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European Journal of Pharmaceutics and Biopharmaceutics 68 (2008) 310–318
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

New levodopa sustained-release floating minitablets coated with insoluble acrylic polymer

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Received 16 May 2007; accepted in revised form 29 June 2007
Available online 6 July 2007

Abstract

The aim of this study was to develop a new coated multiple-unit sustained-release floating system that is able to float over an extended period of time. Levodopa was used as a model drug. The system consisted of a 3 mm drug-containing gas-generating core, prepared by melt granulation and subsequent compression, and coated with a flexible polymeric membrane. Eudragit® RL30D and ATEC were used as a film former and a plasticizer, respectively. The coating level was fixed at 20% (w/w). The floating lag time decreased as the proportion of effervescent agents increased. The optimized coated floating minitablets could float within 20 min and remained buoyant for more than 13 h. In addition, a sustained release of levodopa for more than 20 h was observed.

Keywords: Multiple-unit system; Minitablets; Floating; Sustained release; Coating; Eudragit® RL30D; Levodopa

1. Introduction

Gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations connected with gastric emptying time. In fact, variable and too rapid gastrointestinal transit can result in incomplete drug release above the absorption zone. This leads to diminished efficacy of the administered dose, especially for drugs that are absorbed to the greatest extent in the upper part of the small intestine [1].

Because of this, Levodopa (L-dopa) was chosen as a model drug for the development of a floating sustained release (SR) delivery system with prolonged gastric residence time (GRT). Moreover, as L-dopa is characterized by a relatively short elimination plasma half-time ($t_{1/2} = 1$ h) [2], a slow-release formulation could reduce fluctuations in the therapeutic effect and so improve its clinical efficacy [3].

Among the various attempts made to increase the retention of an oral dosage form [1,4–7], it seems that floating systems offer the most effective and rational protection against early and random times of gastric emptying. In comparison to the single-unit systems, which are characterized by an all-or-nothing process, the multiple-unit dosage forms have been shown to reduce inter- and intra-subject variability [8]. Moreover, they have also shown a more reproducible GRT and have offered a better dispersion throughout the gastrointestinal tract, lowering the possibility of mucosal damage [9].

In a previous work [10], floating minitablets (FMT) containing gas-generating agents were developed. The generated gas was trapped in a swellable hydrocolloid that was also able to control drug release. However, only 46% (w/w) drug could be incorporated into the minitablets due to the high amount of gel-forming polymer required to obtain good floating properties. The same problem was observed with floating pellets developed by Hamdani et al. [11] and

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doi:10.1016/j.ejpb.2007.06.017

the floating pills developed by Ichikawa et al. [12] in which only 40% (w/w) and 23% (w/w) of active drug could be incorporated, respectively. In order to increase the incorporated amount of the active drug, a coating can be used instead of a gel-forming polymer both to trap the generated carbon dioxide and to sustain the release of the drug.

The present study relates to the development of L-dopa SR granulates prepared by melt granulation and compressed into minitablets (MT). These MT, comprising only L-dopa, Precirol® ATO and effervescent compounds, were then coated with a water-insoluble acrylic polymer, Eudragit® RL30D in order to obtain FMT. Both the melt granulation and the fluidized-bed coating processes are very easy, short manufacturing processes that can be easily scaled up. Other coated multiple-unit floating sustained release systems are already described in the literature [12,13]. 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 to the other sophisticated multiple-unit floating systems described before in the literature [1,7,14], our coated FMT (CFMT) are based on a very simple composition, can contain a high amount of active drug and show applicability for industrialization.

The objective of this work was to investigate the effects of manufacturing parameters – such as the core diameter, the core composition and the level and formulation of the coating – on the CFMT floating capability and the L-dopa release rate in order to design the most suitable form for a future in vivo study. The aim was to optimize and select a dosage form that would be able to provide a low floating lag time value, a long floating duration and a constant sustained release of L-dopa.

2. Materials and methods

2.1. Materials

Levodopa (Newsmart, China) was used as a model drug. Glyceryl palmitostearate (Precirol® ATO 5 = Gelucire® 52/02), supplied by Gattefosse (France), was used as a meltable binder. Tartaric acid (Federa, Belgium), sodium bicarbonate (Merck, Germany) and calcium carbonate (Welpher, Belgium) were employed as carbon dioxide-generating agents. Lactose 450 mesh (DMV Int., Netherlands) was used as hydrophilic diluent.

The insoluble polymer used to make the gas-trapping membrane was Eudragit® RL30D (in the form of an aqueous colloidal dispersion of poly(ethylacrylate-methylmethacrylate-trimethylammoniumethyl-methacrylate chloride), Rhöm Pharma, Darmstadt, Germany). Citroflex 2® (triethyl citrate) and Citroflex A2® (acetyl triethylcitrate), used as plasticizers, were supplied by Reilly, Belgium. Talc with a mean particle size of approximately 10 μm (Aldrich Chemical Co. Ltd., England) and antifoam emulsion (silicone emulsion, Vel. S.A. Belgium) were used as received.

