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Development and in vitro evaluation of a novel floating multiple unit dosage form obtained by melt pelletization

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Abstract

The feasibility of preparing floating pellets by melt pelletization was investigated. The pellets were prepared in a high shear mixer. Formulations were based on a mixture of Compritol® and Precirol® as lipidic binders and on sodium bicarbonate as a gas-generating agent. The floating ability of the pellets was evaluated in vitro. Good floating capabilities were obtained for formulations containing the gas-generating agent in both the inner matrix and the outer coating layer of the pellets. As an example, a placebo formulation containing 50% lactose 450 Me, 22% Compritol®, 15% Precirol®, 8% sodium bicarbonate and 5% Methocel® K100 (w/w) in the inner matrix, and 66% Precirol® and 34% sodium bicarbonate (w/w) as a coating effervescent layer, showed very good floating capabilities. The percentage of floating placebo pellets was around 80% after 1 h and still above 75% for 23 h. Floating pellet formulations with high drug content, based on the use of tetracycline hydrochloride and theophylline were also evaluated. They showed a comparable floating ability to placebo formulations, combined with sustained release properties thanks to the lipophilic character of the binders used.

Keywords: Melt pelletization; High shear mixer; Controlled-release; Floating pellets

1. Introduction

In the three past decades, scientific and technological advancements have been focused on the research of sustained or controlled oral delivery systems. Some advantages of those systems are known as: (a) reduction in dosing frequency, (b) reduced fluctuations in circulating drug levels, (c) increased patient compliance, and (d) more uniform pharmacological response (Welling and Dobrinska, 1987). An oral sustained release dosage form is particularly useful if the drug is well absorbed throughout the whole gastro-intestinal (GI) tract. However, some drugs tend to be absorbed in some specific areas of the intestine, the so-called absorption window. By increasing the residence time of the dosage form in the stomach or somewhere in the upper small intestine above the absorption site, the absorption capacities of such drugs can be improved (Rouge et al., 1996; Hwang et al., 1998; Baumgartner et al., 2000).

Several approaches have been proposed to control the residence of drug delivery systems (DDS) in the upper part of the GI tract (Moës, 1993; Hwang et al., 1998; Singh and Kim, 2000; Soppimath et al., 2001), namely: high density DDS, mucoadhesive DDS, magnetic DDS, swelling/expanding DDS and floating DDS. However, some of these systems seem to be less efficient and/or less recommendable than others. As an example, bioadhesive systems may be a potential cause of drug-induced injuries, which can range from local irritation to perforation depending on the ulcerogenic properties of drug (Moës, 1993). In the same way, accumulation of expandable gastroretentive dosage forms in the stomach might have serious implications for the patient. In this particular purpose, a fast biodegradation process would enhance the safety profile of such gastroretentive dosage forms (Klausner et al., 2003).

The current work is focused on floating drug delivery systems; these forms are expected to remain lastingly buoyant on the gastric contents, without affecting the intrinsic rate of gastric emptying, as their bulk density is lower than that of the gastric fluids. The buoyancy principle providing floating dosage forms with a prolonged gastric residence time seems to offer a

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greater safety of use compared to the other approaches (Moës, 1993). Retention time of the floating device depends, on several physiological factors, on the presence of food and on the type of dosage form. It is well known that monolithic dosage forms are more subjected to the gastric emptying variability's, as generally unreliable and non reproducible residence times in the stomach are observed after their oral administration (the so-called "all-or-nothing"). More over an early gastric emptying of a monolithic device may cause a rapid lack of efficacy in the case of a drug having only one absorption window in the upper part of the intestine. Multi-particulate floating DDS have been proposed to undergo this problem as a long lasting effect results from their gradually emptying from the stomach (Bulgarelli et al., 2000). Moreover, since each dose consists of many subunits, the risk of dose dumping is reduced (Iannuccelli et al., 1998).

Several approaches to achieve buoyancy have been proposed in the formulation of multiple unit floating devices. Based on this approach, two different technologies could be distinguished, i.e. non-effervescent and effervescent systems.

As non-effervescent systems, the use of low density hollow microspheres (Kawashima et al., 1992; Thanoo et al., 1993; Choi and Kim, 1996; Joseph et al., 2002), obtained by an emulsion–solvent diffusion method, as well as the use of highly porous calcium alginate beads (Whitehead, 1998; Whitehead et al., 2000; Iannuccelli et al., 1998; Murata et al., 2000) was an interesting approach in order to achieve buoyancy. As effervescent systems, multilayer gas-generating microballoons were notably described by Ichikawa et al. (1991), as conventional sustained-release pill coated with both an effervescent layer (sodium bicarbonate/tartaric acid) and a swellable membrane layer to achieve sustained drug release properties. Atyabi et al. (1996) have developed a floating system utilizing ion exchange resins. The system consisted of resin beads, which were loaded with sodium bicarbonate and theophylline as cationic model drug that was bound to the resin. The resultant beads were then coated with a semipermeable membrane. Finally, to achieve controlled-release properties, resin beads were coated with Eudragit RS.

