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Evaluation and Floating Enhancement of Levodopa Sustained Release Floating Minitablets Coated with Insoluble Acrylic Polymer

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This article describes the in vitro evaluation and the enhancement of the floating properties of coated sustained release (SR) minitablets (MTs). The evaluated system consisted of a 3-mm drug-containing gas-generating core prepared by melt granulation and subsequent compression, which was then coated with a flexible polymeric membrane. Eudragit® RL30D and acetyl triethylcitrate were used as a film former and a plasticizer, respectively. The coating level was fixed at 20% (wt/wt). The optimally coated floating MTs floated within 10 min and remained buoyant for more than 13 h, regardless of the pH of the test medium. By evaluating the dissolution profiles of levodopa at different pH, it was found that the release of levodopa was sustained for more than 12 h regardless of the pH, even if the coating did not cancel the effect of the pH-dependent solubility of the active drug. Finally, the robustness of the coated floating MTs was assessed by testing the drug release variability in function of the stirring conditions during dissolution tests.

Keywords multiple-unit system; minitablets; floating; sustained release; coating; Eudragit®; RL30D; levodopa

INTRODUCTION

Oral administration is recognized to be the predominant route for drug delivery. More than 50% of drug delivery systems (DDSs) available in the market are oral DDSs (Deshpande, Rhodes, Shah, & Malick, 1996). These dosage forms (DFs) are easy to administer and increase patient compliance. However, the development process of such systems is precluded by several physiological difficulties. In fact, orally administrated DFs are exposed to a wide range of highly variable conditions during their transit throughout the gastrointestinal (GI) tract. Food ingestion and the type of meal—caloric content, volume, viscosity, physical state—influence the gastric physiology and thus the dissolution of the active drug from the DFs. The gastric pH fluctuates around pH 1–3 in the fasted state and within a range of pH 3–7 in fed condition, whereas intestinal pH ranges between 6 and 8 (Dressman, Amidon, Reppas, & Shah, 1998; Russel et al., 1993). Motility patterns and the pyloric valve diameter are different in digestive or interdigestive conditions, affecting the gastric emptying rate of ingested DDSs (Deshpande et al., 1996). Kamba et al. have shown that the human stomach potentially imparts a mechanical destructive force of 1.50 and 1.89 N in fasted and fed conditions, respectively (Kamba, Seta, Kusai, Ikeda, & Nishimura, 2000). These potential crushing forces are due to pressure from the gastric wall and the friction between the surface of the DFs and the gastric wall or gastric contents (Katori, Aoyagi, & Terao, 1995). This proves that the intensity of gastric agitation also depends on whether the subject's condition is fasted or fed. The influences of these parameters on the dissolution behavior of an incorporated drug as well as knowledge of its chemical properties have to be well understood to design an oral DF.

Sustained release (SR) DFs capable of having a prolonged retention time in the stomach to extend the duration of drug delivery have received much attention in the past two decades, especially for drugs that have a narrow absorption window (NAW) in the upper part of the GI tract (Hoffman et al., 2004). In fact, variable and/or too rapid GI transit can result in incomplete drug release from the DFs above the absorption zone, leading to a decrease in the efficacy of the administered dose (Iannuccelli, Coppi, Bernabei, & Cameroni, 1998a). Moreover, progressive and complete dissolution of the active drug in the stomach may avoid possible dose-dumping due to pH variability between the gastric and the intestinal juices.