2.2. Methods

2.2.1. Preparation of the 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 [15]. 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 reached sufficiently high values to soften the binder, the torque increased due to granule formation [10]. The IS was reduced to 600 rpm after the granule formation step in order to avoid any further product temperature increase, while the CS was increased to 1000 rpm to break any 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 granules were cooled at ambient temperature.

The volume size distribution of the granulates was measured with a Mastersizer 2000 Laser Diffractometer in dry powder 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. Minitablets preparation. MT were prepared by direct compression. Granules were fed manually into the die of an instrumented single-punch tableting machine (Korch, Germany) to produce MT using concave-faced punches and dies. The compression forces, the weight and the

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

Composition No.	C1	C2	C3	C4	C5
Levodopa	37.5	37.5	37.5	25.0	68.0
Precirol® ATO5	12.0	12.0	12.0	12.0	12.0
$CaCO_3$	10.0	5.0	1.7	10.0	10.0
$NaHCO_3$	4.0	4.0	1.4	4.0	4.0
Tartaric acid	3.0	3.0	1.0	3.0	3.0
Lactose 450 mesh	33.5	38.5	46.4	46.0	3.0
Diameter (mm)		3		4	
Weight (mg)		20		40	
Compression forces (N)		50–100		2000–3000	
Hardness (N) ($n = 10$)		5 ± 1		22 ± 3	

hardness for each diameter of the MT 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 0.11 ± 0.02%. This indicated that they were able to withstand the mechanical stress of the subsequent coating process.

2.2.1.3. Preparation of the coating dispersion. The different aqueous dispersions used for the coating of the MT are 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). Dispersions containing Eudragit® RL30D require the addition of 20% (w/w) (relative to film former content) of plasticizing agent. The plasticizer was added to the polymer aqueous dispersions 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.

2.2.1.4. Preparation of the coated MT. MT were transferred into a fluidized-bed coating apparatus (Uni-Glatt®, Glatt GmbH, Germany) equipped with a bottom-spray coating process in a Würster column and coated with the coating dispersions 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 and 35 ± 2 °C, respectively; flow rate, 6 g/min; pneumatic air pressure, 1 bar. After coating, the coated MT were further fluidized for 10 min and subsequently cured at 60 °C for 8 h [16,17].

2.2.2. Determination of the physicochemical properties of FMT

2.2.2.1. In vitro evaluation of floating capabilities. The CFMT ($n = 3$) were placed in 70 ml of 0.1 N HCl solution containing 0.05% (w/v) Polysorbate 20 (pH 1.2, 37 °C), and were then subject to 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 CFMT, 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 Timmermans [18] 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 will sink. CFMT were placed in a specially designed basket sample holder that was immersed in 1200 ml of preheated 0.1 N HCl solution containing 0.05% (w/v) Polysorbate 20 (pH 1.2, 37 °C). The RW was measured every minute for 13 h ($n = 1$).

Table 2
Formulations used for the coating of levodopa CFMT

Formulation	F1	F2
Eudragit® RL30D (g) (dry basis)	200	200
TEC (g)	40	–
ATEC (g)	–	40
Talc (g)	50	50
Antifoam (g)	2	2
Water (g)	842	842
Solid content (% w/w)	25.6	25.6
Coating level (%)	12–15–20	20

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. Dissolution tests were performed in a dark room to avoid possible drug alteration. The rotational speed employed was 50 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 3.0. 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/visible 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 FDA's Guidances for Industry, the similarity factor f_2 was used to determine the similarity of dissolution profiles [19,20]. The compared dissolution profiles were obtained under the same test conditions and their dissolution time points were the same, e.g. for the controlled release products, they were 1, 3, 5 and 8 h. As indicated by Shah et al. [20], 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. Design of the coated floating minitablets

In order to develop the desired sustained-release CFMT, it was necessary to optimize both the floating properties and the release rate of the drug from the system. In a previous study [10], Methocel® K15M was used both to trap the carbon dioxide generated from the effervescent components and to provide a sustained release of the drug. In the present study, the generated gas was retained by a flexible polymeric membrane that was also able to sustain the release of the drug. An ideal coating material for a floating system should be highly water-permeable in order to initiate rapidly the effervescent reaction and the subsequent floating process [13]. However, the hydrated coating should also, to some extent, be impermeable to the generated carbon dioxide

so as to promote and maintain floatation [21]. Moreover, the polymer should be sufficiently impermeable to the active drug to obtain a sustained release. Eudragit® RL30D was selected over other polymers – Eudragit® RS30D, NE30D – (data not shown) as the film former polymer in the gas-entrapped flexible polymeric membrane because of its higher water permeability. To trap the generated gas, the hydrated coating must not adhere to the core; therefore, hydroxypropylmethylcellulose was not incorporated in the formulations as a binder (Table 2). To develop the optimized CFMT, several studies had to be conducted in order to identify and establish the formulation variables that provided the desired system properties. The influence of the core composition, the core diameter, the coating level and coating composition on the floating ability of the CFMT and drug release of levodopa was thus evaluated.