Most of those techniques appear to be sophisticated and show a limited applicability for an industrial scale production, as they are multiple step process using organic solvents (emulsion formation, solvent diffusion, solvent evaporation, loading resin beads, coating and drying beads).

The aim of this work is to use the melt pelletization process in order to develop sustained-release floating pellets, using the gas-generation principle for achieving buoyancy. As a method to obtain multiple unit system, the melt pelletization process is a very short and a one-step single-pot production process. The melt pelletization is a solvent free process in which granulation is obtained through the addition of a binder, melting or softening at a relatively low temperature. After melting, the binder acts like a binding liquid (Schaefer et al., 1990; Schaefer, 1996). Since the drying phase is eliminated, the process is less consuming in terms of time and energy. In a previous work, formulations using Compritol® and Precirol® as lipidic binders were proposed in order to develop "conventional" non-floating sustained-release pellets by using this short production process. Compritol® (melting range: 67–72 °C) and Precirol® (melting range: 46–54 °C) due to low HLB values (HLB = 2) were used both as lipidic binders as well as sustained-release agents (Hamdani et al., 2002).

2. Materials and methods

2.1. Materials

Lactose 450 mesh (DMV International, Netherlands) was used as a diluent. Methocel® K100 (Colorcon, USA) was used as a gel forming excipient and sodium bicarbonate (Federa, Belgium) as a gas (CO_2) generating agent in an acid medium. Ciprofloxacin hydrochloride (Siris, India), tetracycline hydrochloride (Welpar, Belgium) and theophylline (BASF, Germany), were used as model drugs. Glyceryl palmito-stearate (Precirol® ATO 5) and glyceryl behenate (Compritol® 888), were supplied by Gattefosse (France) and used as lipophilic binders. The binders occur as fine, white free-flowing powders. Chemicals were of analytical grade. The size distribution by volume of the lactose and the drugs was determined by a Malvern Mastersizer 2000 (Malvern Instruments, UK).

2.2. Methods

2.2.1. Equipment and pellet manufacture

Pellets were prepared in a vertical small laboratory scale high-shear mixer, Mi-Pro® (Pro-C-epT, Belgium), equipped with a transparent bowl and a heating jacket. The bowl capacity and batch sizes were 1700 ml and 250 g, respectively. The rotational speed of vertically positioned mixing arm (impeller) and chopper can be varied between 0–1800 and 0–4000 rpm, respectively. The production conditions were largely discussed in a previous work (Hamdani et al., 2002); however, some minor adaptations had to be done. Briefly, all experiments were carried out in three steps: granulation, massing/pelletization and coating. The temperature of heating jacket was kept constant during the whole process (50–55 °C). The granulation step was started at an impeller speed (IS) of 1800 rpm and a chopper speed (CS) of 130 rpm. When the product temperature reached sufficiently high values in order to provoke the binder softening, the torque increased sharply resulting from the granule formation and indicating the beginning of the massing/pelletization step. In order to avoid any further increase of temperature of the product during this step, the impeller speed was reduced to 800 rpm and a controlled-flow cooling air (2–3 m^3/h) was injected, through the bowl lid. The chopper speed was increased to 4000 rpm and the massing times (MT) varied between 10 and 25 min. The product temperature was carefully controlled in order to avoid excessive particle size increase and/or agglomeration during the pelletization step. Finally, a very short (2 min) "coating step" came to achieve the process. In this purpose, the mixer-granulator could be stopped in order to add the coating mix (Precirol® and gas-generation agent) to the pellets. Then, the process was restarted, the heating jacket temperature, IS, CS and the cooling airflow were kept identical to the experimental conditions used during

the massing/pelletization step. The duration of the whole pellet manufacturing process was around 40 min.

At the end of the process, the pellets were cooled at ambient temperature. The adhesion to the bowl was estimated as the difference between the amount of materials placed in the bowl and the amount emptied. Only pellet size fractions in the range of 1250–2000 μm were considered for in vitro floating evaluation studies as well as for dissolution studies.

2.2.2. Pellet characterization

2.2.2.1. Scanning electron microscopy. Microphotographs were obtained from pellets coated with a thin gold–palladium layer, using a scanning electron microscope (SEM). Surface structure studies were carried out using a combined mapping X-ray microscopy technique (JSM-6100 scanning electron microscope, EDAX CDU "LEAP" Detector, JEOL, Japan). Samples were examined with 5 kV power, at magnifications from 50 to 500 times.