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In a previous study (Goole, Deleuze, Vanderbist, & Amighi, 2008), SR-coated minitablets (MTs) that floated within 20 min and remained buoyant for more than 13 h were developed. The core was based on the compression of granulates prepared by melt granulation. Granulates were based on a very simple composition comprising levodopa (L-dopa) as a model drug, Precirol® ATO as a meltable binder, and carbon dioxide-generating agents. These MTs were coated with Eudragit® RL30D, an insoluble but readily permeable polymethacrylate polymer (Amighi & Moës, 1995), to produce coated floating minitablets (CFMTs). This polymer provided a flexible membrane that was able to retain the generated gas inside the DF and to sustain the release of the active drug for more than 12 h. Acetyl triethylcitrate (ATEC), which is slightly soluble in water (Gutiérrez-Rocca & McGinity, 1994), was used as a plasticizer to improve the mechanical properties and the resistance of the polymeric film for a prolonged period of time. Lactose was also added to increase the drug diffusion through the coating film. A coating level of 20% (wt/wt) was found appropriate to maintain DF shape integrity for at least 20 h. Other coated multiple-unit floating SR systems are already described in the literature (Ichikawa, Watanabe, & Miyake, 1991; Sungthongjeen, Paeratakul, Limmatvapirat, & Puttipipatkhachorn, 2006). Both developments are based on pellets coated with double layers: an inner effervescent layer and an outer gas-entrapping polymeric membrane. The manufacture of the core seemed to take longer than our granulation, and compression processes as the pellets are made by an extrusion–spheronization process that needs at least three steps: a mixing step, an extrusion–spheronization process with addition of water, and thus a drying step. Moreover, in comparison with the other sophisticated multiple-unit floating systems described before in the literature (Iannuccelli et al., 1998a; Sato, Kawashima, Takeuchi, & Yamamoto, 2004; Streubel, Siepmann, & Bodmeier, 2003), our CFMTs are based on a very simple composition, can contain a high amount of active drug, and show applicability for industrialization.

This article aims to evaluate the influence of several dissolution test conditions on the in vitro release profiles of levodopa to assess the robustness of the CFMTs. The influence of pH on the floating properties of the CFMTs was also evaluated to obtain the same floating capabilities regardless of the pH.

MATERIALS AND METHODS

Materials

Levodopa (Newsmart, Nantongl, China), (–)-2-amino-3-(3,4-dihydroxyphényl) propanoic acid, was used as a model drug. Glyceryl palmitostearate (Precirol® ATO 5 = Gelucire® 52/02), supplied by Gattefosse (Saint-Priest, France), was used as a meltable binder. Tartaric acid (Federa, Brussels, Belgium), sodium bicarbonate (Merck, Darmstadt, Germany), and calcium carbonate (Welphar, Brussels, Belgium) were used as carbon dioxide-generating agents. Lactose 450 mesh (DMV Int., Veghel, Netherlands) was used as a hydrophilic diluent.

The insoluble polymer used to manufacture the gas-trapping membrane was Eudragit® RL30D, in the form of an aqueous colloidal dispersion of poly(ethylacrylate-methylmethacrylate-trimethylammonium-methacrylate chloride) (Rhöm Pharma, Darmstadt, Germany). Citroflex A2® (ATEC), used as plasticizer, was supplied by Reilly Int. (Hautrage, Belgium). Talc, with a mean particle size of approximately 10 μm (Aldrich chemical Co Ltd., Gillingham, England), and an antifoam emulsion (silicone emulsion, Vel. S.A., Seneffe, Belgium) were used as received. Sodium croscarmellose (Ac-Di-Sol®, FMC, Philadelphia, PA, USA) was used as a disintegrating agent that was filled into hard gelatin capsules to facilitate the dispersion of the CFMTs in the dissolution medium.

Granulate Manufacture

Granulates were made in a small, vertical, laboratory-scale, high-shear mixer, Mi-Pro® (Pro-C-EpT, Zelzate, Belgium), equipped with a transparent bowl and a heating jacket (Hamdani, Moës, & Amighi, 2002). The compositions of granulates are listed in Table 1.

All experiments were started at an impeller speed (IS) of 1,800 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 reached sufficiently high values to soften the binder, the torque increased because of granule formation (Goole, Vanderbist, & Amighi, 2007). The IS was reduced to 600 rpm after the granule formation step to avoid any further product temperature increase, whereas the CS was increased to 1,000 rpm to break possible agglomerates. The massing time was kept constant at 5 min. The length of the whole granulate manufacturing process was around 30 min. At the end of the process, the granules were cooled at ambient temperature.

