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Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms

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Abstract

This work relates to the development and the in vitro evaluation of sustained-release minitablets (MT), prepared by melt granulation and subsequent compression, which are designed to float over an extended period of time. Levodopa was used as a model drug. The importance of the composition and manufacturing parameters of the MT on their floating and dissolution properties was then examined. The investigation showed that MT composition and MT diameter had the greatest influence on drug release, which was sustained for more than 8 h. By using the same formulation, the best floating properties were obtained with 3 mm MT prepared at low compression forces ranging between 50 and 100 N. Their resultant-weight (RW) values were always higher than those obtained with a marketed HBS dosage form within 13 h. When they were filled into gelatin capsules, no sticking was observed. By evaluating the dissolution profiles of levodopa at different pH values, it was found that dissolution profiles depend more on the prolonged-release ability of Methocel® K15M than on the pH-dependent solubility of levodopa. Finally, the robustness of the floating MT was assessed by testing the drug release variability in function of the stirring conditions during dissolution tests.

Keywords: Minitablets; Floating; Sustained-release; Melt granulation; Levodopa

1. Introduction

Oral sustained-drug-delivery formulations show some limitations connected with the gastric emptying time (GET). In particular, unpredictable GET leads to variations in the amount of drug absorbed. Moreover, a too rapid gastrointestinal transit can result in incomplete drug release from the device above the absorption zone, leading to diminish effectiveness of the administered dose when the drug presents an absorption window. A prolongation of gastric residence time (GRT) of a rate-controlled oral drug delivery system can overcome these problems by reducing the inter-subject variability, the so called "peak and trough" effect, and leads to a more predictable effect with increased bioavailability, especially for drugs with a narrow absorption window (NAW) in the upper part of the gastrointestinal tract (Hoffman et al., 2004). Moreover, extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs (i) that are locally active in the stomach, (ii) that are unstable in the intestinal or colonic environment, and/or (iii) have low solubility at higher pH values (Streubel et al., 2003). As the total gastrointestinal transit time is also prolonged, the number of doses in the regimen can be reduced and so the patient compliance is improved.

Among the various attempts made to increase the retention of an oral dosage form (Moës, 1993; Iannucelli et al., 1998a; Talwar et al., 2001; Klausner et al., 2003; Sato et al., 2004), it seems that the floating drug delivery systems offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the GRT of solid dosage forms (Moës, 1993). In this way, Seth and Tossounian (1978, 1984) have developed a Hydrodynamically Balanced capsule System (HBS™) based on a mixture of drugs and hydrocolloid. Upon contact with gastric fluids, the capsule shell dissolves and the hydrocolloid begins to swell, maintaining a relative integrity of shape, a bulk density lower than 1 g/ml and regulating the drug release. Unfortunately, most single-unit floating systems are generally unreliable and non-reproducible in prolonging the GRT. They also show a higher

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inter- and intra-subject variability resulting from their unpredictable all-or-nothing emptying process (Hwang et al., 1998). In contrast, multiple-unit dosage forms, such as pellets or MT, have a more reproducible GRT, a reduced inter-subject variability in absorption and offer a better dispersion through the gastrointestinal tract which offers less chance of localised mucosal damage (Singh and Kim, 2000). Co-administration of units with different release profiles or containing non-compatible substances is also possible with multiple-unit dosage forms. Rouge et al. have described 3 mm floating MT based on HPMC and using sodium bicarbonate as the gas-generating agent, prepared by direct compression. By using Methocel® K15M as the swellable polymer, the lag time of the MT was 17 min in water containing 0.05% (m/v) Polysorbate 20, and 42 min in artificial gastric fluid containing 0.05% (m/v) Polysorbate 20. The floating duration was above 8 h in both solutions (Rouge et al., 1997a). Floating properties of these systems may be improved by introducing a granulation step (Streubel et al., 2003).

Up to now, when a granulation step has been needed, wet granulation has been commonly used. In this work, granulates are made by a melt granulation process, followed by direct compression. Melt granulation, in which granulation is obtained through the melting or softening of a binder with a low melting point, is a very short one-step single-pot production process. As it is a solvent-free process, the drying phase is eliminated and thus it becomes less consuming in terms of time and energy (Hamdani et al., 2002).

