



- (51) **International Patent Classification:**
A61K 9/00 (2006.01) *A61K 31/5415* (2006.01)
- (21) **International Application Number:**
PCT/EP2011/056883
- (22) **International Filing Date:**
29 April 2011 (29.04.2011)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
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- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title:** THIN GELATIN CAPSULES FOR RAPID DRUG RELEASE IN THE MOUTH

(57) **Abstract:** A new pharmaceutical composition is disclosed, suitable for the buccal administration of drugs. The composition consists of small-sized fluid cores containing a drug, the cores being singly entrapped within a thin gelatine-based shell, further detailed in the description. The composition dissolves rapidly in the mouth, allows a quick buccal absorption of the drug, and ensures a quick onset of action. The composition is particularly suitable for the administration of drugs needed for urgent medication and/or which are unstable in the acidic gastric fluids.



WO 2012/146314 A1

TITLE**THIN GELATIN CAPSULES FOR RAPID DRUG RELEASE IN THE MOUTH**

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FIELD OF THE INVENTION

The present invention generally relates to the field of pharmaceutical compositions suitable to obtain a fast drug action. More specifically, it relates to pharmaceutical compositions for oral use useful for a fast delivery of an active ingredient into the circulatory system upon administration. The invention further relates to a pharmaceutical formulation based on drug substance dispersed and/or dissolved in a mixture of hydrocarbons and then formulated as special made cores (pearls and/or soft gel capsules) suitable to be chewed and/or dissolved in mouth. The invention further relates to an innovative pharmaceutical formulation having the drug substance in a form suitable for fast absorption. The invention further relates to an innovative approach to administer the active ingredients in pearls and/or soft gel capsules chewable and/or dissolving in mouth. The invention further relates to an innovative formulation chewable and/or melting in mouth suitable for those patients who have difficulty in swallowing tablets, including fast melting ones. The invention further relates to an improved oral form of administration for acid-unstable drugs. The invention further relates to an innovative formulation suitable to be taken at any time and even when water is not available. The invention further relates to a composition preferably containing a non-steroidal anti-inflammatory agent as drug substance (e.g. Lornoxicam, Flufenamic Acid, Diclofenac, Ibuprofen, Ketoprofen, Naproxen), or any other drugs, especially those needed for urgent medication.

30

STATE OF THE ART

The quick onset of action is a generally desired goal for a large number of medicaments, especially those needed for life-threatening conditions, or
5 strongly disturbing symptoms like e.g. acute pain.

A quick onset of drug action may be sought, for example, by enhancing the rate of disgregation of the oral pharmaceutical form. Fast melting tablets are thus known in the art: these are capable to disintegrate quickly, sometimes even
10 directly in the oral cavity, allowing the drug to be released in a shorter time than traditional tablets; these products are however difficult to formulate since they require a careful balance between drug, disintegrating and suspending agents; in addition they may be disagreeable to the patient because of the powdery feeling and drug taste released in the mouth; finally, the fast disintegration does not necessarily translate into a fast dissolution rate, thus it may fail in obtaining
15 a quick onset of action.

A quick onset of action is particularly difficult to achieve in case of drugs which are insoluble at the acidic pH of the stomach; the solubilization in the gastric fluid is in fact a condition necessary for a drug to be absorbed from the stomach
20 into the bloodstream. This problem is particularly felt in case of non steroidal anti-inflammatory agents: although their effect is urgently needed to reduce painful conditions, the majority of them have acidic nature and thus they are hardly soluble in the acidic gastric fluids.

In these cases, fast melting tablets are of no practical help: in fact they provoke
25 a strong salivation in the mouth and a swallowing stimulus, such that the drug is quickly forced into the stomach where it remains insoluble and cannot be absorbed for long time.

An attempt to obtain a fast action for acid-insoluble drugs is disclosed in
30 WO0015195, wherein the acid-insoluble drug is formulated with an ingredient

capable to form an alkaline area around the tablet during dissolution in the stomach; this approach is however scarcely effective because the alkaline area is easily washed away by peristaltic movements; moreover the substantial amount of alkaline ingredient needed adds to the bulk of the pharmaceutical form, making ingestion and patient compliance difficult.