3.2. Influence of the core composition on drug release and floating behaviour

The amount of levodopa and lipidic binder was kept constant at 37.5% (w/w) and 12.0% (w/w), respectively (Table 1). Only the level of the effervescent components incorporated into the core was modified to evaluate its influence on the release rate and the floating properties. The influence of the core composition on the dissolution profile was evaluated for the 4 mm CFMT coated with the coating dispersion F1 (Table 2). The coating level was fixed at 12% (w/w). The CFMT in which the core was composed of C1 (Table 1) provided a sustained release of levodopa immediately after immersion (Fig. 1a). It has to be noted that no lag time was observed on the dissolution profile. This was probably due to the large surface area provided by the MT and the high water permeability of the film former polymer Eudragit® RL30D. In the time interval of 9 h, a constant sustained release occurred and only 30% of the incorporated drug was released. After then, the release rate of the drug showed an increase that could be attributed to the presence of small cracks on the surface of the film (bubbles of gas diffusing through the coating were visually observed – data not shown). Indeed, it is thought that the coating level is not high enough to withstand the pressure of the generated carbon dioxide and avoid cracking after a period of 9 h. However, based on the low values of the standard deviations observed throughout the period of the test, it has to be noted that the appearance of the cracks was sufficiently reproducible to provide a bimodal dissolution profile. The level of the effervescent components incorporated into the core was then decreased to 12.0% (w/w) and 4.1% (w/w) in C2 and C3, respectively, in order to reduce the pressure applied on the membrane by the generated carbon dioxide. Even though a sustained release of the active drug occurred immediately after immersion, the decrease of the level of carbon dioxide-generating agents did not eliminate the cracking of the coating that still occurred

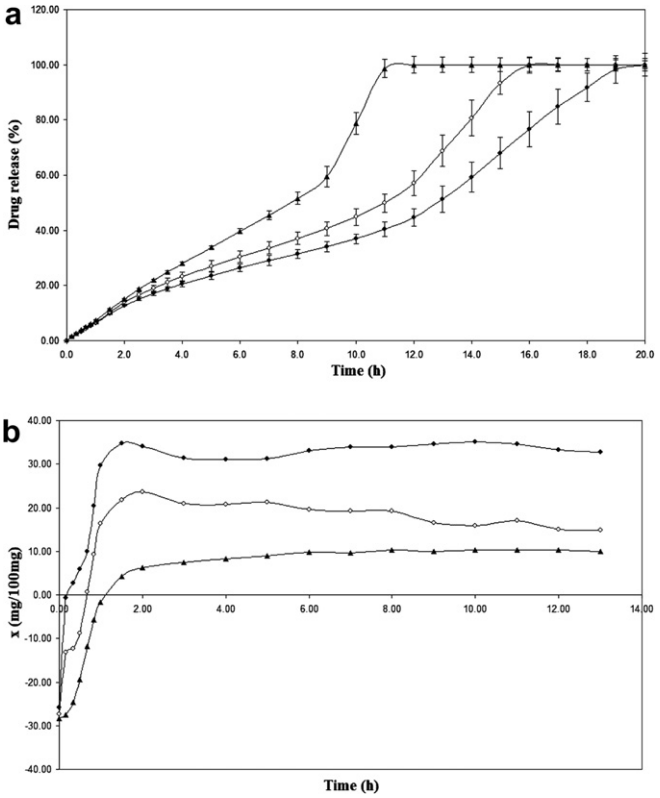

Fig. 1. Influence of the core composition – (●) C1, (○) C2, (▲) C3 – on (a) the drug release at pH 3.0, 50 rpm ($n = 5$) and (b) the floating properties using the RW method ($n = 1$) for 4 mm CFMT coated with F1 (12% w/w).

after a period of 9 h regardless of the composition of the core. However, even if the dissolution profiles remained statistically similar during the first 9 h period (e.g. the lowest f_2 value was 59.0), the drug release tended to be slower with increasing amounts of effervescent agents. A faster and higher carbon dioxide generation caused by the increase of the level of effervescent agents incorporated into the core resulted in a higher distortion of the membrane and subsequent prolongation of the drug release as the distance between the core and the coating was thus increased.

Besides the effect of the level of effervescent agents on drug release, its influence on floating properties was also evaluated using the RW method (Fig. 1b). The lag time values increased as the level of effervescent agents decreased and were 20, 40 and 90 min for C1, C2 and C3, respectively. A higher amount of effervescent agents caused a faster and higher carbon dioxide generation [21]. The maximal RW values also decreased with decreasing levels of gas-generating agents and were about 30, 20 and 10 mg/100 mg for C1, C2 and C3, respectively. However, regardless of the core composition, all the CFMT floated for more than 13 h. The lag time values and the total floating durations were corroborated by the horizontal shaking method, which also showed that the CFMT remained buoyant for 24 h.

As C1 showed the better floating properties in terms of lag time and maximal RW value, it was selected to evaluate the influence of the core diameter on the drug release and floating properties of the CFMT.