The present investigation concerns the development and the in vitro evaluation of oral sustained-release floating granulates, made by melt granulation and compressed into MT, which are designed to float on the surface of aqueous fluids – including gastric juice and intestinal fluids – over an extended period of time. The drug used as a model was levodopa because of its NAW in the upper part of the small intestine (Rouge et al., 1996). Moreover, this drug is characterized by a relatively short elimination plasma half-life time in humans ($t_{1/2}$ = 1 h) (Clarke, 1986), which makes it an attractive candidate for a gastric retentive dosage form.

This paper aims to evaluate the influence of formulation and manufacturing parameters and dissolution test conditions on the in vitro release profiles of levodopa.

2. Materials and methods

2.1. Materials

Levodopa (Newsmart, China) was used as a model drug. Dissolution tests were performed in a dark room to avoid possible drug alteration. Glyceryl palmitostearate (Precirol® ATO 5 = Gelucire® 54/02) and glyceryl behenate (Compritol® 888 = Gelucire® 70/02), supplied by Gattefosse (France), were used as a meltable binder and a lipophilic diluent, respectively. The lipidic materials have to occur as fine white free-flowing powders. High and low viscosity grades HPMC (Methocel® K15M and Methocel® E5, Colorcon, England) were used as a gel-forming polymer and a coating agent, respectively. Tartaric acid (Federa, Belgium), sodium bicarbonate (Merck, Germany) and calcium carbonate (Welpher, Belgium) were employed as carbon dioxide-generating agents. Lactose 450 mesh (DMV International, Netherlands) was used as a hydrophilic diluent. The disintegrating agent used as protective filler against MT sticking and filled into capsules in some tests was sodium croscarmellose (Ac-Di-Sol®, FMC, Philadelphia, USA). Prolopa® HBS 125 (Roche, Belgium) is used as a model to compare its resultant-weight profiles with our multiple-units dosage form.

2.2. Methods

2.2.1. Preparation of minitablets

2.2.1.1. Granulate manufacture. Granulates were made in a small vertical laboratory-scale high-shear mixer, Mi-Pro® (Pro-C-epT, Belgium), equipped with a transparent bowl and a heating jacket (Hamdani et al., 2002). The granulate compositions are listed in Table 1.

All experiments were started at an impeller speed (IS) of 1800 rpm and a chopper speed (CS) of 130 rpm while the temperature of the heating jacket was set at 60 °C. When the product temperature reaches sufficiently high values to soften the binder, torque increases sharply due to granule formation (Hamdani et al., 2002). In order to avoid any further product temperature increase, the IS was reduced to 600 rpm after the granule formation step while the CS was increased to 1000 rpm to break the possible agglomerates. The massing time was kept constant at 5 min. The length of the whole granulate manufacturing process was around 20 min. At the end of the process, the granulates were cooled at ambient temperature.

The volume size distribution of the granulates was measured with a Mastersizer 2000 Laser Diffractometer in dry powder

Table 1
Compositions of the investigated granulates (all quantities are given as percentages, w/w) and corresponding MT properties

	Formulation number			
	F1	F2	F3	F4
Levodopa	37.5	37.5	37.5	37.5
Precirol® ATO5	12.0	12.0	12.0	12.0
Compritol® 888	–	–	–	6.0
Methocel® K15M	25.0	15.0	15.0	15.0
$CaCO_3$	10.0	10.0	5.0	5.0
$NaHCO_3$	4.0	4.0	4.0	4.0
Tartaric acid	3.0	3.0	3.0	3.0
Lactose 450 mesh	8.5	18.5	23.5	17.5

	Diameter (mm)		
	3	4	5
Weight (mg)	20	40	60
Compression forces (N)	(a) 50–100 (b) 100–200 (c) 200–400 (d) 1000–2000	2000–3000	3000–4000
Hardness (N) (n = 10)	(a) 5 ± 1 (b) 8 ± 1 (c) 11 ± 1 (d) 14 ± 1	22 ± 3	28 ± 2

form (Scirocco 2000, Malvern Instrument, UK) with a suitable Standard Operating Procedure (SOP) (refractive index 1.52, dispersive air pressure 1 bar, vibration rate 50%, measurement time 30 s). The mean particle size, represented by the equivalent volume diameter $D[4,3]$, of granulates should be around 150 μm to provide good flow properties.