Additional difficulties are experienced when the drug is unstable at the acidic pH of the stomach. In this case the formulator must apply enteric coatings which prevent dissolution in the stomach and allow release the drug only in the intestine: however this delays considerably the drug release and the desired onset of action. Alternatively, to obtain a quick action, the acid-unstable drug is administered intravenously: this is however a much less convenient administration route, generally disagreed by patients compared to oral, often requiring assistance to be performed.

15

The need thus remains for an oral pharmaceutical composition which is suitable to allow a fast onset of action, especially for acid-insoluble or acid-unstable drugs. The need is also present for pharmaceutical compositions which allow a rapid drug absorption, without causing patient discomfort due to unpleasant mouth feeling. The need is also felt for quick-release pharmaceutical compositions which also allow an acid-unstable drug to be absorbed quickly in the bloodstream, without being precipitated or inactivated by the acid pH of the stomach.

25

SUMMARY OF THE INVENTION

The present inventors have developed a new pharmaceutical composition, suitable for buccal absorption of a drug, in the form of small sized drug-containing fluid cores, singly entrapped within a thin gelatine shell. The shell dissolves substantially immediately in the mouth upon contact with the saliva;

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upon dissolution of the shell, the fluid core is made immediately available in the oral cavity for buccal absorption of the drug. This mode of administration is particularly advantageous for acid-unstable drugs, as they can be quickly absorbed via the buccal mucosa and exert an immediate therapeutic effect while avoiding passing through the stomach and undergo precipitation and/or degradation.

DETAILED DESCRIPTION OF INVENTION

The gelatin making up the shell can be anyone as commercially available (e.g. Gelatin-MJ, Nippi Fuji Inc.). Preferably the shell further includes one or more plasticizing agents (plasticizers) which allow a more uniform and coherent sealing of each single core. Typical plasticizers are glycerol, triacetin, etc.; in order to be most effective, the gelatin:plasticizer ratio in the shell should be in the range between 3:1 and 20:1, for example about 4:1, 6:1, 8:1, 10:1, 12:1, 14:1, 16:1, 18:1, 20:1, and sub-ranges defined therewith. Additionally, the shell may include conventional ingredients of pharmaceutical coatings like fillers, dyes, flavors, etc.

An important feature of the invention is the thickness of the shell: this must be considerably thinner, i.e. about one half or less, than those used in traditional gelatin capsules; typically the thickness is comprised between 20 and 400 micrometers, preferably between 30 and 200 micrometers, most preferably between 50 and 100 micrometers. Said shell can be formed by using currently available technologies; non-limiting reference is made to the Jintan technology developed by Morishita, obtaining small-size seamless pearls or capsules containing a fluid core; these are produced by a dropping technology using interfacial tension forces to form the shell: an inner nozzle of concentric double nozzle ejects the core fluid, whereas an outer nozzles supplies the core-entrapping fluid; this simultaneous action provides that the entrapping fluid wraps around the core drop; the cores are then dried and sieved. The above

referred thickness ranges are meant to be measured onto the finally dried cores. By using triple or higher nozzles it is also possible, within the scope of the invention, to coat the cores with multiple layers.

- 5 The small size of the thus obtained cores is a further important factor, since it allows to split the drug active dose into smaller units making up, as a whole, a large surface area from which the drug can be quickly released. The units are typically spherical or substantially spherical (spheroids). Their average diameter is comprised between 5 and 10 mm, preferably between 4 and 9 mm, more
10 preferably between 5 and 8 mm. The term "average diameter" means that the above size ranges are fulfilled by at least 80% of the cores making up the pharmaceutical composition; preferably they are satisfied by more than 90%, more preferably by more than 95%, most preferably by more than 99% of the cores. In case of spheroids, the term "diameter" means the longest measurable
15 diameter of the concerned unit observed under bi-dimensional microscopy. The above diameter sizes include the thickness of the gelatine shell.

