such as stearates, preferably calcium, magnesium, aluminium or zinc stearate, or stearylfumarate, preferably sodium

stearylfumarate, and/or glycerol behenate, it being possible for said agent to comprise only one or a mixture of the above-mentioned products;

- they have a particle size of between 50 and 1000 microns;
- and they are designed so as to be able to reside in the small intestine for a period of at least about 5 hours, thereby allowing the absorption of the AP during at least part of their residence time in the small intestine.

Said document relates only to dry pharmaceutical forms based on microcapsules and makes no mention of oral liquid pharmaceutical forms based on microcapsules.

These modified-release solid pharmaceutical formulations are not always advantageous, especially when they are administered to very young children or to very elderly patients with swallowing difficulties.

Such is the case when the active principles in question have to be administered orally in high doses, for example of 500 to 1000 milligrams or more, e.g. when the active principle is metformin. It is clear that such solid galenical systems are unsuitable because they are too bulky and hence very difficult to swallow, especially by young children or the elderly. This can be the cause of poor patient compliance and consequently jeopardize the success of the therapeutic treatment.

Likewise, in the case of paediatric forms, where the therapeutic dose has to be adapted according to the child's weight, the suspensions of the invention are suitable for the already existing bottles provided with syringes graduated in kg, and does not therefore necessitate the development of a novel device. The modified-release forms rarely employed hitherto for children are therefore now accessible by virtue of the invention. The advantages of such forms are the reduction in the number of daily dosage units and the optimization of the efficacy of the treatment between successive dosage units (e.g. for antibiotics, anti-inflammatories, cardiovascular treatments, etc.). Thus a controlled-release liquid pharmaceutical formulation which were easy to prepare would represent a significant advance.

In this case it would be even more advantageous to use modified-release galenical systems consisting of a plurality of microcapsules with a diameter of less than 1000 microns. In fact, in these systems, the dose of active principle(s) to be administered is distributed over a large number of microcapsules (typically 10,000 for a 500 mg dose) and thus has the following intrinsic advantages:

- The use of a mixture of microcapsules with different modified-release profiles affords release profiles which have several release pulses or which, by appropriate regulation of the different fractions, ensure a constant plasma concentration level of the AP.

- It avoids bringing the tissues into contact with a high dose of AP (dose dumping). Each microcapsule actually contains only a very reduced dose of active principle(s), thereby circumventing the risk of damage to the tissues due to a local overconcentration of aggressive active principle(s).
- It is possible to combine several galenical forms (for immediate or modified release) containing one or more active principles in these "multimicrocapsular" systems.

Liquid multiparticulate galenical forms or, more precisely, colloidal suspensions are known which are preferred to the solid forms for oral administration in the case of high-dosage active principles or paediatric applications.

Liquid suspensions for the modified release of active principle(s) are difficult to produce. The main difficulty to be overcome is that of avoiding the release of the active principle(s) into the liquid phase during storage of the suspension, while allowing modified release as soon as it enters the gastrointestinal tract. This objective is particularly difficult to achieve because the active principle(s) is (are) stored in a liquid for a very long time compared with the desired release time in the gastrointestinal tract fluids. Furthermore, its prolonged residence in the liquid phase during storage must not perturb the modified-release system to the point of degrading the release profile and release time of the active principle(s).

Furthermore, for these liquid formulations to be fully effective, it is known to be important that:

- the microcapsules are very small (<1000 microns),
- and the weight fraction of coating excipients is limited, this modality being all the more difficult to achieve because, due to their small size, the microcapsules have a large specific surface area, accelerating the release.

As regards the prior art concerning oral liquid pharmaceutical forms for the modified release of active principles, French patent application FR-A-2 634 377 should be mentioned first of all; said document discloses a novel modified-release pharmaceutical form based on a resin/active principle complex coated with an ionic polymer whose polarity is opposite to that of the resin, and fixed thereto by ionic bonding. The active principle is also ionic and has a polarity opposite to that of the resin. The latter can be sodium polystyrenesulfonate and the ionic coating polymer is selected from acrylic and methacrylic acid ester polymers (EUDRAGIT®). The resin is impregnated with an aqueous solution of the active principle. The resin particles impregnated with active principle are then coated with an organic solution of ionic polymer. The resulting microcapsules can be

converted to an oral suspension (Example 2 in particular). The use of an ionic resin and an ionic coating polymer limits the possible applications to ionic active principles.

American patents US-B-4,999,189 and US-B-5,186,930 relate to liquid pharmaceutical compositions comprising *ion exchange ionic resin/active principle* complexes suspended in a liquid phase. These particles of *resin/active principle* complex are coated with a first layer of pharmaceutically acceptable wax of high melting point and with a second, outer layer of a pharmaceutically acceptable water-insoluble polymer (ethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, Eudragit®, etc.). A plasticizer such as dibutyl sebacate can be introduced into this second, outer layer. The active principle is fixed by ionic bonding to the ion exchange resin. The liquid phase consists of a glucose syrup with a high fructose content and of several other ingredients such as glycerol or propylene glycol.

US-B-5,186,930 differs from the first US patent in that it makes provision for a sufficient amount of the first layer (wax) to prevent the particles of resin/active principle complexes from swelling and crackling.

These US patents do not provide any data that allow the quality of the modified release of active principles to be assessed. Moreover, using ion exchange resins as the active principle support is rather inconvenient and restrictive in terms of the variety of active principles involved. Furthermore, this galenical system has nothing convincing to offer in terms of the stability and preservation of the modified-release properties of the active principle.