2.2.1.2. Minitablet preparation. MT were prepared by direct compression. Granulates were fed manually into the die of an instrumented single-punch tableting machine (Korch, Germany) to produce FMT using concave-faced punches and dies. The compression forces, the weight and the hardness according to the diameter of the FMT are summarized in Table 1. The hardness was measured with a hardness tester (Computest, Kreamer Gmbh, EL Ektronik, Darmstadt, Germany).

2.2.2. Determination of physicochemical properties of FMT

2.2.2.1. In vitro evaluation of floating capabilities. The FMT ($n = 3$) were placed in 70 ml of 0.1N HCl solution containing 0.05% (w/v) Polysorbate 20 (pH 1.2, 37 °C), followed by horizontal shaking at 100 cycles/min (GFL 1086, Germany). The floating lag time and floating duration were determined by visual observation.

To determine the buoyancy capabilities of the FMT, an apparatus designed for dynamic measurement of the total force acting vertically on an immersed object was also used. This is the RW apparatus proposed by Timmermans and Moës (1990) for studying floating magnitude evolution as a function of time. By convention, a positive RW signifies that the object is able to float, whereas a negative RW means that the object sinks. FMT were placed in a specially designed basket sample holder, which was immersed in 1200 ml of preheated 0.1N HCl solution containing 0.05% (w/v) Polysorbate 20 (pH 1.2, 37 °C). The RW was measured every minute for 13 h.

2.2.2.2. Dissolution studies. A Disteck 2100C USP 29 dissolution apparatus (Distek Inc., North Brunswick, NJ, USA) Type II (paddle method) was used for the dissolution tests. The rotational speeds employed were 50, 60, 75 and 100 rpm. Release testing was carried out in 900 ml of phosphate buffer solutions (0.05 M) containing 0.05% (w/v) Polysorbate 20 at pH 1.5, 3.0 and 6.5. The temperature of the dissolution media was maintained at 37.0 ± 0.2 °C. Dissolutions were carried out on an equivalent of 150 mg of levodopa and the amount of drug released was detected spectrophotometrically at 280 nm (Agilent 8453 UV–vis Dissolution Testing System, Agilent, USA). The percentages of drug release were measured at preselected time intervals and averaged ($n = 5$).

2.2.3. Statistical evaluation

As recommended in the FDAs Guidances for Industry, the similarity factor f_2 was used as a determination for assessing the similarity of dissolution profiles (FDA, 1997; Shah et al., 1998). The compared dissolution profiles were obtained under the same test conditions and their dissolution time points were the same, e.g. for controlled release products, they were 1, 3, 5 and 8 h. As indicated by Shah et al. (1998), the similarity factor f_2 value has to be higher than 50 in order to assess the similarity between two dissolution profiles.

3. Results and discussion

3.1. Influence of the formulation on the drug release and the floating behaviour

In order to develop the desired sustained-release FMT, it was necessary to optimize both the floating properties and the release rate of the drug from the system. A swelling agent was used both to trap the carbon dioxide generated by the effervescent components and to provide the sustained release of the drug. Methocel® K15M was used because Wan et al. showed that the normalized increase in matrix thickness after 30 min swelling for HPMC matrix tablets increased with molecular weight (Wan et al., 1995). Moreover, compared to polymers that had a lower molecular weight, the higher molecular weight HPMC polymers, such as Methocel® K15M, swelled but did not erode to a significant extent because of their higher intrinsic water-holding capacity (Kavanah and Corrigan, 2004). These properties consequently allowed avoidance of the burst effect and improved prolonged release. Rouge et al. have also shown that the lag time decreased with increased molecular weight of Methocel® type K (Rouge et al., 1997a). The gas-generating blend decreases the lag time by accelerating the hydratation of the swelling polymer, thus allowing a higher floating duration because of the constant generation and subsequent trapping of carbon dioxide. Tartaric acid permits the generation of carbon dioxide even if gastric pH is abnormally high.

Precirol® was used as lipidic binder, softening at a relatively low temperature. After softening, the binder acts like a liquid binder. Moreover Precirol® and Compritol®, as lipidic agents, are able to slow down the water diffusion inside the dosage form providing a prolonged release of the incorporated drugs.