- Another feature of the invention consists in that the drug-containing core is in the fluid state: the feature "fluid" is herein assessed at room temperature (20°C),
20 and identifies any material which is liquid, pasty, creamy, oily, etc. at this temperature: the drug, present in a dissolved or suspended form in the core, is more compatible with the buccal mucosa and is most readily absorbed, as compared to drugs in solid form. Typically, the fluid core comprises 1-15% by weight of the drug, 65-90% by weight of a medium chain (e.g. C₈-C₁₀)
25 triglyceride and/or vegetable oil, 5-25% by weight of a sweetener and/or flavour. The above triglycerides are fluid at room temperature, preferably they are oils. Typical vegetable oils are palm kernel oil, palm origin oil, etc. Typical sweeteners are aspartame, sucralose, xylitol, sorbitol, mannitol, maltitol, saccharin and combinations thereof. Typical flavours are Lemon, Honey,
30 Caramel, Menthol, Ginger, Grapefruit, Grape, Orange, and Cherry flavour, and

combinations thereof. Further conventional ingredients, like fillers (e.g. silica), preservatives, dyes, etc. may be present in the core.

In the final form, i.e. after suitable drying of the external shell, the core:shell
5 weight ratio is generally comprised between about 85:15 and about 95:5, preferably being about 90:10.

The drug included in the composition can be any drugs for which buccal absorption may be desired. A preferred drug is one useful for urgent
10 medication, preferably for the treatment of mild, moderate or acute pain, in particular acute pain; the term "acute" describes an injury or illness that comes and goes (as opposed to chronic, which is persistent); examples of acute pain are low back pain, post-operative pain, dental pain, neck pain, dysmenorrhoea and headache. After surgery, a medical procedure, or an injury, the patient may
15 still have pain. Relief from acute pain is very important. It may help the recovery of the patient. Typical drugs useful in the treatment of acute pain are non steroidal anti-inflammatory agents like e.g. Lornoxicam, Diclofenac, Flufenamic acid, Ibuprofen, Ketoprofene, Mefenamic acid, Naproxen; a most preferred agent is Lornoxicam.

20 Other class of drugs advantageously used in the invention are, without limitation, cardioactive drugs like e.g. antiangina, or antiemetic, anti Alzheimer, anti migraine, analgesic, antihistaminic drugs, drugs for erectile dysfunctions, and combinations among them or with other drugs.

25 Advantageously, the drug is an "acid-unstable drug", meaning with this term a drug which precipitates, partially or totally in the acid pH range of the stomach, typically between pH 0.5 and 4, or between pH 1 and 3. Typically, but with no limitation, acid-unstable drugs are those whose solubility is lower than 1mg/100 ml in HCl 0.1 N. The term "acid-unstable" further extends to drugs which, within
30 the above pH ranges, (irrespective of their solubility) are partially or totally

inactivated and/or degraded, and/or converted into non-active forms, and/or not absorbed for any other reasons.

Further advantageously, the drug may be lipophilic: in this case the oily vehicle of the core not only suspends the drug, but even dissolves it: in this condition the rate of absorption through the buccal mucosa, after dissolution of the shell, is further increased.

The drug dose, i.e. the amount of drug contained in the total of cores making up a single unit dose, can range widely depending on the activity of the drug used, severity of condition to be treated, weight of the patient, posology, etc; non limiting examples of drug doses are between 1 and 20 mg, typically used in case of non steroidal antiinflammatory agents.

A main advantage of the present compositions is that they dissolve substantially immediately in the mouth by contact with the saliva; the drug is thus made immediately available in the oral cavity, typically within 30 seconds after ingestion; moreover the drug is released from the fluid core in a dissolved or suspended form, which is more compatible with the buccal mucosa and more prone to absorption, in comparison to dry forms. Accordingly the compositions not only dissolve quickly, but also obtain a quick absorption via the buccal mucosa, thus they provide an immediate therapeutic benefit, while avoiding the passage through the stomach.

The present compositions can be taken at any time and condition: this is a particular advantage in consideration of the urgency medication character of the preferred drugs used therein: thus for example a patient suffering from sudden symptoms of pain can take the medication at the first signs of occurrence, even in absence of water, and benefit immediately from the therapeutic effect. The compositions can be provided in any form suitable for buccal administration,

e.g. as chewable or mouth-melting compositions; the actual mode of ingestion can be selected depending on the particular drug, the dosage requirements, the severity of the symptoms, the type of patient, etc.