2.2.2.2. In vitro evaluation of floating ability.

2.2.2.2.1. Counting method. In order to determine the percentage of floating pellets, the method described by Ichikawa et al. (1991), was used. A precise number, between 100 and 150 of pellets, was immersed in 70 ml of 0.1 N HCl containing 0.05% (w/v) Polysorbate 20, in a 100 ml beaker maintained at 37 °C. Then, the beaker was kept shaking horizontally at a speed of 100 cycles/min, during 23 h at 37 °C. The number of floating pellets was estimated by photographing the liquid surface in the beaker and counting the number of floating pellets in the picture. Before taking pictures, it was confirmed that neither submerging of pellets beneath other pellets occurred. When such undesirable phenomenon was observed, the beaker was gently shaken before taking pictures in order to gain monolayer of floating pellets on the liquid surface. Experiments were achieved in triplicate. The percentage of floating pellets was calculated by the following equation:

$$\text{floating pellets (\%)} = \left(\frac{\text{number of floating pellets at the measured time}}{\text{initial number of the pellets}}\right) \times 100. \quad (1)$$

2.2.2.2.2. Resultant weight method. The resultant weight (RW) of pellets was measured at known time intervals using the apparatus and method of Timmermans and Moës (1990a, b). The medium used was 0.1 N HCl containing 0.05% (w/v) Polysorbate 20. Experiments were achieved in triplicate at 37 °C. The pellets were placed in a specifically designed basket sample holder, attachable to the resultant weight apparatus (Fig. 1). As described by Timmermans and Moës (1990a, b), the resultant-weight apparatus enables to monitor in vitro the total force F acting vertically on an immersed object. This force F determines the RW of the object in immersed conditions and can be used to quantify its floating or non-floating abilities. The magnitude and the direction of force F, and hence of the RW, correspond to the vectorial sum of the buoyancy (F_{buoy}) and gravity (F_{grav}) forces

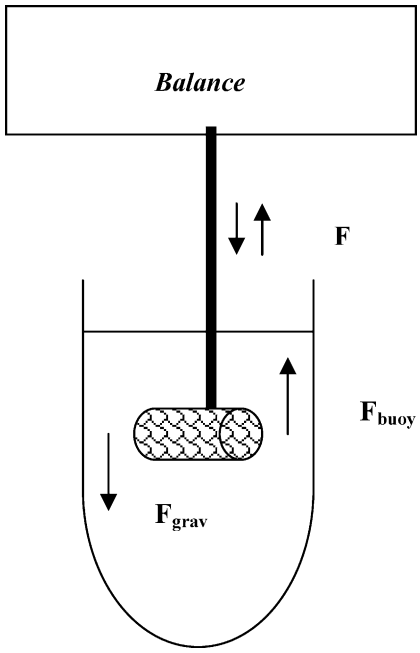

Fig. 1. A schematic view of the resultant weight apparatus (Timmermans and Moës, 1990a). The floating pellets were introduced in the basket holder.

acting on the object. By convention, the more F is positive (forces directed upward), the better the object floats. As described by Eq. (2), where F is the total vertical force (resultant-weight of the object), g the acceleration of gravity, d_f the fluid density, d_s the object density, M the object mass and V the object volume.

$$F = F_{buoy} - F_{grav} = d_f gV - d_s gV = (d_f - d_s)gV = \left(d_f - \frac{M}{V}\right) gV \quad (2)$$

It was assumed that pellets have good floating capacities if the resultant weight values are still positives during 800 min and if the percentage of floating pellets still up to 60% after 8 h.

2.2.2.3. In vitro dissolution test. The drug release determinations were carried out at 37 °C using USP 25 no. 2 dissolution testing apparatus, at a rotational speed of 60 rpm. The media used was 900 ml deaerated 0.1 N HCl, containing 0.05% (w/v) of Polysorbate 20. The drug release from pellets was determined at 356, 317 and 243 nm for tetracycline hydrochloride, ciprofloxacin hydrochloride and theophylline, respectively, using an Agilent 8453 UV–vis Dissolution Testing System (Agilent, USA). The percentages of the drug released were measured at fixed time intervals and averaged ($n = 5$). Only pellet size fractions in the range of 1250–2000 μm were considered for dissolution studies.

3. Results and discussion

After carrying out some preliminary formulations (Hamdani, 2005), it was shown that the best floating capacities can be obtained for formulations based on the use of a gas-generating agent in the inner matrix and the outer coating layer of pellets.