The influence of the formulation was evaluated for the 4 mm minitablets at pH 3.0 with a rotational speed of 60 rpm. The F1 provided a sustained release of levodopa immediately after immersion with no burst effect (Fig. 1a). The polymer percentage, 25% (w/w), was high enough to prolong the release of the drug. In fact, in the time interval of 8 h, approximately 70% of the incorporated drug was released with the whole dose being released after 20 h. Floating capabilities of F1 were then evaluated using the RW method (Fig. 1b). The FMT floated after 12 min and they remained buoyant for more than 780 min. The maximal RW value reached was 29/100 mg. The lag time value was corroborated by the horizontal shaking method, which also showed that the FMT remained buoyant until complete erosion.

The percentage of Methocel® K15M was then decreased to 15% in F2. Unfortunately, by preserving the same percentage of gas-generating agents, the amount of HPMC was not high enough to preserve the integrity of the dosage form. As can be seen in Fig. 1a, the entire dose of levodopa was released after only 1.5 h and the MT showed no floating capability because of their early disintegration. A coating based on Methocel® E5 (2%, w/w) neither preserved the integrity of the shape nor allowed sustained release to occur (data not shown).

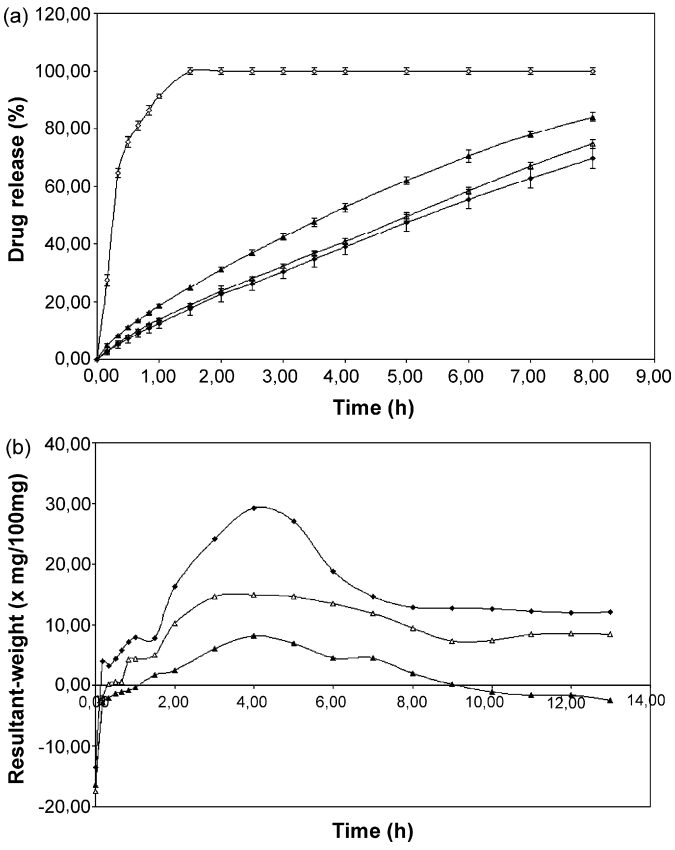

Fig. 1. Influence of the formulation – F1 (●), F2 (◯), F3 (Δ) and F4 (▲) – (a) on levodopa release from the 4 mm FMT at pH 3.0 (apparatus II, 60 rpm) ($n = 5$) and (b) on the floating properties of the 4 mm FMT in a 0.1N HCl solution using the RW method ($n = 1$).