- 5 Another significant advantage is the strong taste masking obtained. This is consequent to several factors, e.g. the drug-diluting effect of the fluid making up the core; another contributing factor is the suitability of the cores to quickly melt in the mouth by simple positioning in the sublingual area: this area contains lesser taste-sensible terminations compared to the other parts of the mouth,
10 therefore the perceived taste is lower, compared to standard chewable compositions; the significant amount of sweeteners/flavours present in the core further contributes to taste masking.

- A further advantage lies in that the present composition eliminate completely
15 the powdery feeling and the excessive salivation associated to conventional fast melting tablets, thus promoting a better palatability and a higher patient compliance; further compared to fast melting tablets, the present composition require a smaller amount of excipients: this contributes to a lesser salivation which, in turn, prevents an early swallowing of the medication into the stomach
20 and allows a sufficient time for it to be absorbed through the buccal mucosa.

- The process to prepare the cores according to the invention generally comprises the weighing of the relevant components and the preparation of the separate core- and shell compositions. If the Jintan technology is used, the core
25 and shell compositions are ejected at a suitable temperature (preferably between 10 and 80°C) respectively from the inner and outer nozzle of a concentric double nozzle; preferably, the inner nozzle core liquid formulation is ejected at 10-40°C, and the outer nozzle shell liquid formulation is ejected at 50-80°C; said ejecting results in the formation of discrete gelatin-entrapped drops.
30 The drops are then cooled at temperatures preferably ranging between 2 and 10°C; finally they are dried and sieved through a calibrated net.

The present invention is now described with reference to the following non-limiting examples.

Formulations in accordance with the invention

- 5 A number of formulations of the invention were made, using the following ingredients.

Example 1

CORE		%
	Lornoxicam	3,16
	Vegetable Oil	77,61
	Aspartame	1,07
	Lemon Flavor	11,16
SHELL	Gelatine	5,59
	Plasticizer	1,4
	Sucralose	0,01
		100

10 Example 2

CORE		%
	Lornoxicam	3,16
	Vegetable Oil	78,68
	Lemon Flavor	11,16
SHELL	Gelatine	5,6
	Plasticizer	0,35
	Xylitol	1,05
		100

Example 3

CORE		%
	Lornoxicam	4,7
	Vegetable Oil	74,9
	Silica	1,8
	Lemon Flavor	9,1
SHELL	Gelatine	7,2
	Plasticizer	1,8
	Sucralose	0,5
		100

Example 4

CORE		%
	Lornoxicam	9,5
	Vegetable Oil	70,2
	Silica	1,8
	Sucralose	0,25
	Lemon Flavor	9
SHELL	Gelatine	7,2
	Plasticizer	1,8
	Sucralose	0,25
		100

Example 5

CORE		%
	Lornoxicam	9,4
	Vegetable Oil	65,1
	Menthol	4,6
	Aspartame	1,8
	Silica	0,9
	Lemon Flavor	9,1
SHELL	Gelatine	7,2
	Plasticizer	1,8
	Sucralose	0,1
		100

Example 6

CORE		%
	Lornoxicam	9,4
	Vegetable Oil	65,1
	Menthol	4,6
	Silica	0,9
	Aspartame	1,8
	Grapefruit Flavor	9,1
SHELL	Gelatine	7,2
	Plasticizer	1,8
	Sucralose	0,1
		100

5 Example 7

CORE		
	Lornoxicam	9,4
	Vegetable Oil	67,3
	Lemon Flavor	6,4
	Honey Flavor	2,7
	Menthol	2,7
	Aspartame	1,8
	Silica	0,5
	Sucralose	0,03
SHELL	Gelatine	7,2
	Plasticizer	0,5
	Sucralose	0,07
	Sorbitol	1,4
		100

To obtain the product of the invention, core- and shell compositions made of the components according to Examples 1-7 were prepared, heated, and ejected through a concentric double nozzle.