3.3. Influence of the core diameter

The 4 mm CFMT provided a very slow release of the active drug. A simple and practicable way to modify the drug release kinetic from solid dosage forms was to change their diameters. In fact, the release rate of the drug increased as the core diameter decreased. Dissolution tests, performed with C1-CFMT (Table 1) coated with F1 (12% w/w) (Table 2), showed a faster dissolution rate for the 3 mm CFMT than for the 4 mm CFMT (Fig. 2a). The 3 mm CFMT showed, during the first 4 h of the test, a constant sustained release, with 27% of the active drug being released versus release of 20% for the 4 mm. This observation can be attributed to the higher relative surface area of the dosage form when the CFMT diameter decreased, which gave a greater area of contact between the CFMT and the dissolution media. However, as in the case of the 4 mm CFMT after 9 h, the release rate of the drug sharply increased after a period of 4 h, probably due to partial rupturing of the coating. The entire dose of levodopa was released after 11 h. It was noted that, even after the rupturing of the coating, a sustained release could be observed, certainly due to the presence of the lipidic binder and to the granulated form.

The RW measurements showed that the lag time values increased with increased diameter and were 7 and 20 min for the 3 and 4 mm CFMT, respectively (Fig. 2b). After a period of 5 h, the 3 and 4 mm CFMT had the same RW value, which was about 30 mg/100 mg. After that, the RW values of the 3 mm CFMT decreased, while those corresponding to the 4 mm did not. This could be explained by the greater surface area provided by the smaller diameter, which facilitated the dissolution of the membrane.

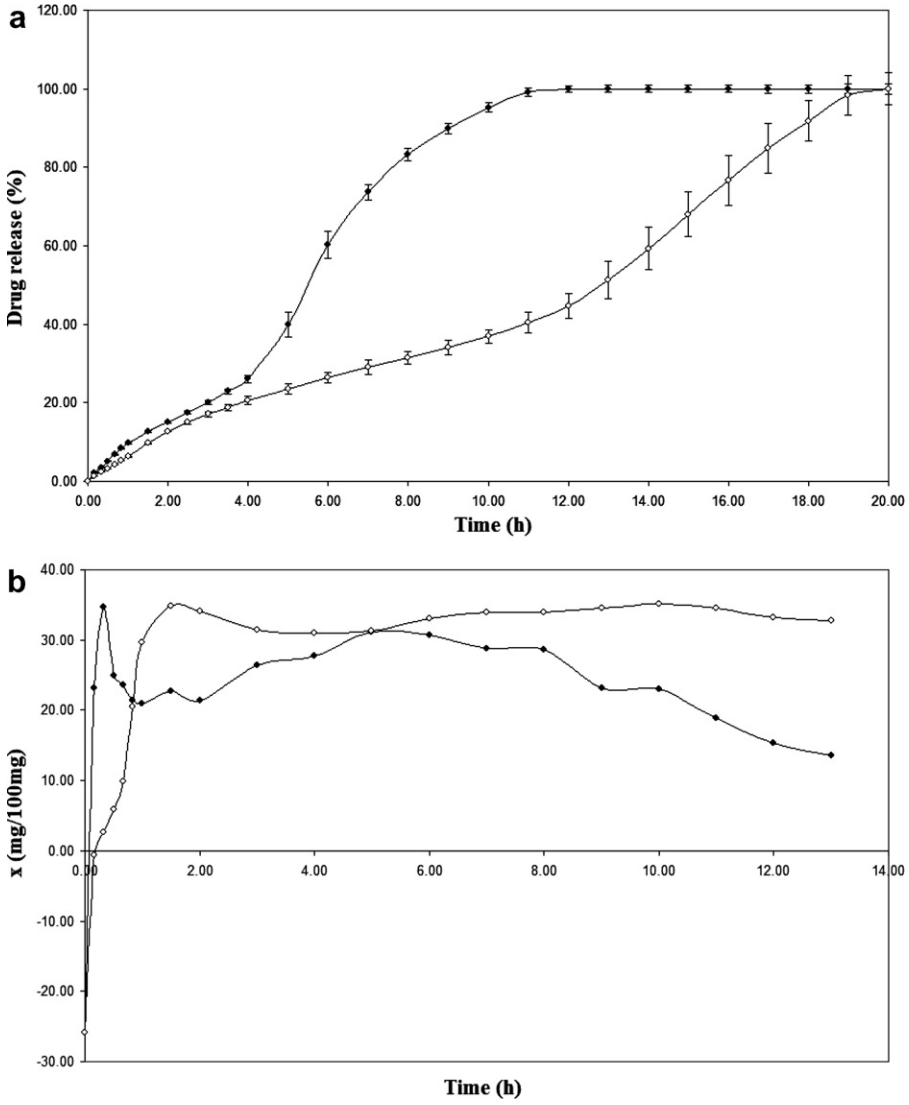

Fig. 2. Influence of the diameter – (●) 3 mm, (○) 4 mm – on (a) the drug release at pH 3.0, 50 rpm ($n = 5$) and (b) the floating properties using the RW method ($n = 1$) for CFMT using C1 coated with F1 (12% w/w).

As the 3 mm CFMT showed the highest RW values in the first hours of the RW test and as they seemed able to provide a faster release of the active drug, this diameter was selected to evaluate the influence of the coating level on the drug release and the floating properties.

3.4. Influence of the coating level

As shown, a coating level of 12% (w/w) was not able to provide a constant sustained release of the drug throughout the whole length of the dissolution tests, regardless of the composition and the diameter of the core. A constant sustained release was sought that would last for a period of time that would be at least similar to the floating duration. The influence of the coating level was evaluated for the 3 mm C1-CFMT (Table 1) coated with F1 (Table 2).