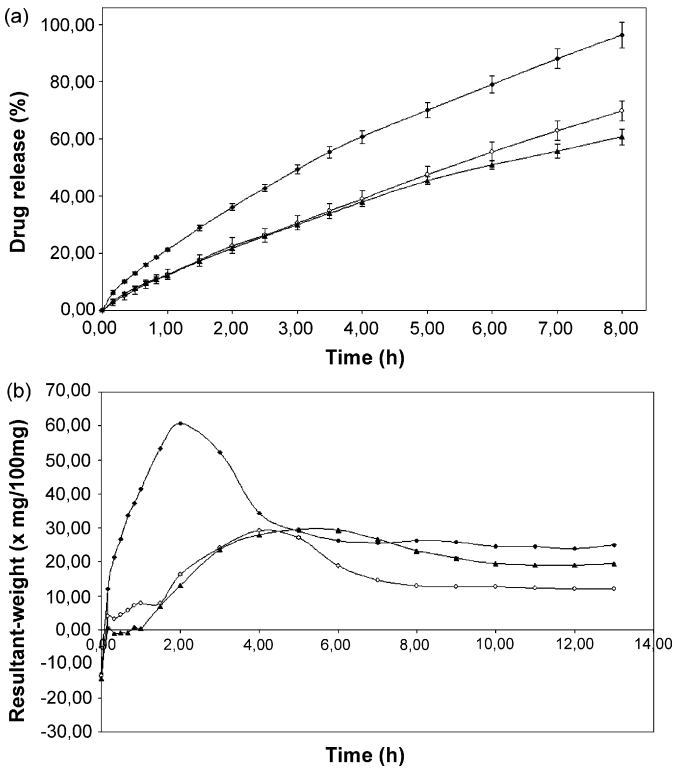

Fig. 2. Influence of the MT diameter – 3 mm (●), 4 mm (◯) and 5 mm (▲) – (a) on levodopa release from FMT composed according to F1 at pH 3.0 (apparatus II, 60 rpm) ($n = 5$) and (b) on the floating properties of the FMT in a 0.1N HCl solution using the RW method ($n = 1$).

The amount of carbon dioxide-generating agents was therefore decreased to 12% in F3. Using the new formula, the integrity of the shape was maintained resulting in a sustained release of the drug. The floating lag time increased to 90 min and the maximal RW decreased to 8/100 mg. Moreover, as the FMT sank after 9 h, the total floating duration was only 7.5 h. The dissolution rate of the drug obtained with F3 was faster than that obtained with F1 due to the lower amount of HPMC.

In order to decrease the drug release rate and improve the floating properties, Compritol® 888 was added to F4. This lipidic diluent was able to sustain the release of the drug because of its hydrophobic nature and was able to improve the floating properties because of its relatively low density. This formulation had the same release profile as that obtained with the F1. In comparison with F3, the floating properties were improved. The floating lag time was 20 min and the maximal RW value reached 15 mg/ml. If these results were better than those obtained with F3, they were inferior to those obtained with F1. So, F1 was selected to evaluate the influence of the FMT diameter on the drug release and floating properties.

3.2. Influence of the minitablets diameter

A simple, but very effective way to modify the drug release kinetic from MT was to change their diameters. Varying the radius of the FMT and thus their hardness and weight, strongly affected their floating properties and the resulting drug release. In fact, the release rate of the drug increased proportionally to the decrease in FMT diameter. This can be attributed to the higher relative surface area of the dosage form when the FMT diameter decreased which gave a proportionately greater area of contact between the FMT and the solution.

Dissolution tests, performed at pH 3.0 with FMT according to F1 (60 rpm), have shown relatively faster dissolution profiles for 3 mm FMT in comparison to that obtained from 4 to 5 mm FMT (Fig. 2a). Moreover, even with the 3 mm FMT, the sustained release occurred immediately after immersion, with no burst effect.

The RW measurement showed that the lag time values increased according to the increase in the diameter and were 1, 12 and 45 min for the 3, 4 and 5 mm FMT, respectively (Fig. 2b). This can be explained by the increase in the initial weight that occurred as the diameter increased. The 3 mm FMT showed the highest maximal RW value – about 60/100 mg – and floated for more than 13 h. Thus, the 3 mm FMT were selected to evaluate the influence of the compression force on the drug release and the floating properties.

3.3. Influence of the compression force

The dissolution results (pH 3.0, 60 rpm) of the 3 mm FMT, composed according to F1 and compressed at different compression forces (Table 1), showed that the drug release rate did