PCT patent application WO-A-87/07833 and patent US-B-4,902,513 disclose aqueous suspensions of microcapsules of active principle (e.g. theophylline) with modified release of the active principle (e.g. 12 h). These suspensions are prepared by saturating the aqueous phase with the active principle before incorporating the microcapsules of active principle into this aqueous phase. The composition of the coating agent for the microcapsules that allows the modified release of the active principle is not described in said documents. Now, this coating composition is a decisive factor in guaranteeing the maintenance of the modified-release profile of the microcapsules after storage in the aqueous phase. The technical proposal described appears not to disclose the means of solving the dual problem of producing a liquid suspension of a modified-release microcapsular form without interfering with the stability of the modified-release profile of the active principle after the microcapsules have been stored in the liquid phase.

European patent application EP-A-0 601 508 relates to an aqueous suspension for the oral administration of naxopren according to a modified-release profile. This suspension comprises coated microgranules of naxopren suspended in a syrupy aqueous

liquid phase. The technical problem underlying this invention is to provide a modified-release form of naxopren containing a 1000 mg dose and capable of administration in a single daily dosage unit.

The microgranules consist of naxopren, polyvinylpyrrolidone and lactose (90-300 μm). Their coating is made up of 4 layers. The first comprises diethyl cellulose/diethyl phthalate/polyethylene glycol. The second is based on EUDRAGIT (meth)acrylate/(meth)acrylic copolymers. The third comprises glycerol stearate/wax/fatty alcohols and the fourth consists of an enteric covering based on cellulose acetate/phthalate. The naxopren undergoes modified release over 24 hours.

Example 22 of said European patent application EP-A-0 601 508 contains a demonstration of the stability of the release profile after 30 days' storage of the liquid suspension.

One of the disadvantages of this suspension derives from the enteric layer, which prohibits the use of a suspension of neutral pH because this layer is designed to disintegrate and become liquid at neutral pH. Another disadvantage of this enteric layer is that it blocks the release of the active principle in the stomach at acidic pH. Now, for AP whose absorption window is situated in the upper parts of the gastrointestinal tract, it is often advantageous to release the active principle in the stomach in order to increase the bioavailability. Furthermore, this multilayer solution to the problem is very complex and in addition specific to naproxen.

PCT patent application WO-A-96/01628 discloses a liquid pharmaceutical formulation for the oral administration, according to a modified-release profile (12 hours), of an active principle consisting of moguisteine. The object is to propose a modified-release liquid formulation of moguisteine which is easy to measure out and ingest, has a release time that makes it possible to avoid multiple dosage units, is stable over time in aqueous suspension and is pleasantly flavoured in order to favour compliance, and whose manufacture does not involve the use of toxic substances like solvents. To achieve this object, the invention according to PCT patent application WO-A-96/01628 proposes a suspension, in a weakly hydrated liquid phase (essentially based on sorbitol and glycerol), of microgranules (90-300 μm) of moguisteine coated with a first, hydrophilic layer consisting of cellulose acetate/phthalate and diethyl phthalate, a second, hydrophobic layer containing glycerol stearate/wax/fatty alcohols, and a third, hydrophilic layer identical to the first.

This multilayer form is very complex to prepare and in addition is specific to moguisteine.

In this state of the art, the essential objective of the present invention is to propose an aqueous suspension of microcapsules of active principle(s), excluding amoxicillin, for the oral administration of the latter according to a modified-release profile, in which the coating of the microcapsules is designed in such a way that the release profile is not perturbed and does not depend on the maceration time of the microcapsules in the liquid (preferably aqueous) phase. Thus the active principle(s) contained in the microcapsules would be prevented from escaping into the liquid phase throughout the storage of the suspension, but a modified release of the active principle(s) would be allowed as soon as it entered an environment suitable for triggering the release, namely in vivo in the gastrointestinal tract and in vitro under the conditions of a dissolution test performed just after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, for a volume of 900 ml, at a temperature of 37°C.

Another objective of the present invention is to provide an aqueous liquid suspension of microcapsules of active principle(s) (excluding amoxicillin) comprising a film coating formed of a single layer.

Another objective of the present invention is to provide an aqueous liquid suspension of microcapsules of active principle(s) (excluding amoxicillin) in which the dissolved fraction originating from the microcapsules is less than or equal to 15% and preferably 5% of the total weight of active principles present in the microcapsules.

Another objective of the present invention is to provide an aqueous liquid suspension of microcapsules of active principle(s) (excluding amoxicillin) in which one part of the active principle(s) is in an immediate-release form and the other part of the active principle(s) is in a modified-release form (microcapsules).

Another essential objective of the present invention is to provide an aqueous suspension of microcapsules for the modified release of active principles (excluding amoxicillin) which makes it possible to release the active principle according to a release profile that is not degraded by the ageing of the suspension.

Another essential objective of the present invention is to provide an aqueous suspension of microcapsules which is made up of individually coated particles of active principle(s) (excluding amoxicillin) and makes it possible to release the latter according to a prolonged and/or optionally delayed profile such that the release half-life $t_{1/2}$ is between 0.5 and 30 hours.

Another objective of the present invention is to propose an oral galenical form which is liquid and consists of a large number (for example in the order of several thousands) of microcapsules, this multiplicity statistically ensuring a good reproducibility

of the transit kinetics of the AP throughout the gastrointestinal tract, thereby improving control of the bioavailability and hence improving efficacy.

One essential objective of the present invention is to propose an oral liquid galenical form made up of a plurality of coated microcapsules which avoids the use of large amounts of coating agent, the weight fraction of coating agent being comparable to that of the monolithic forms.

Another essential objective of the present invention is to provide a modified-release aqueous suspension in which the active principle(s) (excluding amoxicillin) is (are) in the form of a plurality of particles individually coated to form microcapsules and allowing the mixing of several active principles having different respective release times.

Another essential objective of the present invention is to propose the use, as a means of treating human or veterinary diseases, of a (preferably aqueous) suspension of microcapsules consisting of particles of active principle(s) (excluding amoxicillin) individually coated so as to determine the modified release of the active principle(s) without the modified-release profile being affected by storage of the microcapsules in this liquid form in suspension.