The drug release decreased with increasing coating levels, which ranged from 0% (w/w) to 20% (w/w) (Fig. 3a). A higher membrane thickness slowed water penetration, resulting in a decrease in drug release [21]. In the absence of a coating, the integrity of the MT was not maintained. The entire dose of levodopa was released after 2 h. The slight sustained-release properties observed for the composition without coating were due to the presence of the lipidic binder incorporated into the granules. Even with a coating level of 15% (w/w), the release rate of the drug sharply increased after 4 h, resulting in 100% of drug being dissolved after 11 h. A constant release only occurred during the whole length of the test with a coating level of 20% (w/w). No release lag time was observed and 75% of the entire dose of levodopa was dissolved after 20 h.

An increase in the coating level slightly affected the floating properties of the CFMT (Fig. 3b). Indeed, the lag time values were 5, 7 and 10 min with coating levels of 12% (w/w), 15% (w/w) and 20% (w/w), respectively. Moreover, while the RW values slowly decreased after 5 h with coating levels of 11% (w/w) and 15% (w/w), the RW values corresponding to a coating level of 20% (w/w)

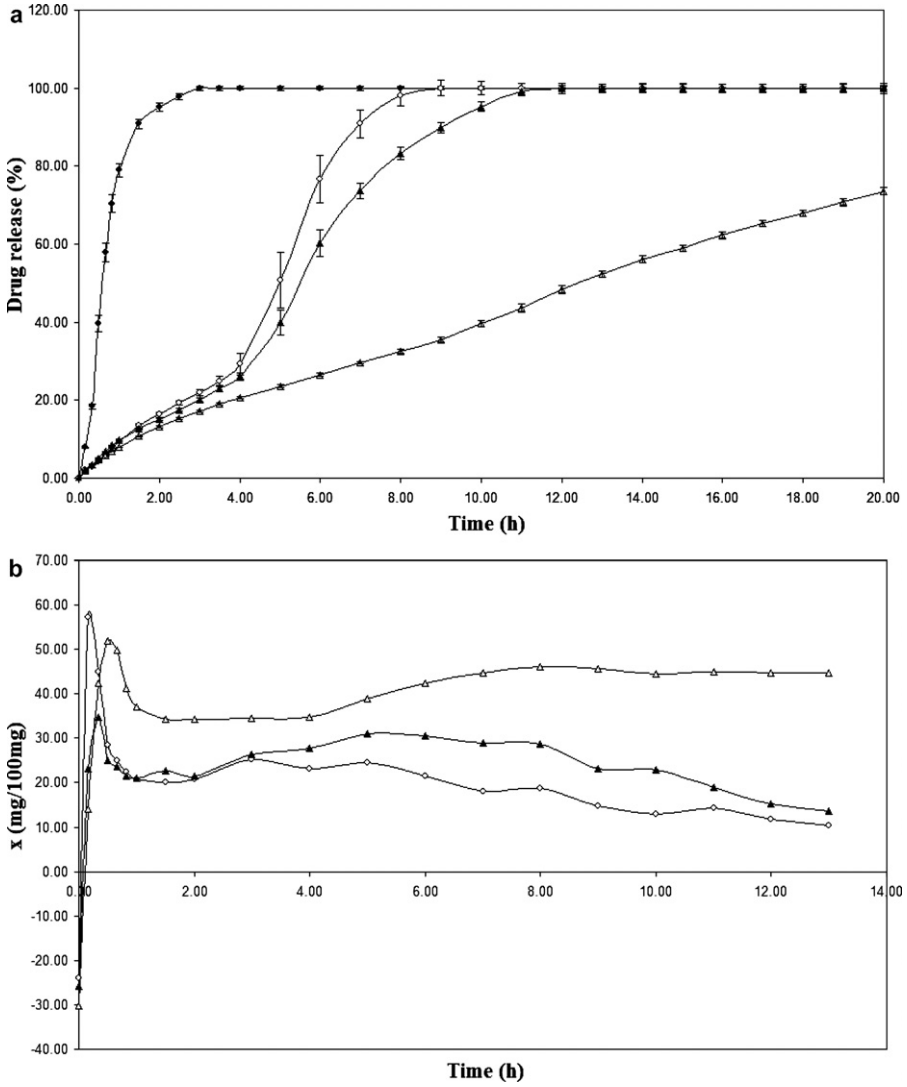

Fig. 3. Influence of the coating level – (●) 0% (w/w), (○) 12% (w/w), (▲) 15% (w/w), (Δ) 20% (w/w) – on (a) the drug release at pH 3.0, 50 rpm ($n = 5$) and (b) the floating properties using the RW method ($n = 1$) of 3 mm CFMT using C1 coated with F1.

did not (40–50 mg/100 mg). The coating level was high enough to preserve the same floating magnitude for 13 h. The horizontal shaking method showed that the total floating duration was at least 24 h.

The 3 mm C1-CFMT coated with F1 provided a 20-h constant sustained release of levodopa and good floating properties when the coating level reached 20% (w/w). However, it could be useful to accelerate the drug release to dissolve the entire dose of the active drug within the floating duration of the CFMT.