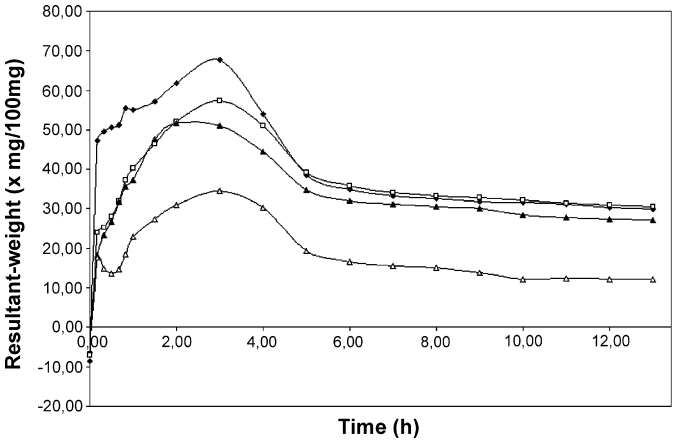

Fig. 3. Floating properties of the 3 mm FMT composed according to F1 and compressed at 50–100 N (●), 100–200 N (□), 200–400 N (▲) and 1000–2000 N (Δ), in a 0.1N HCl solution using the RW method ($n = 1$).

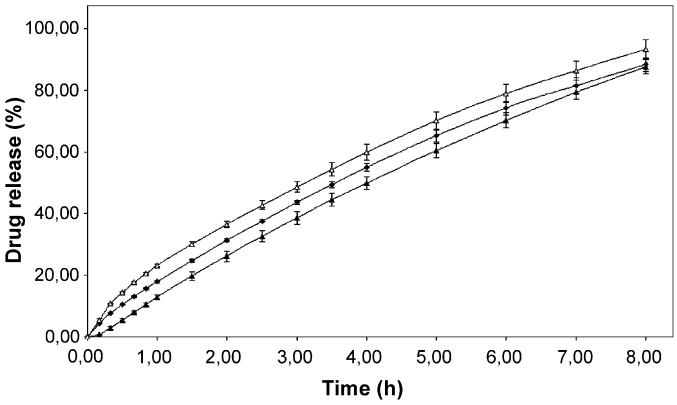

Fig. 4. Dissolution profiles for 3 mm FMT composed according to F1 and filled into a gelatin capsule, with (Δ) or without (▲) a disintegrating agent, or not filled (●) into a capsule (apparatus II, 60 rpm, pH 3.0) ($n = 5$).

not change as compression forces increased from 50 to 2000 N (data not shown). All dissolution profiles were statistically similar, regardless of compression pressure applied, e.g. the lowest f_2 value was 96.38. Even at the lowest compression force, no burst effect was observed. This was probably due to the high amount of effervescent compounds, which helped to accelerate the hydratation of the swelling polymer.

By contrast, the floating properties were influenced by the level of compression force (Fig. 3). Even if all floating lag time values were lower than 10 min (about 1 min), the highest RW value was obtained with the lowest compression force and was 68/100 mg.

Friability evaluation according to the European Pharmacopeae showed that the loss of weight was lower than 1% whatever the compression force used. As it seemed that low compaction pressures improved floating ability, the robustness of our FMT was tested by using a 50–100 N compression force.

3.4. Sticking evaluation

According to Rouge et al., hydrophilic minimatrices introduced into a capsule exhibit a strong tendency to adhere to one another due to the presence of the gelatin capsule and to the earlier hydratation of the minitablets (Rouge et al., 1997b). An incomplete dispersion of FMT could involve therapeutic problems due to the possible inter- and intra-subject variation. As the sticking of MT occurs in a random way, it can be evaluated in vitro by analysis of the dissolution profile and more particularly by the increase of the standard deviations. A disintegrating agent – Ac-Di-Sol® – was used to prevent possible adhesion between FMT during the dissolution of the capsule shell.

Gelatin capsules 0 were filled with the FMT, and, the empty space between the FMT within the capsule was filled with the disintegrating agent. The total amount of the protective filler was about 150 mg. FMT filled into capsules without the disintegrating agent were also tested for comparison. Dissolution tests were performed at pH 3.0, 60 rpm.

When FMT were filled into the capsule without the disintegrating agent, the dissolution of levodopa was slightly delayed by about 10 min (Fig. 4). We observed visually that the gelatin capsule opened within 1–2 min after immersion in the liquid and was completely dissolved after 10 min. FMT were dispersed and floated immediately after the complete dissolution of the capsule shell. In contrast, in the presence of the disintegrating agent, the complete disintegration of the capsule occurred 1–2 min after its opening. In this case, the release of the drug was not delayed but the MT did not float immediately. The standard deviations did not increase in the absence of the protective filler. Moreover, with ($f_2 = 82.6$) or without ($f_2 = 85.5$) disintegrating agent, the dissolution profiles were statistically similar to that obtained with the FMT not filled into a gelatin capsule. Thus, it seems that with the present FMT, the use of a disintegrating agent is not required.