Another essential objective of the present invention is to propose a drug based on a preferably aqueous suspension of microcapsules consisting of particles of active principle(s) (excluding amoxicillin) individually coated so as to determine the modified release of the active principle(s) without the modified-release profile being affected by storage of the microcapsules in this liquid form in suspension.

Having set themselves all the above objectives, among others, the inventors have succeeded in developing a multimicrocapsular galenical system in the form of a preferably aqueous suspension for the modified release of active principle(s), excluding amoxicillin, which:

- does not degrade the optionally retarded, modified-release profile,
- and is stable, easy to prepare, economic and effective.

To do this the inventors have proposed to:

- select a totally specific coating composition for the microcapsules,
- and suspend the microcapsules in a (preferably aqueous) liquid phase saturated with active principle(s) or capable of being saturated with active principle(s) on contact with the microcapsules, using an amount of solvent (preferably water) that is limited but nevertheless sufficient for the suspension to be easy to swallow.

Thus the invention which meets the objectives described above, among others, relates to a suspension of microcapsules in an aqueous liquid phase that allows the modified release of at least one active principle (excluding amoxicillin) and is intended for oral administration, characterized in that:

- it comprises a plurality of microcapsules each consisting of a core containing at least one active principle (excluding amoxicillin) and of a film coating that:
  - is applied to the core,
  - controls the modified release of the active principle(s),
  - and has a composition corresponding to one of the following three families A, B and C:
    - ⇨ Family A
      - ♦ 1A - at least one film-forming polymer (P1) insoluble in the tract fluids, present in an amount of 50 to 90 and preferably of 50 to 80% by dry weight, based on the total weight of the coating composition, and consisting of at least one water-insoluble cellulose derivative;
      - ♦ 2A - at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25 and preferably of 5 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one polyacrylamide and/or poly-N-vinylamide and/or poly-N-vinyllactam;
      - ♦ 3A - at least one plasticizer present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one of the following compounds: glycerol esters, phthalates, citrates, sebacates, cetyl alcohol esters and castor oil;
      - ♦ 4A - at least one surfactant and/or lubricant present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and selected from anionic surfactants and/or non-ionic surfactants and/or lubricants, it being possible for said agent to comprise only one or a mixture of the above-mentioned products;
    - ⇨ Family B
      - ~ 1B - at least one hydrophilic polymer carrying groups ionized at neutral pH and preferably selected from cellulose derivatives;
      - ~ 2B - at least one hydrophobic compound different from A;
    - ⇨ Family C
      - ♦ 1C - at least one film-forming polymer insoluble in the gastrointestinal tract fluids;
      - ♦ 2C - at least one water-soluble polymer;

- ♦ 3C - at least one plasticizer;
- ♦ 4C - optionally at least one surfactant/lubricant preferably selected from the following group of products:
  - ~ anionic surfactants;
  - ~ and/or non-ionic surfactants,
- ▪ and the liquid phase is saturated or becomes saturated with active principle(s) on contact with the microcapsules.

In terms of the present disclosure, the expression "*microcapsules* of active principle(s)" denotes microcapsules whose core comprises one or more active principles and optionally at least one excipient.

This suspension according to the invention makes it possible to overcome the two main obstacles to the production of an aqueous suspension of microcapsules consisting of individually coated microparticles of active principles and allowing the modified release of the latter, these two obstacles being as follows:

a) limiting the fraction of active principles immediately releasable from the microcapsules to a value of less than 15% and preferably 5% of the total weight of active principles used in the microcapsules;
b) obtaining a modified-release system that is sufficiently robust to avoid any change or degradation of the release profile of the active principle(s) during storage of the aqueous suspension.

Also, this suspension makes it possible to facilitate the oral administration of drugs which have high therapeutic doses, especially in the case of the elderly and children, there being a significant gain in terms of compliance and success of the treatment.

Furthermore, for AP which have a limited absorption window, it is particularly advantageous for the modified-release form to be a plurality of microcapsules, as indicated in the preamble of the present disclosure.

In one preferred embodiment of the invention, the families A, B and C from which the constituents of the coating composition are selected are as follows:

⇨ <u>Family A</u>

- ♦ 1A - ethyl cellulose and/or cellulose acetate;
- ♦ 2A - polyacrylamide and/or polyvinylpyrrolidone;
- ♦ 3A - castor oil;
- ♦ 4A - an alkali metal or alkaline earth metal salt of fatty acids, stearic and/or

oleic acid being preferred, a polyethoxylated sorbitan ester, a polyethoxylated castor oil derivative, a stearate, preferably calcium, magnesium, aluminium or zinc stearate, a stearylfumarate, preferably sodium stearylfumarate, or glycerol behenate, taken individually or in a mixture with one another;

⇨ Family B

♦ 1B

~ cellulose acetate-phthalate;

~ hydroxypropyl methyl cellulose phthalate;

~ hydroxypropyl methyl cellulose acetate-succinate;

~ (meth)acrylic acid/(meth)acrylic acid alkyl (methyl) ester copolymer (EUDRAGIT® S or L);

~ and mixtures thereof;

♦ 2B

~ hydrogenated vegetable waxes (Dynasan® P60, Dynasan® 116);

~ triglycerides (tristearin, tripalmitin, Lubritab®, Cutina HR, etc.);

~ animal and vegetable fats (beeswax, carnauba wax, etc.);

~ and mixtures thereof.