3.5. Influence of the plasticizer

Plasticizers are often added to improve the mechanical properties of the polymeric films, such as the flexibility or distensibility of the polymeric material. The permanence of the plasticizer in the coating under wet conditions depends primarily on its solubility in water and its affinity for the polymer [22]. It has been shown that the higher proportion of quaternary ammonium groups in Eudragit® RL films leads to a fast hydration and leaching of the plasticizer used in the film composition [22]. It could thus be useful to incorporate a less soluble plasticizer than TEC in the CFMT under investigation. ATEC was therefore tested since it presents a water solubility of 0.7 g/100 ml at room temperature compared to TEC, which presents a higher water solubility of 7 g/100 ml [23]. The effect of the plasticizer was evaluated on the 3 mm C1-CFMT (Table 1) coated either with F1 or F2 using a coating level of 20% (w/w) (Table 2). The release rate was increased by incorporating ATEC (Fig. 4a). Indeed, 95% of the entire dose of levodopa was released within 20 h instead of the 75% achieved using TEC. As the less soluble plasticizer remained inside the coating for a longer period of time, the flexibility of the film became greater. The distortion of the membrane thus increased as the generated gas remained inside the dosage form for a longer period of time. This phenomenon seemed to increase the

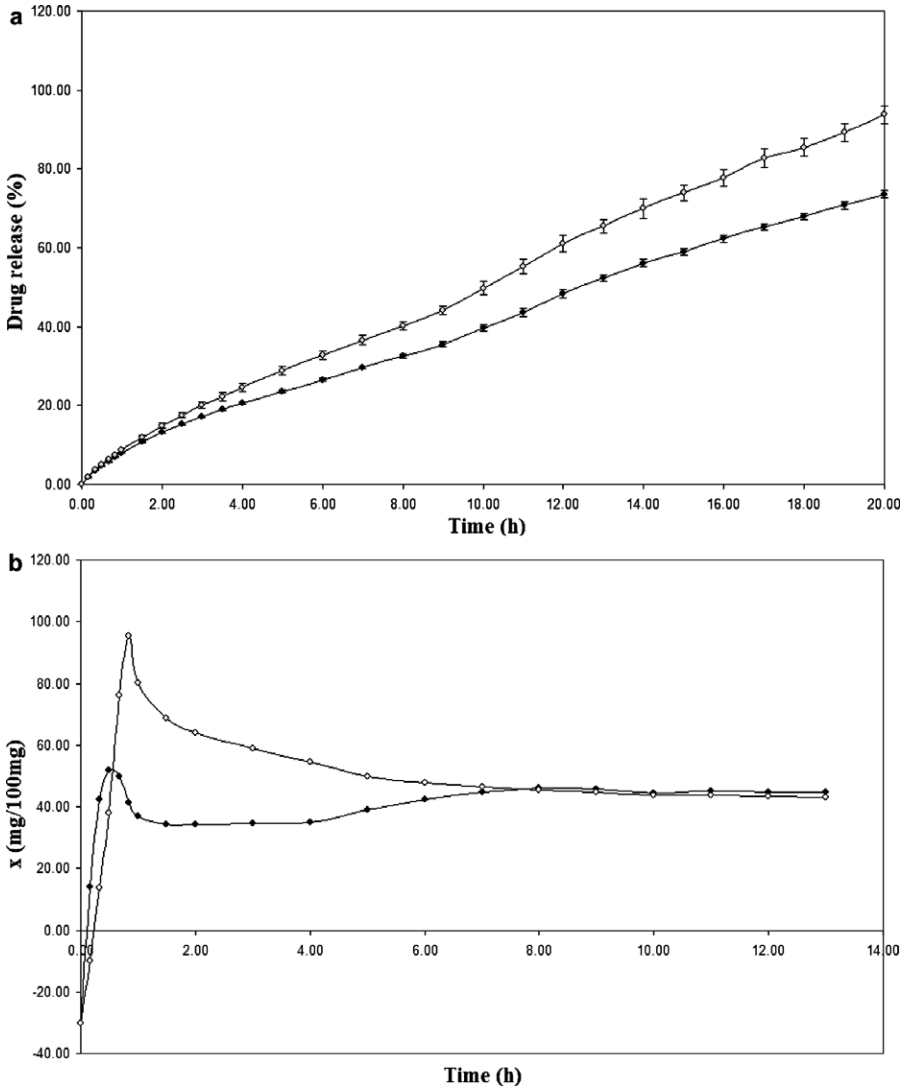

Fig. 4. Influence of the plasticizer – (●) TEC, (○) ATEC – on (a) the drug release at pH 3.0, 50 rpm ($n = 5$) and (b) the floating properties using the RW method ($n = 1$) of 3 mm CFMT using C1 coated with F1 and F2 (20% w/w).

release rate of the drug while the integrity of the dosage form was still preserved. It should be noted that our minitablets sustained the release of the active drug for a longer period of time than several other multiple-unit floating dosage forms. Indeed, the floating minitablets containing a gel-forming polymer sustained the release of the drug for only 9 h due to the erosion process [10]. Using the same percentage of lipidic binder, floating pellets released the entire dose of the active drug within a period of less than 4 h, probably due to the greater surface area [11]. The bi-layered coated pills sustained the release of the drug for no more than 12 h, probably due to the lower coating level, which was 5% (w/w) instead of 20% (w/w) in this case [13].