3.5. Effect of pH on drug release

First of all, the solubility of levodopa was evaluated in function of the pH by using the same phosphate buffer as that used for the dissolution tests. It was found that its solubility at 37.0 °C was 760, 400, and 365 μg/ml at pH values of 1.5, 3.0 and 6.5, respectively. This suggested that levodopa was a drug with a pH-dependent solubility. Thus, the dissolution rates of levodopa were tested at 60 rpm in phosphate buffers at pH values of 1.5, 3.0 and 6.5. These pH values were selected to simulate gastric pH in fasted and fed (standard meal) conditions and duodenal pH, respectively.

At each of the three pH values, a sustained release of levodopa occurred immediately after immersion, with no burst effect (Fig. 5). Even though the release of the drug was faster at pH 1.5, all dissolution profiles were statistically similar, e.g. f_2 (pH 1.5–6.5) = 57.2. It seems that the dissolution rate depends more on the prolonged-release ability of Methocel® K15M than on the pH-dependent solubility of the drug. The FMT seem to be able to provide a constant sustained release of levodopa from the stomach to the intestine.

3.6. Agitation rate

Different mass transport processes may occur during drug release from polymer-based matrix systems, including (i) water

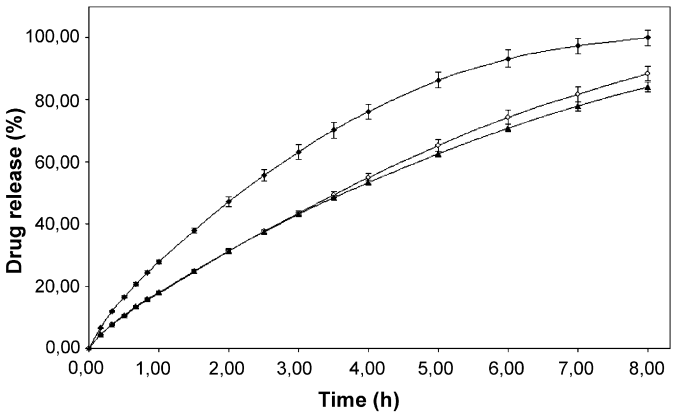

Fig. 5. In vitro dissolution profiles of levodopa from 3 mm FMT composed according to F1 (apparatus II, 60 rpm) at pH 1.5 (●), 3.0 (◯) and 6.5 (▲) ($n = 5$).

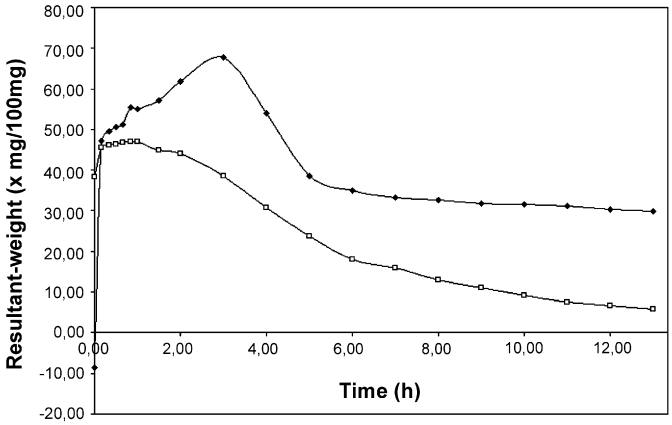

Fig. 7. RW profiles obtained with 3 mm FMT composed according to F1 (●) and HBS dosage form (□) ($n = 1$).

imbibition into the system, (ii) polymer swelling, (iii) polymer dissolution and/or erosion, (iv) drug diffusion out of the dosage form and (v) drug dissolution.

In addition to their influence on the release rate of the drug, it was considered that factors affecting swelling and erosion of the polymer could also influence the dissolution of the active substance. Thus, the susceptibility of this type of hydrophilic polymer matrice to change in its sustained-release ability in function of the agitation rate was considered as an indication of the robustness of the delivery system.