⇨ Family C

♦ 1C

~ water-insoluble cellulose derivatives, ethyl cellulose and/or cellulose acetate being particularly preferred;

~ acrylic derivatives;

~ polyvinyl acetates;

~ and mixtures thereof;

♦ 2C

~ water-soluble cellulose derivatives;

~ polyacrylamides;

~ poly-N-vinylamides;

~ poly-N-vinyllactams;

~ polyvinyl alcohols (PVA);

~ polyoxyethylenes (POE);

~ polyvinylpyrrolidones (PVP) (the latter being preferred);

~ and mixtures thereof;

♦ 3C

~ glycerol and its esters, preferably from the following subgroup: acetylated

glycerides, glycerol monostearate, glyceryl triacetate and glycerol tributyrate;

- ~ phthalates, preferably from the following subgroup: dibutyl phthalate, diethyl phthalate, dimethyl phthalate and dioctyl phthalate;
- ~ citrates, preferably from the following subgroup: acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate and triethyl citrate;
- ~ sebacates, preferably from the following subgroup: diethyl sebacate and dibutyl sebacate;
- ~ adipates;
- ~ azelates;
- ~ benzoates;
- ~ vegetable oils;
- ~ fumarates, preferably diethyl fumarate;
- ~ malates, preferably diethyl malate;
- ~ oxalates, preferably diethyl oxalate;
- ~ succinates, preferably dibutyl succinate;
- ~ butyrates;
- ~ cetyl alcohol esters;
- ~ salicylic acid;
- ~ triacetin;
- ~ malonates, preferably diethyl malonate;
- ~ cutin;
- ~ castor oil (this being particularly preferred);
- ~ and mixtures thereof;

◆ 4C

- ~ alkali metal or alkaline earth metal salts of fatty acids, stearic and/or oleic acid being preferred;
- ~ polyethoxylated oils, preferably polyethoxylated hydrogenated castor oil;
  polyoxyethylene/polyoxypropylene copolymers;
  polyethoxylated sorbitan esters;
  polyethoxylated castor oil derivatives;
  stearates, preferably calcium, magnesium, aluminium or zinc stearate;
  stearylfumarates, preferably sodium stearylfumarate;
  glycerol behenate;
  and mixtures thereof.

Preferably, the film coating consists of a single layer whose weight represents from 1 to 50% and preferably from 5 to 40% of the total weight of the microcapsules.

According to one preferred characteristic of the invention, the liquid phase is aqueous; even more preferably, it contains at least 20% of water and preferably at least 50% by weight of water.

This suspension according to the invention advantageously contains:

- 30 to 95% by weight and preferably 60 to 85% by weight of liquid phase (advantageously water);
- and 5 to 70% by weight and preferably 15 to 40% by weight of microcapsules.

Advantageously, the amount of solvent liquid phase (preferably water) for the active principle(s) (excluding amoxicillin) is such that the proportion of dissolved active principle(s) originating from the microcapsules is less than or equal to 15% and preferably less than or equal to 5% by weight, based on the total weight of the active principle(s) contained in the microcapsules.

In a first embodiment of the invention, the liquid phase is at least partially and preferably totally saturated with active principle(s) (excluding amoxicillin) following the incorporation of the microcapsules into this liquid phase.

In this embodiment, it is the active principle(s) contained in the microcapsules that saturate the liquid phase.

In a second embodiment of the invention, the liquid phase is at least partially and preferably totally saturated with active principle(s) (excluding amoxicillin) by means of non-encapsulated active principle(s) prior to the incorporation of the microcapsules into this liquid phase. This embodiment is of particular value for the administration of amoxicillin in that it makes it possible to combine an immediate-release fraction with a modified-release fraction.

In practice, this amounts to saturating the liquid phase with active principle(s) before the introduction of the microcapsules into the suspension, so that the active principle contained in the microcapsules plays no part, or virtually no part, in the saturation of the liquid phase. The diffusion of the active principle contained in the microcapsules is therefore suppressed or virtually suppressed.

According to one preferred characteristic of the invention enabling this liquid oral formulation to be fully effective, the microcapsules have a particle size less than or equal to 1000 microns, preferably of between 200 and 800 microns and particularly preferably of between 200 and 600 microns.

"Particle size" is understood in terms of the invention as meaning that a proportion of at least 75% by weight of microcapsules have a diameter between the screen size limits in question.

Again with the aim of improving efficacy, the amount of coating agent for the microcapsules advantageously represents from 1 to 50% and preferably 5 to 40% of the weight of the coated microcapsules. This advantageous characteristic is all the ... to acquire because, due to their small size, the microcapsules have a large specific surface area, accelerating the release.

To control the in vivo in vitro release of the active principle(s), it is preferable according to the invention to use a film coating for the microcapsules which belongs to family A or C.

For more detailed qualitative and quantitative information on this coating composition of family A, reference may be made to European patent EP-B-0 709 087, the content of which forms part of the present disclosure by way of reference.

Another possible way of defining the liquid suspension according to the invention consists in considering an in vitro release profile obtained using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8 and at a temperature of 37°C, such that:

- the proportion PI of active principle(s) released from the microcapsules during the first 15 minutes of the dissolution test is such that:

$$PI \leq 15$$

preferably $PI \leq 5$;

- the active principle(s) remaining in the microcapsules is (are) released over a period such that the release time of 50% by weight of AP ($t_{½}$) is defined as follows (in hours):

$$0.5 \leq t_{½} \leq 30$$

preferably $0.5 \leq t_{½} \leq 20$.

Still with regard to its in vitro dissolution properties, the suspension according to the invention is characterized in that:

- the initial in vitro release profile Pfi obtained just after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, for a volume of 900 ml, at a temperature of 37°C,
- and the in vitro release profile Pf_{10} obtained 10 days after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C,

are similar.