The RW measurement showed that the lag time increased from 10 to 20 min when ATEC was used as the plasticizer instead of TEC (Fig. 4b). The polymeric membrane became less water-permeable when ATEC was incorporated, resulting in a higher lag time value due to a delay in the generation of carbon dioxide. However, the RW values increased from 40 min to 7 h when ATEC was incorporated instead of TEC. The higher flexibility of the membrane seemed to improve floating strength. After 30 min, the RW values were never lower than 40 mg/100 mg, which were much higher values than those obtained with floating pellets [11].

3.6. Influence of the amount of the active drug incorporated into the core

As has been explained, a coating step was used both to trap the generated carbon dioxide and to sustain the release of levodopa (replacing the use of a swelling agent) to allow incorporation of more active drug into the dosage form. The amount of lipidic binder and effervescent agents was kept constant at 12% (w/w) and 17% (w/w), respectively (Table 1). Only the level of levodopa incorporated into the core was modified to evaluate its influence on the release rate and the floating properties: this was 25.0% (w/w), 37.5% (w/w) and 68.0% (w/w) in C1, C4 and C5, respectively. The influence of the amount of levodopa incorporated into the core on the dissolution profile was evaluated for the 3 mm CFMT coated with the coating dispersion F2 (Table 2). The coating level was kept constant at 20% (w/w). Regardless of the amount of levodopa incorporated into the core, a sustained release occurred immediately after immersion without any lag time and the integrity of the coating was preserved, as no change in the release rate was observed during the whole period of the test (Fig. 5). However, the dissolution profile was more sustained when the incorporated amount of levodopa increased from 25.0% (w/w) to 68.0% (w/w). This was probably due to the decrease in the number of minitablets immersed in the dissolution baths as a consequence of the increase in the incorporated amount of levodopa. Indeed, by increasing the level of levodopa incorporated into the core, a lower number of CMFT was needed to give 150 mg of drug. A decrease in the number of minitablets involved a lower area of contact between the CFMT and the dissolution media, decreasing the release rate of the drug as a consequence.

On the other hand, the floating properties of the CFMT did not change with modification of the level of levodopa (data not shown). The floating lag time and the resultant-weight values remained similar regardless of the amount of the active drug incorporated into the core. As the level of the gas-generating agents and the nature of the film-forming polymer did not change, the carbon dioxide-generation process and the subsequent floating properties did not change either.

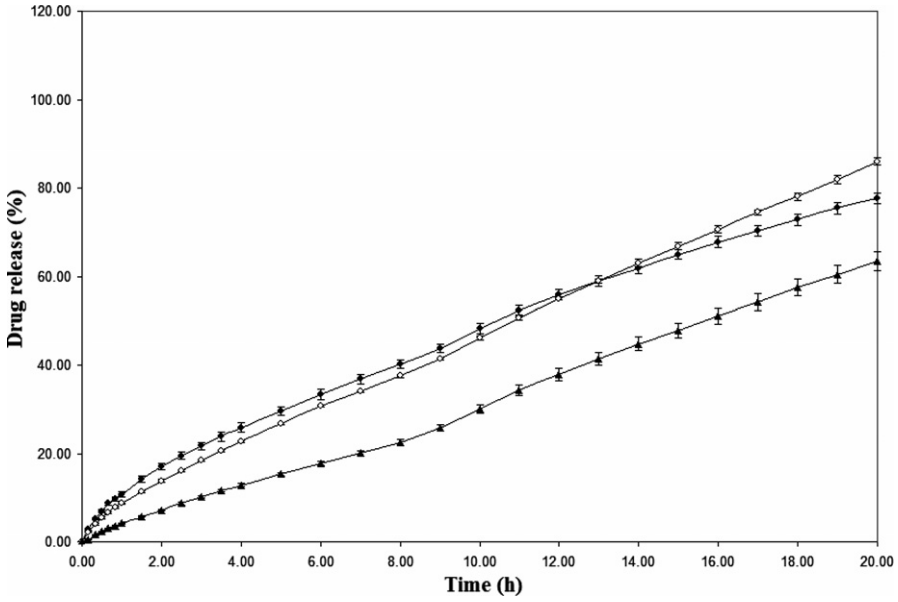

Fig. 5. Influence of the amount of levodopa incorporated into the core – (●) 25.0% (w/w), (○) 37.5% (w/w), (▲) 68.0% (w/w) – on the drug release at pH 3.0, 50 rpm ($n = 5$) of 3 mm CFMT coated with F2 (20% w/w).

4. Conclusion

In conclusion, a new coated multiple-unit floating system based on a very simple composition was developed. The system consisted of an effervescent drug-containing core, made by melt granulation and subsequent compression, coated with a polymeric membrane. The floating ability and the drug release properties of the system were dependent on the composition and the diameter of the core but also on the composition of the coating and the coating level. The most successful formulation was a 3 mm MT that contained variable and rather high percentages of drug, 12% of meltable binder and 17% of carbon dioxide-generating agents and that was coated with a flexible polymeric membrane. Indeed, as modification of the level of levodopa incorporated into the core did not change the floating properties but did change the dissolution profiles, it became possible to modulate the release rate of the active drug. Eudragit® RL30D and ATEC were selected as a film former and a plasticizer, respectively. The coating level was fixed at 20% (w/w). These CFMT floated after 20 min and remained buoyant for more than 13 h. In addition to their very simple composition and manufacturing process, their ability to sustain the drug release for more than 20 h and their high resultant-weight values have shown the potential novelty of these new coated floating minitablets.