The effect of agitation rate on the levodopa dissolution rate was examined at pH 3.0 by using the paddle method. The release rate of the drug increased as the stirring rate increased (Fig. 6) according to the reduction of the thickness of the stagnant layer as described in the Noyes–Whitney equation (Fukunaka et al., 2006). It was also due to a more rapid erosion of matrix tablets at the higher stirring rates that occurred because of the increased rate of detachment of polymer chains away from the matrix surface. This led to a thinner layer of gel forming at the surface of the dosage form at higher agitation rates.

However, even if an influence of the agitation rate on drug release was observed, there was no burst effect and no disintegration of the FMT, regardless of the agitation rate, within the

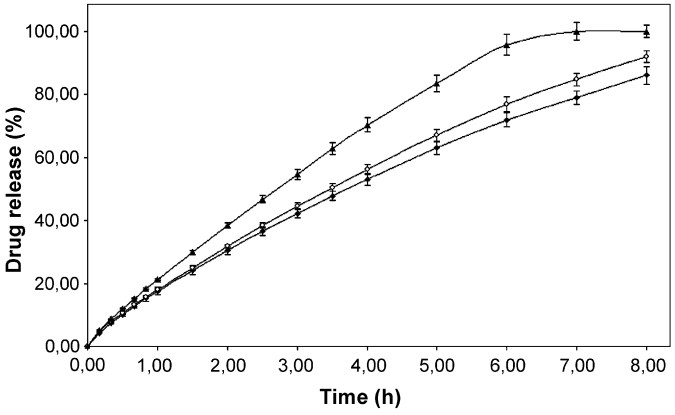

Fig. 6. Influence of the stirring rate – 50 rpm (●), 75 rpm (◯), 100 rpm (▲) – on the levodopa release rate from 3 mm FMT composed according to F1 at pH 3.0 using the paddle method ($n = 5$).

experimental period. Moreover, as all dissolution profiles were statistically similar – e.g. f_2 (50–100 rpm) = 62.7 – it can be concluded that our FMT show a good level of robustness.

The results obtained using the basket method were similar than those obtained using the paddle method (date not shown).

3.7. Floating properties obtained with FMT and HBS dosage form

Two different approaches, using either polymer-mediated non-effervescent or effervescent systems, have been proposed in the literature for the development of floating drug delivery systems (Singh and Kim, 2000). The commercial HBS dosage form is a non-effervescent system, while the present FMT is an effervescent one. Their floating properties were compared using the RW apparatus since the GRT of buoyant units depends not only on the initial density but also on the evolution of their density as a function of time.

The HBS capsule system presented no lag time due to its very low initial density. Its maximal RW value (∼45/100 mg) was obtained after 10 min and remained constant for about 1 h (Fig. 7). During this time period, the increase in volume was greater than the increase in mass during swelling. However, afterwards, its floating strength decreased as a result of the development of its hydrodynamic equilibrum. The lag time of our FMT was only 1 min. From 10 min to the end of the test, the RW values were higher than those obtained with the commercial HBS dosage form. In fact, the floating capabilities of FMT did not decrease until the end of the test because carbon dioxide was continuously produced and entrapped in the swelling polymer. It seems that the incorporation of gas-generating agents improve the floating properties. Different studies reported in the literature have indicated that pharmaceutical dosage forms exhibiting good in vitro floating behaviour show prolonged gastric residence in vivo (Iannucelli et al., 1998b; Singh and Kim, 2000).

4. Conclusion

In conclusion, a new multiple-unit floating drug delivery system has been developed which is based on the use of a very

simple composition, produced by melt granulation and subsequent compression. The most successful mixture (F1) contained 37.5% of drug, 12.0% of meltable binder, 25.0% of Methocel® K15M and 17.0% of carbon dioxide generating agent. The most suitable diameter of the FMT was 3 mm and their compression force was ranged between 50 and 100 N. These MT floated after only 1 min and remained buoyant more than 13 h. Their ability to sustain drug release over an extended period of time (more than 8 h) has been demonstrated. Their robustness under varying pHs or agitation rates was also demonstrated. They showed no sticking tendency when they were filled into a capsule.

If these results are encouraging, it has to be pointed out that good in vitro floating behaviour alone is not sufficient proof of efficient prolonged gastric retention in vivo. Therefore, to validate the in vitro evaluations, in vivo studies shall be conducted in the near future with these FMT.

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