The release profiles compared according to the recommendations of *The European Agency for the Evaluation of Medicinal Products (EMEA) - Human Medicines Evaluation Unit - / Committee for proprietary medicinal products (CPMP) - London, 29 July 1999, CPMP/QWP/604/96: note for guidance on quality of modified release products: A: oral dosage forms, B: transdermal dosage forms - section I (quality) - Annex 3: Similarity factor f_2*, produce a value of >50 for the similarity factors f_2 and can therefore be declared similar.

These advantageous characteristics of the suspension according to the invention enable high doses of active principle(s) to be administered orally without difficulty and without detracting from the modified and optionally delayed release mode of the active principle.

According to another of its advantageous physicochemical characteristics, the pH of the liquid suspension according to the invention can arbitrarily be acidic or neutral.

It may be quite valuable to add at least one rheology modifier to the suspension. In particular, this can be one or more "viscosifiers" selected ... those commonly employed in the pharmaceutical industry and especially those disclosed in *Handbook of pharmaceutical excipients - 3rd edition, Am. Pharmaceutical Association, Arthur H. KIBBE, 2000, ISBN 0917330-96-X. Europe. 0-85369-381-1.* Examples which may be mentioned are:

- water-soluble cellulose derivatives (hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropyl methyl cellulose, etc.);
- polyethylene glycols;
- alginates and derivatives thereof;
- carrageenans;
- agar-agar;

- gelatin;
- maltodextrins;
- polydextrose;
- guar, carob, acacia, xanthan, gellan and other gums;
- polyvinyl alcohol;
- povidone;
- pectins;
- silica gel;
- native and modified starches and derivatives thereof;
- dextrans;
- etc.

It can also be advisable to introduce into the suspension at least one agent for modifying the solubility of the active principle in the solvent (preferably aqueous) liquid phase, for example salts, sugars, glycerol, etc. In fact, in the case of very soluble active principles, these solutes can limit the escape of the active principle from the microcapsules by lowering the saturation concentration of the active principle in the aqueous phase.

For the suspension to have all the qualities of an oral galenical form that is easy to swallow, stable and palatable, it advantageously contains at least one other additive selected from the group comprising surfactants, colourants, dispersants, preservatives, taste improvers, flavourings, sweeteners, antioxidants and mixtures thereof.

Examples of these additives which may be mentioned are those commonly employed in the pharmaceutical industry and especially those disclosed in *Handbook of pharmaceutical excipients - 3rd edition, Am. Pharmaceutical Association, Arthur H. KIBBE, 2000, ISBN 0917330-96-X. Europe. 0-85369-381-1*, or, in the case of emulsifiers, those described on page 5, lines 14 to 29, of EP-A-0 273 890, or again, in the case of thickeners, those indicated on page 5, lines 19 and 20, of EP-A-0 601 508.

The active principles used to prepare the controlled-release suspensions according to the invention can be selected from at least one of the following wide varieties of active substances: antiulcer drugs, antidiabetics, anticoagulants, antithrombics, hypolipidaemics, antiarrhythmics, vasodilators, antiangina drugs, antihypertensives, vasoprotectors, fertility promoters, labour inducers and inhibitors, contraceptives, antibiotics, antifungals, antivirals, anticancer drugs, anti-inflammatories, analgesics, antiepileptics, antiparkinsonism drugs, neuroleptics, hypnotics, anxiolytics, psychostimulants, antimigraine drugs, antidepressants, antitussives, antihistamines and antiallergics.

Without implying a limitation, the invention applies more particularly to pharmaceutical active principles which have to be administered orally in high doses, for example of 500 to 1000 milligrams or more, and to paediatric suspensions.

The active principle(s) is (are) preferably selected from the following compounds: pentoxifylline, prazosin, aciclovir, nifedipine, diltiazem, naproxen, ibuprofen, flurbiprofen, ketoprofen, fenoprofen, indomethacin, diclofenac, fentiazac, oestradiol valerate, metoprolol, sulpiride, captopril, cimetidine, zidovudine, nicardipine, terfenadine, atenolol, salbutamol, carbamazepine, ranitidine, enalapril, simvastatin, fluoxetine, alprazolam, famotidine, ganciclovir, famciclovir, spironolactone, 5-asa, quinidine, perindopril, morphine, pentazocine, metformin, paracetamol, omeprazole, metoclopramide, atenolol, salbutamol morphine, verapamil, erythromycin, caffeine, furosemide, cephalosporins, montelukast, valaciclovir, ascorbic acid salts, diazepam, theophylline, ciprofloxacin, vancomycin, aminoglycosides, penicillins (except for amoxicillin) and mixtures thereof.

According to another of its features, the present invention relates to a drug, characterized in that it comprises a suspension of modified-release microcapsules of active principle(s), as defined above.

In more concrete terms, the invention further relates to a drug, or more exactly a galenical pack, characterized in that it comprises a kit for preparing the suspension as defined above, said kit containing:

- microcapsules in substantially dry form containing the active principle(s) for saturating the liquid phase with active principle(s) once the two solid and liquid phases have been brought into contact;
- and/or a mixture of microcapsules in substantially dry form containing the active principle(s) in the dose that is just necessary for modified release, together with immediate-release uncoated active principle(s) in a necessary and sufficient amount to saturate the liquid phase with active principle(s) once the saturation dose of active principle(s) and the liquid phase have been brought into contact;
- and the liquid phase and/or at least part of the ingredients useful for its preparation, and/or the protocol for preparation of the suspension.

This type of presentation of the drug according to the invention enables patients easily to prepare the modified-release suspension in a form that is stable, particularly in terms of modified release, for at least several days. The patient is thus guaranteed to have a drug that is easy to administer orally and perfectly effective from the therapeutic point of view.

The microcapsules constituting the solid phase of the suspension according to the invention can be prepared by microencapsulation techniques available to those skilled in the art, the main techniques being summarized in the article by C. DUVERNEY and J.P. BENOIT in "L'actualité chimique", December 1986. More precisely, the technique in question is microencapsulation by film coating, which yields individualized "reservoir" systems as opposed to matrix systems.