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

TABLE 1
Compositions of the Investigated Granulates (All Quantities are Given as Percentages wt/wt) and Corresponding minitablet (MT) Properties

Composition No.	C1	C2	C3	C4
Levodopa	37.5	37.5	37.5	37.5
Precirol® ATO5	12.0	12.0	12.0	12.0
$CaCO_3$	10.0	10.0	10.0	10.0
$NaHCO_3$	4.0	4.0	4.0	4.0
Tartaric acid	3.0	7.0	10.0	15.0
Lactose 450 mesh	33.5	29.5	26.5	21.5
Diameter (mm)	3			
Weight (mg)	20			
Compression force (N)	50–100			
Hardness (N) (n = 10)	6 ± 1			

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

Minitablet Preparation

MTs were prepared by direct compression. Granules were fed manually into the die of an instrumented single-punch tableting machine (Korch, Radeberg, Germany) to produce MTs using concave-faced punches and dies. The die, composed of eight holes, each 3 mm in diameter, was specially designed for our laboratory. The compression forces, the weight, and the hardness are summarized in Table 1. The hardness was measured with a hardness tester (Computest; Kreamer Gmbh, El Ektronik, Darmstadt, Germany). The friability of the MT was 0.15 ± 0.03%. This indicated that they were able to withstand the mechanical stress of the subsequent coating process.

Preparation of the Coating Dispersion

The aqueous dispersion used for the coating of the MT is given in Table 2. Talc was previously dispersed in water in the presence of an antifoam agent and mixed with the water-soluble additive using a T45 Ultra-Turrax® (Janke & Kunkel GmbH, Staufen, Germany). A dispersion containing Eudragit® RL30D required the addition of 20% wt/wt (relative to the polymer content in the film) of plasticizing agent. The plasticizer was added to the polymer aqueous dispersion under gentle stirring. All the components of the coating dispersion were then mixed under magnetic stirring for at least 1 h before starting the coating process.

TABLE 2
Formulation Used for the Coating of Levodopa CFMTs

Formulation	F1
Eudragit® RL30D (g) (dry basis)	200
ATEC (g)	40
Talc (g)	50
Lactose (g)	20
Antifoam (g)	2
Water (g)	842
Solid content (% wt/wt)	25.6
Coating level (%)	20

ATEC, acetyl triethylcitrate; CFMTs, coated floating minitablets.

Preparation of CFMTs

MTs were transferred into a fluidized bed-coating apparatus (Uni-Glatt®, Glatt GmbH, Binzen, Germany) equipped with a bottom-spray coating process in a Würster column and coated with the coating dispersion until the desired film weight was deposited. During the coating operation, the aqueous dispersion was stirred continuously to prevent sedimentation of insoluble particles. The conditions for layering were shown to be as follows: preheating temperature, 40 ± 2°C; preheating time, 10 min; inlet and outlet temperatures, 40 ± 2°C and 35 ± 2°C, respectively; flow rate, 6 g/min; and pneumatic air pressure, 1 bar. After coating, the CFMTs were further fluidized for 10 min and subsequently cured at 60°C for 8 h (Amighi & Moës, 1995, 1997).

In Vitro Evaluation of Floating Capabilities

To determine the buoyancy capabilities of the CFMTs, an apparatus designed for dynamic measurement of the total force acting vertically on an immersed object was also used. This was the resultant weight (RW) apparatus proposed by J. Timmermans for studying floating magnitude evolution as a function of time (Timmermans & Moës, 1990). By convention, a positive RW signifies that the object is able to float, whereas a negative RW means that the object will sink. CFMTs were placed in a specially designed basket sample holder that was immersed in 1,200 mL of preheated 0.1 N HCl solution containing 0.05% (wt/vol) Polysorbate 20 (pH 1.2, 37°C). The RW was measured every minute for 13 h (n = 1).

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 used were 50, 75, and 100 rpm. Release testing was carried out in 900 mL of phosphate buffer solutions (0.05 M) containing 0.05% (wt/vol) Polysorbate 20 at pH 1.5, 3.0, and 6.5. The temperature of the dissolution media was maintained at 37 ± 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, Santa Clara, CA, USA). The percentages of drug released were measured at preselected time intervals and averaged (n = 5).