The inner nozzle ejected the core fluid formulation at the temperature of 30°C; the outer nozzle ejected the shell liquid formulation at the temperature of 65°C. The core- and shell compositions were in the fluid state at the ejecting temperature, without addition of any solvents. After cooling to 2-10°C, drying
5 and sieving, gelatin-entrapped cores were obtained weighing on average 110 mg (containing about 90% core fluid and 10% shell layer), having average diameter of 6 mm.

DISSOLUTION TESTS IN VIVO

10 10 human volunteers were given a unit dose consisting in one core of Lornoxicam obtained in the above Example no. 7

All volunteers placed the dose in the sublingual area; after a time of 30 seconds they were asked to move the tongue and test if solid matter was left in the mouth: none of the volunteers perceived any solid matter left, neither the same
15 was evident from a visual inspection of the mouth: the administered dose unit was thus completely dissolved in a time lower than 30 seconds.

The above pearls containing NSAID active ingredient (Lornoxicam) thus showed excellent dissolution profile. Further bioavailability studies could confirm the absorption through the buccal route.

CLAIMS

1. A pharmaceutical composition comprising one or more drug-containing fluid cores, singly entrapped within a gelatine shell with thickness comprised between 20 and 400 micrometers, said cores having average diameter ranging from 5 to 10 mm.
5
2. A pharmaceutical composition according to claims 1-2, wherein the core comprises 1-15% of drug, 65-90% of a medium chain triglyceride and/or vegetable oil, 5-25% of a sweetener and/or flavour.
10
3. A pharmaceutical composition according to claims 1-2, wherein the gelatine shell further includes a plasticizer, with a gelatine:plasticizer ratio comprised between 3:1 and 20:1.
15
4. A pharmaceutical composition according to claims 1-3, being a chewable or mouth-melting composition.
5. Pharmaceutical composition according to claims 1-4 suitable to be taken at any time and even when water is not available.
20
6. Pharmaceutical composition according to claims 1-5, dissolving within 30 seconds after placing into the mouth
7. Pharmaceutical composition according to claims 1-6, containing a drug needed for urgent medication.
25

8. Pharmaceutical composition according to claims 1-7, where the drug is selected among one or more agents effective on pain, in particular acute and/or severe pain.
- 5 9. Pharmaceutical composition according to claims 1-8, where the drug is a non-steroidal anti-inflammatory agent.
- 10 10. Pharmaceutical composition according to claims 1-9, wherein the drug is one or more among Lornoxicam, Diclofenac, Ketoprofene, Dex ketoprofene.
- 15 11. Pharmaceutical composition according to claims 1-7, where the drug is selected among one or more cardioactive, antiemetic, anti Alzheimer, anti migraine, analgesic, antihistaminic drugs, or drugs for erectile dysfunctions.
12. Pharmaceutical composition according to claims 1-11, where the drug is acid-unstable.
- 20 13. Pharmaceutical compositions according to claims 2-12, in which the said flavor is one or more among Lemon, Honey, Caramel, Menthol, Ginger, Grapefruit, Grape, Orange, Cherry.
- 25 14. Pharmaceutical compositions according to claims 2-13, in which the sweetener is one or more among Aspartame, Sucralose, Saccharin, Sorbitol.

15. Pharmaceutical composition according to any of claims 1-14, for use in the buccal administration of a drug.

5 16. Pharmaceutical composition for use according to claims 15, where the drug is acid-unstable and/or lipophilic.

10 17. Pharmaceutical composition for use according to claims 15-16, where the drug is one or more among non-steroidal anti-inflammatory agents, cardioactive, antiemetic, anti Alzheimer, anti migraine, antihistaminic drugs.

18. Pharmaceutical composition for use according to claims 15-17, where the drug is one or more among Lornoxicam, Diclofenac, Flufenamic acid, Ibuprofen, Ketoprofene, Mefenamic acid, Naproxen.

15

19. A process to prepare a composition according to claims 1-14, comprising applying to a drug-containing fluid core, a thin gelatine shell, having thickness comprised between 20 and 400 micrometers, wherein the thus treated cores have average diameter ranging from 5 to 10 mm.

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20. A process according to claim 19, performed by using a concentric nozzle dripping simultaneously the core and shell compositions at a suitable temperature.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/056883

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/5415
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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

5 January 2012

Date of mailing of the international search report

23/01/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/056883

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/056883

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