For further details, reference may be made to patent EP-B-0 953 359 cited above.

To produce the core based on active principle(s) (excluding amoxicillin) of the microcapsules according to the invention, it is advantageous to use, as starting materials, particles of active principle(s) of the desired size. Said particles can be crystals of active principle(s) which are pure and/or have undergone a pretreatment by one of the techniques conventionally employed in the art, for example granulation, in the presence of a small amount of at least one conventional binder and/or an agent for modifying the intrinsic solubility characteristics of the AP.

The invention will be understood more clearly from the point of view of its composition, properties and preparation with the aid of the Examples below, given solely by way of illustration, which demonstrate the variants and the advantages of the invention.

Description of the Figures:

- **Figure 1** shows the initial dissolution profile and the dissolution profile after 10 days' storage of the suspension according to Example 1, in % dissolved (D) as a function of the time (t) in hours.
- **Figure 2** shows the initial dissolution profile and the dissolution profile after 19 days' storage of the suspension according to Example 2, in % dissolved (D) as a function of the time (t) in hours.
- **Figure 3** shows the initial dissolution profile and the dissolution profile after 12 days' storage of the suspension according to Example 3, in % dissolved (D) as a function of the time (t) in hours. This suspension combines 29% of free metformin with 71% of encapsulated metformin.

Example 1

Preparation of microcapsules of aciclovir:

1000 g of aciclovir and 30 g of povidone® are mixed dry for 5 minutes. The mixture is granulated with water. The granules are dried at 40°C in a ventilated oven and then graded

on a 500 μm screen. The 200-500 μm fraction is selected.
700 g of granules obtained above are coated with 27.3 g of ethyl cellulose, 3.7 g of castor oil, 3.7 g of magnesium stearate and 2.9 g of povidone® dissolved in a 60/40 w/w acetone/isopropanol mixture, in a Glatt GPC-G1 fluidized air bed apparatus. Temperature of product: 40°C.

Preparation of the suspension:
0.58 g of microcapsules obtained above is placed in 37 ml of phosphate buffer of pH 6.8.

Test:
The above suspension is stored for 10 days at room temperature. After 10 days the suspension is analysed for dissolution using a type II apparatus according to the European Pharmacopoeia 3rd edition, phosphate buffer medium of pH 6.8, volume of 900 ml, temperature of 37°C, blade stirring at 100 rpm, UV detection at 252 nm.

The result is shown in Figure 1 attached.

The profiles are apparently identical: similarity factor f_2 greater than 50. The microcapsules remain highly effective in aqueous suspension.

Example 2

Preparation of microcapsules of spironolactone:

Step 1: Granules
45 g of spironolactone, 25 g of PEG 40 - hydrogenated castor oil and 30 g of povidone are first solubilized in a water/acetone/isopropanol mixture (5/57/38 w/w). This solution is then sprayed onto 800 g of cellulose spheres (of diameter between 300 and 500 □m) in a Glatt GPC-G1 fluidized air bed apparatus.

Step 2: Coating
50 g of granules obtained above are coated with 1.44 g of ethyl cellulose, 0.16 g of castor oil, 0.64 g of poloxamer 188 and 0.96 g of povidone dissolved in an acetone/ isopropanol mixture (60/40 w/w), in a miniGlatt fluidized air bed apparatus.

Preparation of the suspension:

0.07 g of microcapsules obtained above is placed in 0.165 ml of phosphate buffer of pH 6.8.

Test:

The above suspension is stored for 19 days at room temperature. After 19 days the suspension is analysed for dissolution using a type II apparatus according to the European Pharmacopoeia 3rd edition, phosphate buffer medium of pH 6.8, volume of 1000 ml, temperature of 37°C, blade stirring at 100 rpm, UV detection at 240 nm.

The result is shown in Figure 2 attached.

The profiles are apparently identical: similarity factor f_2 greater than 50. The microcapsules remain very effective in aqueous suspension.

Example 3

Preparation of microcapsules of metformin:

740 g of metformin crystals (200-500 µm fraction) are coated with 192.4 g of ethyl cellulose, 26 g of castor oil, 26 g of magnesium stearate and 20.8 g of povidone® dissolved in a 60/40 w/w acetone/isopropanol mixture, in a Glatt GPC-G1 fluidized air bed apparatus. Temperature of product: 40°C.

Preparation of the suspension (29% of free form and 71% of encapsulated form):

50 g of microcapsules obtained above are mixed dry with 15 g of metformin crystals and 0.7 g of xanthan gum in a 100 ml glass flask. 34.3 g of purified water are then added to the powder mixture. After manual stirring, a suspension is obtained which produces a sediment very slowly.

The total metformin titre in the suspension is 0.52 g/ml.

Stability test:

The above suspension is stored for 12 days at room temperature. After 12 days the suspension is analysed for dissolution using a type II apparatus according to the European Pharmacopoeia 3rd edition, phosphate buffer medium of pH 6.8, volume of 900 ml, temperature of 37°C, blade stirring at 100 rpm, UV detection at 232 nm.

The result is shown in Figure 3 attached.

The profiles are apparently identical: similarity factor f_2 greater than 50. The microcapsules remain very effective in aqueous suspension.

Homogeneity test:

The above suspension is stirred manually and then six 5 ml samples are taken with a graduated syringe. The metformin content of each sample is determined by HPLC and is shown below:

Sample no.	**Metformin content for 5 ml of suspension (in g)**
1	2.58
2	2.60
3	2.62
4	2.59
5	2.60
6	2.63

It is seen that the samples are very homogeneous and that the dosage corresponds to the expected value of 2.60 g for 5 ml.

This formulation can therefore be administered without risk of overdosing or underdosing.