Statistical Evaluation

As recommended in the FDA's Guidance for Industry, the similarity factor f_2 was used to determine the similarity of dissolution profiles (FDA, 1997; Shah, Tsong, Sathe, & Liu, 1998). The compared dissolution profiles were obtained under the same test conditions and their dissolution time points were the same, for example, for the 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 to assess the similarity between two dissolution profiles.

RESULTS AND DISCUSSION

Influence of Capsule

Tensile strengths, resulting from the carbon dioxide generation upon contact with the dissolution medium, may appear between the CFMTs filled into the hard gelatin capsules. Indeed, the distortion of the membrane due to gas generation could weaken the coating, resulting in higher variability and a decrease in the efficiency to sustain the drug release (Goole et al., 2008). As this phenomenon occurs in a random way, it can be evaluated in vitro by the analysis of the dissolution profile and more particularly by any increase of standard deviations. Moreover, it has been shown in a previous study (Goole et al., 2008) that the presence of small cracks on the surface of the film (bubbles of gas diffusing through the membrane were observed visually) provided a bimodal dissolution profile. A disintegrating agent—Ac-Di-Sol®—was used to accelerate the dispersion of the CFMTs in the dissolution medium and, consequently, to prevent possible weakening of the coating before the complete dissolution of the capsule shell.

Dissolution tests were performed at pH 3.0, 50 rpm on CFMTs in which the core was composed according to C1 (Table 1) and coated with F1 (Table 2). Size 0 gelatin capsules were filled with the CFMTs, and the empty space between the CFMTs within the capsule was filled with the disintegrating agent. Its total amount was about 120 mg. The CFMTs, filled into capsules without the disintegrating agent, were also tested for comparison.

No delay in the dissolution of levodopa was observed at the beginning of the test when CFMTs were filled into capsule, even when the disintegrating agent was not used (Figure 1). It was observed visually that the gelatin capsule opened within 1–2 min after immersion in the liquid and was completely dissolved in the following 10 min. CFMTs were dispersed and floated within 20 min as already observed in a previous study (Goole et al., 2008). Standard deviations did not increase and no bimodal dissolution profiles appeared when CFMTs were filled in the capsule, both with and without the disintegrating agent. Moreover, after 8 h, with (f_2 = 70.7) or without (f_2 = 83.3) the disintegrating agent, the dissolution profiles were statistically similar to that obtained with the CFMTs not filled into a gelatine capsule and remained statistically similar after 20 h. However, the filling into capsule modified the dissolution rate of levodopa as the entire dosage of levodopa was released in 14 h when CFMTs were filled into capsule instead of over more than 20 h when CFMTs were not filled into capsule.

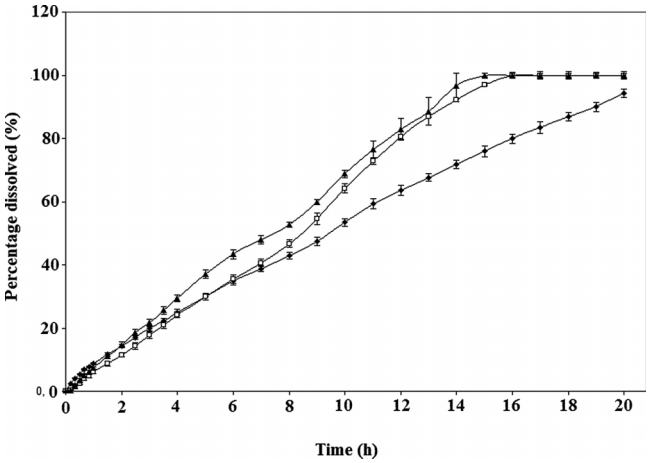

FIGURE 1. Dissolution profiles for 3-mm coated floating minitablets (CFMTs) composed according to C1–F1 and filled into a gelatin capsule, (▲) with or (□) without a disintegrating agent, or (◆) not filled into a capsule (apparatus II, 60 rpm, pH 3.0) (n = 5).