In the near future, the influence of some of the dissolution parameters on the dissolution profile of levodopa from these CFMT will be examined in order to evaluate their robustness. Moreover, in vivo pharmacoscintigraphic studies on human volunteers will be conducted to validate the experimental results obtained in vitro.

References

[1] V. Ianuccelli, G. Coppi, M.T. Bernabei, R. Cameroni, Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study, Int. J. Pharm. 174 (1998) 47–54.
[2] Clarke's Isolation and Identification of Drugs in Pharmaceutics, Body Fluids, and Post-Mortem Material, second ed., The Pharmaceutical Press, London, 1986.
[3] F. Stocchi, N.P. Quinn, L. Barbato, P.N. Patsalos, M.T. O'Connel, S. Ruggieri, C.D. Mardsen, Comparison between a fast and a slow release preparation of levodopa and combination of the two: a clinical and pharmacokinetic study, Clin. Neuropharmacol. 17 (1994) 38–44.
[4] A.J. Moës, Gastroretentive dosage forms, Crit. Rev. Ther. Drug Carrier Syst. 10 (1993) 143–195.
[5] N. Talwar, H. Sen, J.N. Staniforth, Orally administered controlled drug delivery system providing temporal and special control, US patent 6,261,601 (2001).
[6] E.A. Klausner, E. Lavy, M. Friedman, A. Hoffman, Expandable gastroretentive dosage forms, J. Control. Release 90 (2003) 143–162.
[7] Y. Sato, Y. Kawashima, H. Takeuchi, H. Yamamoto, In vitro and in vivo evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans, Int. J. Pharm. 275 (2004) 97–107.
[8] S.-J. Hwang, H. Park, K. Park, Gastric retentive drug-delivery systems, Crit. Rev. Ther. Drug Carrier Syst. 15 (1998) 243–284.
[9] B.N. Singh, K.H. Kim, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, J. Control. Release 63 (2000) 235–259.
[10] J. Goole, F. Vanderbist, K. Amighi, Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms, Int. J. Pharm. 334 (2007) 35–41.
[11] J. Hamdani, A.J. Moës, K. Amighi, Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization, Int. J. Pharm 322 (2006) 96–103.
[12] M. Ichikawa, S. Watanabe, Y. Miyake, A new multiple-unit oral floating dosage system. I. Preparation and in vitro evaluation of floating and sustained-release characteristics, J. Pharm. Sci. 80 (1991) 1062–1066.
[13] S. Sungthongjeen, O. Paeratakul, S. Limmatvapirat, S. Puttipipatkhachorn, Preparation and in vitro evaluation of a multiple-unit floating drug delivery system based on gas formation technique, Int. J. Pharm 324 (2006) 136–143.
[14] A. Streubel, J. Siepmann, R. Bodmeier, Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release, Eur. J. Pharm. Sci. 18 (2003) 37–45.
[15] J. Hamdani, A.J. Moës, K. Amighi, Development and evaluation of prolonged release pellets obtained by the melt pelletization process, Int. J. Pharm. 245 (2002) 167–177.
[16] K. Amighi, A.J. Moës, Evaluation of thermal and film forming properties of acrylic aqueous polymer dispersion blends: application to the formulation of sustained-release film coated theophylline pellets, Drug Dev. Ind. Pharm. 21 (1995) 2355–2369.
[17] K. Amighi, A.J. Moës, Influence of curing conditions on the drug release rate from Eudragit NE30D film coated sustained-release theophylline pellets, S.T.P. Pharma Sci. 7 (1997) 141–147.
[18] J. Timmermans, A.J. Moës, Measuring the resultant-weight of an immersed test material. I. Validation of an apparatus and a method dedicated to pharmaceutical applications, Acta Pharm. Technol. 36 (1990) 171–175.
[19] Guidance for Industry, Extended Release Oral Dosage Form: Development Evaluation, and Application of In Vitro/In Vivo correlations, September 1997, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.
[20] V.P. Shah, Y. Tsong, P. Sathe, J-P Liu, In vitro dissolution profile comparison-statistics and analysis of the similarity factor f_2, Pharm. Res. 15 (1998) 889–896.
[21] I. Krögel, R. Bodmeier, Floating or pulsatile drug delivery systems based on coated effervescent cores, Int. J. Pharm. 187 (1999) 175–184.
[22] R. Bodmeier, O. Paeratakul, Leaching of water-soluble plasticizers from polymeric films prepared from aqueous colloidal polymer dispersions, Drug Dev. Ind. Pharm. 18 (1992) 1865–1882.
[23] J.C. Gutiérrez-Rocca, J.W. McGinity, Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers, Int. J. Pharm. 103 (1994) 293–301.