CLAIMS

1. Suspension of microcapsules in an aqueous liquid phase that allows the modified release of at least one active principle (excluding amoxicillin) and is intended for oral administration, characterized in that:

- it comprises a plurality of microcapsules each consisting of a core containing at least one active principle (excluding amoxicillin) and of a film coating that:
  - is applied to the core,
  - controls the modified release of the active principle(s),
  - and has a composition corresponding to one of the following three families A, B and C:
    - ⇨ Family A
      - ♦ 1A - at least one film-forming polymer (P1) insoluble in the tract fluids, present in an amount of 50 to 90 and preferably of 50 to 80% by dry weight, based on the total weight of the coating composition, and consisting of at least one water-insoluble cellulose derivative;
      - ♦ 2A - at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25 and preferably of 5 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one polyacrylamide and/or poly-N-vinylamide and/or poly-N-vinyllactam;
      - ♦ 3A - at least one plasticizer present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and consisting of at least one of the following compounds: glycerol esters, phthalates, citrates, sebacates, cetyl alcohol esters and castor oil;
      - ♦ 4A - at least one surfactant and/or lubricant present in an amount of 2 to 20 and preferably of 4 to 15% by dry weight, based on the total weight of the coating composition, and selected from anionic surfactants and/or non-ionic surfactants and/or lubricants, it being possible for said agent to comprise only one or a mixture of the above-mentioned products;
    - ⇨ Family B
      - ~ 1B - at least one hydrophilic polymer carrying groups ionized at neutral pH and preferably selected from cellulose derivatives;
      - ~ 2B - at least one hydrophobic compound different from A;
    - ⇨ Family C
      - ♦ 1C - at least one film-forming polymer insoluble in the gastrointestinal tract fluids;

- ♦ 2C - at least one water-soluble polymer;
- ♦ 3C - at least one plasticizer;
- ♦ 4C - optionally at least one surfactant/lubricant preferably selected from the following group of products:
  - ~ anionic surfactants;
  - ~ and/or non-ionic surfactants,

■ and the liquid phase is saturated or becomes saturated with active principle(s) on contact with the microcapsules.

2. Suspension according to claim 1, characterized in that the families A, B and C from which the constituents of the coating composition are selected are as follows:

⇨ Family A

- ♦ 1A - ethyl cellulose and/or cellulose acetate;
- ♦ 2A - polyacrylamide and/or polyvinylpyrrolidone;
- ♦ 3A - castor oil;
- ♦ 4A - an alkali metal or alkaline earth metal salt of fatty acids, stearic and/or oleic acid being preferred, a polyethoxylated sorbitan ester, a polyethoxylated castor oil derivative, a stearate, preferably calcium, magnesium, aluminium or zinc stearate, a stearylfumarate, preferably sodium stearylfumarate, or glycerol behenate, taken individually or in a mixture with one another;

⇨ Family B

- ♦ 1B
  - ~ cellulose acetate-phthalate;
  - ~ hydroxypropyl methyl cellulose phthalate;
  - ~ hydroxypropyl methyl cellulose acetate-succinate;
  - ~ (meth)acrylic acid/(meth)acrylic acid alkyl (methyl) ester copolymer;
  - ~ and mixtures thereof;
- ♦ 2B
  - ~ hydrogenated vegetable waxes;
  - ~ triglycerides;
  - ~ animal and vegetable fats (beeswax, carnauba wax, etc.);
  - ~ and mixtures thereof.

⇨ Family C

- ♦ 1C
  - ~ water-insoluble cellulose derivatives, ethyl cellulose and/or cellulose acetate being particularly preferred;

- ~ acrylic derivatives;
- ~ polyvinyl acetates;
- ~ and mixtures thereof;
- ♦ 2C
- ~ water-soluble cellulose derivatives;
- ~ polyacrylamides;
- ~ poly-N-vinylamides;
- ~ poly-N-vinyllactams;
- ~ polyvinyl alcohols (PVA);
- ~ polyoxyethylenes (POE);
- ~ polyvinylpyrrolidones (PVP) (the latter being preferred);
- ~ and mixtures thereof;
- ♦ 3C
- ~ glycerol and its esters, preferably from the following subgroup: acetylated glycerides, glycerol monostearate, glyceryl triacetate and glycerol tributyrate;
- ~ phthalates, preferably from the following subgroup: dibutyl phthalate, diethyl phthalate, dimethyl phthalate and dioctyl phthalate;
- ~ citrates, preferably from the following subgroup: acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate and triethyl citrate;
- ~ sebacates, preferably from the following subgroup: diethyl sebacate and dibutyl sebacate;
- ~ adipates;
- ~ azelates;
- ~ benzoates;
- ~ vegetable oils;
- ~ fumarates, preferably diethyl fumarate;
- ~ malates, preferably diethyl malate;
- ~ oxalates, preferably diethyl oxalate;
- ~ succinates, preferably dibutyl succinate;
- ~ butyrates;
- ~ cetyl alcohol esters;
- ~ salicylic acid;
- ~ triacetin;
- ~ malonates, preferably diethyl malonate;
- ~ cutin;
- ~ castor oil (this being particularly preferred);

- ~ and mixtures thereof;
- ♦ 4C
- ~ alkali metal or alkaline earth metal salts of fatty acids, stearic and/or oleic acid being preferred;
- ~ polyethoxylated oils, preferably polyethoxylated hydrogenated castor oil;
  polyoxyethylene/polyoxypropylene copolymers;
  polyethoxylated sorbitan esters;
  polyethoxylated castor oil derivatives;
  stearates, preferably calcium, magnesium, aluminium or zinc stearate;
  stearylfumarates, preferably sodium stearylfumarate;
  glycerol behenate;
  and mixtures thereof.