Effect of pH on Drug Release

Levodopa is a drug with a pH-dependent solubility that is characterized by four dissociation constants—pKa = 2.3, 8.7, 9.7, and 13.4 (Clarke, 1986). 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 (Goole et al., 2007). Then, the dissolution rates of levodopa from 3-mm CFMTs, in which the core was composed according to C1 and coated with F1, were evaluated at 50 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 (Russel et al., 1993).

At each of the three pH values, a SR of levodopa occurred immediately after immersion (Figure 2). Because of its

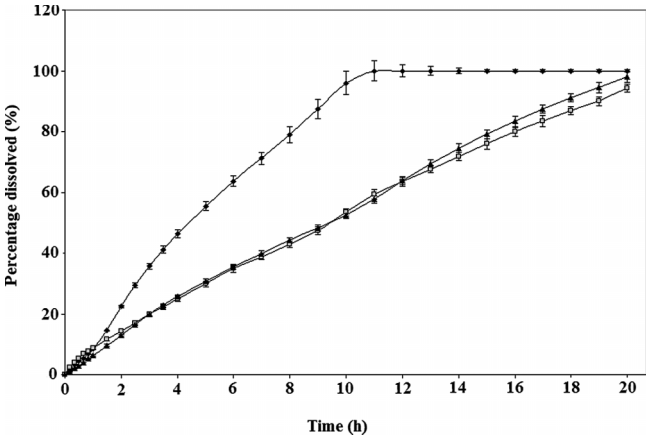

FIGURE 2. In vitro dissolution profiles of levodopa from 3-mm coated floating minitablets (CFMTs) composed according to C1–F1 at pH (◆) 1.5, (□) 3.0, and (▲) 6.5 (apparatus II, 60 rpm, pH 3.0) (n = 5).

pH-dependent solubility, the release of the drug was faster at pH 1.5 than at pH 3.0 and 6.5. Indeed, after 8 h, the dissolution profiles were already not statistically similar, for example, $f_{2(\text{pH } 1.5\text{–}6.5)} = 43.1$. On the contrary, the dissolution profiles remained statistically similar at pH 3.0 and 6.5 even after 20 h with a f_2 of 89.1. Based on these results, it would seem that the coating was not able to cancel out the pH-dependent solubility of levodopa. However, as a floating form has to be administered in fed condition to improve its floating capabilities (Moës, 1993), the CFMTs seem to be able to provide a constant SR of levodopa from the stomach in fed condition to the intestine.

Stirring Rate

According to the Noyes–Whitney equation, the dissolution rate of an active drug from a solid DF could be influenced by the agitation rate (Fukunaka et al., 2006). Thus, the susceptibility of a prolonged release DF to change in its SR ability in function of the stirring rate was considered as an indication of the robustness of the DF.

The effect of the stirring rate on the dissolution rate of levodopa from 3-mm CFMTs in which the core is composed according to C1 and coated with F1 was examined at pH 3.0. The release rate of the drug increased as the stirring rate increased (Figure 3) in accordance with the decrease in the thickness of the stagnant layer as described in the Noyes–Whitney equation. Even if an influence of the stirring rate on drug release was observed, a SR still occurred immediately after immersion and there was no early disintegration of the CFMTs (visually observed), regardless of the agitation rate, within the experimental period. Aside from this, no bimodal dissolution profile was observed. All dissolution profiles were statistically similar after 8 h—for example, $f_{2(50\text{–}100 \text{ rpm})} = 85.5$—and remained similar even after 20 h. These results showed that the dissolution rate depended more on the SR ability of the coating than on the stirring rate. Thus, it can be concluded that our CFMTs show a good robustness versus stirring rate modification.

Influence of pH on Floating Properties

As the influence of several dissolution parameters on the dissolution profile of levodopa was under investigation, the influence of pH on the floating lag time of the CFMTs was then investigated. The composition of the coating was kept constant and was F1 (Table 2). A pH value of 1.2 was obtained using HCl 0.1 N, whereas a pH value of 3.0 was obtained using a 0.05 M phosphate buffer. Both solutions contained 0.05% (wt/vol) Polysorbate 20.

The floating lag time of CFMTs in which the core was composed according to C1 was higher at pH 3.0 than at pH 1.2 and was 80 min, versus 10 min at the lowest pH value (Table 3) At pH 3.0, the amount of tartaric acid incorporated into the core was not high enough to quickly generate a sufficient amount of carbon dioxide to permit a fast floatation of the system.

The percentage of tartaric acid was then increased to 7 and 10% (wt/wt) in C2 and C3, respectively. The CFMTs floated after 60 and 40 min at pH 3.0 when the core contained 7 and 10% (wt/wt) of tartaric acid, respectively. At pH 1.2, the CFMTs floated within 10 min, regardless of the amount of tartaric acid incorporated into the core. Although the floating lag time decreased at pH 3.0 in both cases, they were still much higher than at pH 1.2.

The lowest floating lag time value obtained at pH 3.0 was achieved by incorporating 15% (wt/wt) of tartaric acid into the core and was similar to the floating lag time obtained at pH 1.2. Indeed, the CFMTs floated within 10 min and remained buoyant for more than 13 h, regardless of the pH value (Figure 4). Although the RW values were lower at pH 3.0 than at pH 1.2,

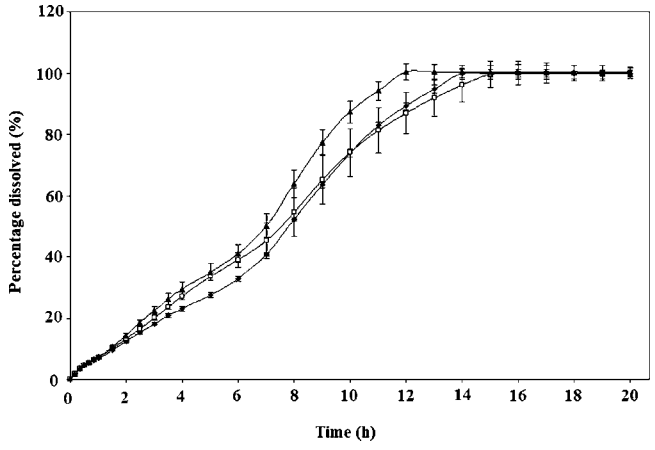

FIGURE 3. Influence of the stirring rate—(◆) 50 rpm, (□) 75 rpm, (▲) 100 rpm—on the levodopa release rate from 3-mm coated floating minitablets (CFMTs) composed according to C1–F1 at pH 3.0 ($n = 5$).

TABLE 3
Influence of pH on the Floating Lag Time of the Coated Floating Minitablets (CFMTs) in Function of the Amount of Tartaric Acid Incorporated into the Core ($n = 6$)

Composition No.	Amount of Tartaric Acid (%)	pH	Floating Lag Time (min)
C1	3	1.2	10 ± 2
		3.0	80 ± 15
C2	7	1.2	10 ± 2
		3.0	60 ± 13
C3	10	1.2	10 ± 1
		3.0	40 ± 8
C4	15	1.2	7 ± 1
		3.0	8 ± 2

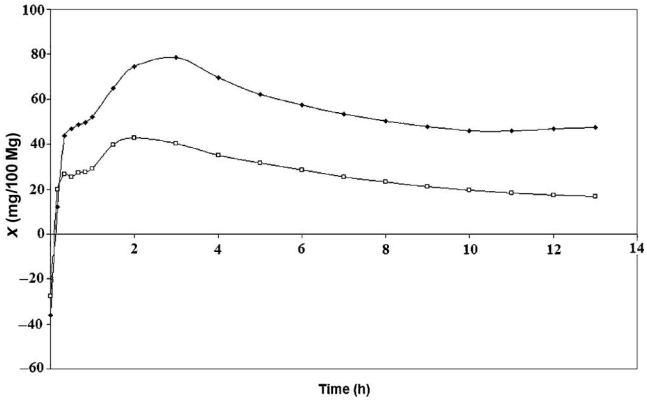

FIGURE 4. Resultant weight profiles obtained from coated floating minitablets (CFMTs) at pH (◆) 1.2, and (□) 3.0 (n = 1).