3. Suspension according to claim 1 or 2, characterized in that the film coating consists of a single layer.

4. Suspension according to claim 1, characterized in that it contains:
- 30 to 95% by weight and preferably 60 to 85% by weight of liquid phase (advantageously water);
- and 5 to 70% by weight and preferably 15 to 40% by weight of microcapsules.

5. Suspension according to claim 1, characterized in that the amount of solvent liquid phase (preferably water) for the active principle(s) is such that the proportion of dissolved active principle(s) originating from the microcapsules is less than or equal to 15% and preferably less than or equal to 5% by weight, based on the total weight of the active principle(s) contained in the microcapsules.

6. Suspension according to claim 1, characterized in that the liquid phase is at least partially and preferably totally saturated with active principle(s) following the incorporation of the microcapsules into this liquid phase.

7. Suspension according to claim 6, characterized in that it is the active principle(s) contained in the microcapsules that saturate the liquid phase.

8. Suspension according to claim 1, characterized in that the liquid phase is at least partially and preferably totally saturated with active principle(s) by means of non-encapsulated active principle(s) prior to the incorporation of the microcapsules into this liquid phase.

9. Suspension according to any one of claims 1 to 8, characterized in that the microcapsules have a particle size less than or equal to 1000 microns, preferably of between 200 and 800 microns and particularly preferably of between 200 and 600 microns.

10. Suspension according to any one of claims 1 to 9, characterized in that the film coating represents from 1 to 50% and preferably from 5 to 40% of the total weight of the coated microcapsules.

11. Suspension according to claim 10, characterized by an in vitro release profile obtained using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8 and at a temperature of 37°C, such that:

- the proportion PI of active principle(s) released during the first 15 minutes of the dissolution test is such that:

$$PI \leq 15$$

preferably $PI \leq 5$;

- the remaining active principle(s) is (are) released over a period such that the release time of 50% by weight of AP ($t_{½}$) is defined as follows (in hours):

$$0.5 \leq t_{½} \leq 30$$

preferably $0.5 \leq t_{½} \leq 20$.

12. Suspension according to any one of claims 1 to 11, characterized in that:

- the initial in vitro release profile Pfi obtained just after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C,
- and the in vitro release profile Pf_{10} obtained 10 days after suspension of the microcapsules in the solvent (preferably aqueous) phase, using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C,

are similar.

13. Suspension according to any one of claims 1 to 12, characterized in that its pH is arbitrarily acidic or neutral.

14. Suspension according to any one of claims 1 to 13, characterized in that it comprises at least one rheology modifier.

15. Suspension according to any one of claims 1 to 14, characterized in that it comprises at least one agent for modifying the solubility of the active principle(s) in the solvent (preferably aqueous) liquid phase.

16. Suspension according to any one of claims 1 to 15, characterized in that it contains at least one additive selected from the group comprising surfactants, colourants, dispersants, preservatives, taste improvers, flavourings, sweeteners, antioxidants and mixtures thereof.

17. Suspension according to any one of claims 1 to 16, characterized in that the active principle(s) belongs (belong) to at least one of the following families of active substances: antiulcer drugs, antidiabetics, anticoagulants, antithrombics, hypolipidaemics, antiarrhythmics, vasodilators, antiangina drugs, antihypertensives, vasoprotectors, fertility promoters, labour inducers and inhibitors, contraceptives, antibiotics, antifungals, antivirals, anticancer drugs, anti-inflammatories, analgesics, antiepileptics, antiparkinsonism drugs, neuroleptics, hypnotics, anxiolytics, psychostimulants, antimigraine drugs, antidepressants, antitussives, antihistamines and antiallergics.

18. Suspension according to claim 17, characterized in that the AP is selected from the following compounds: pentoxifylline, prazosin, aciclovir, nifedipine, diltiazem, naproxen, ibuprofen, flurbiprofen, ketoprofen, fenoprofen, indomethacin, diclofenac, fentiazac, oestradiol valerate, metoprolol, sulpiride, captopril, cimetidine, zidovudine, nicardipine, terfenadine, atenolol, salbutamol, carbamazepine, ranitidine, enalapril, simvastatin, fluoxetine, alprazolam, famotidine, ganciclovir, famciclovir, spironolactone, 5-asa, quinidine, perindopril, morphine, pentazocine, metformin, paracetamol, omeprazole, metoclopramide, atenolol, salbutamol morphine, verapamil, erythromycin, caffeine, furosemide, cephalosporins, montelukast, valaciclovir, ascorbic acid salts, diazepam, theophylline, ciprofloxacin, vancomycin, aminoglycosides, penicillins (except for amoxicillin) and mixtures thereof.

19. Drug, characterized in that it comprises a suspension according to any one of claims 1 to 18.

20. Drug, characterized in that it comprises a kit for preparing the suspension according to any one of claims 1 to 18, said kit containing:

- microcapsules in substantially dry form containing the active principle(s) for saturating the liquid phase with active principle(s) once the two solid and liquid phases have been brought into contact;
- and/or a mixture of microcapsules in substantially dry form containing the active principle(s) in the dose that is just necessary for modified release, together with immediate-release uncoated active principle(s) in a necessary and sufficient dose to saturate the liquid phase with active principle(s) once the saturation dose of active principle(s) and the liquid phase have been brought into contact;
- and the liquid phase and/or at least part of the ingredients useful for its preparation, and/or the protocol for preparation of the suspension.

Key to Figures

Fig. 1:
dissous = dissolved
profil initial = initial profile
profil après 10 jours = profile after 10 days
heures = hours

Fig. 2:
Profil initial = Initial profile
Profil après 19 jours = Profile after 19 days

Fig. 3:
dissous Metformine = metformin dissolved
Profil initial = Initial profile
Profil après 12 jours = Profile after 12 days
Temps (en heures) = Time (in hours)