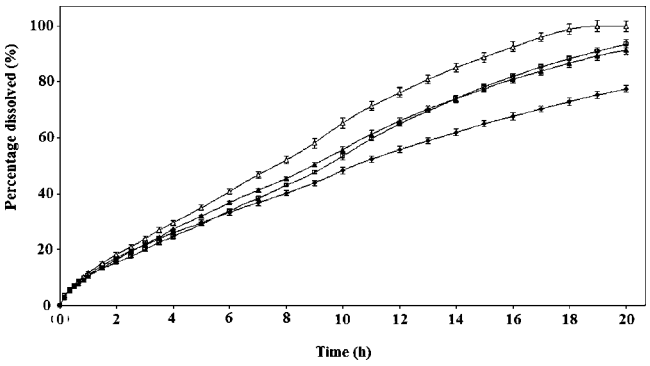

FIGURE 5. Influence of the amount of tartaric acid—(◆) 3.0%, (□) 7.0%, (▲) 10.0%, (△) 15.0% (wt/wt)—incorporated into the core on the release rate of levodopa from 3-mm coated floating minitablets (CFMTs) (apparatus II, 50 rpm, pH 3.0) (n = 5).

the RW profile obtained at pH 3.0 was nevertheless encouraging. Indeed, after 30 min, the RW values were never lower than 20/100 mg regardless of the pH, which were much higher values than those obtained with floating pellets (Hamdani, Moës, & Amighi, 2006). Moreover, the floating lag time of our CFMTs was lower than 10 min, and the CFMTs remained buoyant for more than 13 h as several other floating systems described in the literature and for which the good floating properties obtained in vitro were assessed in vivo (Baumgartner, Kristl, Vrecer, Vodopivec, & Zorko, 2000; Iannuccelli, Coppi, Bernabei, & Cameroni, 1998b; Whitehead, Fell, Collett, Sharma, & Smith, 1998; Xiaoqiang, Minjie, Feng, & Yiqiao, 2006). These floating systems have shown a prolonged gastric residence time and plasmatic concentration profiles corresponding to a SR ability of the administered DF. In this way, the present CFMTs will be selected to be evaluated in vivo to assess the results obtained in vitro.

Influence of the Amount of Tartaric Acid Incorporated Into the Core on Dissolution Profile

As it has been demonstrated, levodopa is characterized by a pH-dependent solubility. In that regard, the amount of tartaric acid incorporated into the core would influence its release rate. Dissolution tests were performed on 3-mm CFMTs coated with F1 at pH 3.0, 50 rpm.

The release rate of the drug increased with an increase of the amount of tartaric acid incorporated into the core (Figure 5). Indeed, by incorporating 15% (wt/wt) of tartaric acid, the entire dose of levodopa was released after 18 h versus 70% within more than 20 h when the percentage of tartaric acid reached 3% (wt/wt). In our case, an increase of the release rate is useful. Indeed, as levodopa is characterized by a NAW in the upper part of the small intestine (Rouge, Buri, & Doelker, 1996), the amount of active drug unreleased above the absorption zone is not absorbed, diminishing the efficacy of the administered dose.

CONCLUSION

In a previous study (Goole et al., 2008), a new coated multiple-unit floating system was developed. In this study, the most successful formulation was evaluated and its floating capabilities were improved. The CFMTs floated within 10 min and remained buoyant for more than 13 h, regardless of the pH (1.2 or 3.0). The floating properties were not influenced by the pH. The release rate of levodopa increased when the CFMTs were filled into a capsule. However, the coating did not show any sign of cracking as the dissolution profiles remained unimodal during the whole period of the test. The coating was not able to cancel out the pH-dependent solubility of levodopa. However, as the dissolution profiles of levodopa were statistically similar at pH 3.0 and 6.5, it seems that in vivo, the CFMTs would be able to provide a constant release of the active drug from the stomach in fed condition to the intestine. Their robustness under varying stirring rates was also demonstrated. In addition to their very simple composition and manufacturing process, their ability to sustain the drug release for more the 12 h and their high RW values have shown the potential novelty of these new CFMTs. In the near future, pharmacoscintigraphic studies will be conducted on these CFMTs to complete the results obtained in vitro.

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