Table 1
Pellets formulations and their manufacture conditions

Formulation	(%w/w)		Fabrication conditions
Placebo	Matrix (250 g)		Granulation
	Precirol®	15	IS: 1800 rpm
	Compritol®	22	CS: 130 rpm
	$NaHCO_3$	8	Heating jacket: 50 °C
	Methocel® K100	5	Pelletization
	Lactose 450 Me ad	100	IS: 800 rpm
	Coating mix (37.5 g)		CS: 4000 rpm
	Precirol®	66	MT: 10 min
	$NaHCO_3$	34	Coating: 2 min
			Cooling air: 2–3 m^3/h
Ciprofloxacine hydrochloride	Matrix (250 g)		Granulation
	Precirol®	15	IS: 1800 rpm
	Compritol®	22	CS: 130 rpm
	$NaHCO_3$	8	Heating jacket: 55 °C
	Methocel® K100	5	Pelletization
	Ciprofloxacine·HCl ad	100	IS: 800 rpm
	Coating mix (37.5 g)		CS: 4000 rpm
	Precirol®	66	MT: 25 min
	$NaHCO_3$	34	Coating: 2 min
			Cooling air: 2–3 m^3/h
Tetracycline hydrochloride	Matrix (250 g)		Granulation
	Precirol®	15	IS: 1800 rpm
	Compritol®	22	CS: 130 rpm
	$NaHCO_3$	8	Heating jacket: 55 °C
	Methocel® K100	5	Pelletization
	Tetracycline·HCl ad	100	IS: 800 rpm
	Coating mix (37.5 g)		CS: 4000 rpm
	Precirol®	66	MT: 12 min
	$NaHCO_3$	34	Coating: 2 min
			Cooling air: 2–3 m^3/h
Theophylline	Matrix (250 g)		Granulation
	Precirol®	15	IS: 1800 rpm
	Compritol®	22	CS: 130 rpm
	$NaHCO_3$	8	Heating jacket: 55 °C
	Methocel® K100	5	Pelletization
	Theophylline ad	100	IS: 800 rpm
	Coating mix (37.5 g)		CS: 4000 rpm
	Precirol®	66	MT: 15 min
	$NaHCO_3$	34	Coating: 2 min
			Cooling air: 2–3 m^3/h

Table 1 shows the selected floating pellets formulations and manufacturing conditions used during the melt pelletization.

Concerning the latter, Fig. 2 shows the three stages that can be observed during the melt pelletization process in a high shear mixer: the granulation, the pelletization and the coating steps, respectively. During the first step, the product temperature increases quickly because of the important heat of friction generated by the fast impeller during the granulation step (1800 rpm) and by the heating jacket. When the binder is sufficiently soften that to be deformed, the torque increases sharply resulting from the granule formation. This indicates the beginning of the pelletization step. As discussed in a previous work (Hamdani et al., 2002), during this step, the impeller speed was decreased from 1800 to 800 rpm and the chopper speed increased from 130 to 4000 rpm in order to keep the product temperature as stable as possible and to avoid any "over wetting" phenomenon. Moreover, the injection of cool air through the bowl lid allows a better

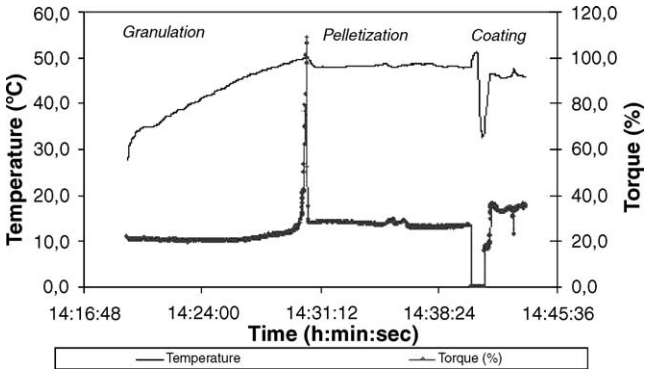

Fig. 2. Measurements of torque and temperature as a function of time.

control of the product temperature during the pelletization step (between 45 and 50 °C). The third and final step consists of a coating process using, a powder mixture composed of Precirol® (fatty binder) and sodium bicarbonate (gas-generating agent). The sudden decrease of torque and product temperature values observed in Fig. 2 are caused by the need to stop the high shear mixer at the end of the pelletization step in order to permit the addition of sodium bicarbonate and Precirol® mixtures.

Focusing on formulations, the description of the composition of floating pellets presented in Table 1, provides some crucial information concerning the floating and controlled-release properties of the pellets. Firstly, the presence of an inner matrix which consists of a mixture of Compritol® and Precirol® as lipidic binders permitted to ensure the sustained-release properties of the formulations. Secondly, the floating capabilities of the pellets are guaranteed by the presence of both sodium bicarbonate, which generates CO_2 in a gastric acid medium (decreasing the density of the dosage form and allowing immediate buoyancy) and Methocel® K100 as a swellable excipient (entrapping CO_2 bubbles and thus ensuring lasted buoyancy). The drug or lactose (placebo) completes the inner matrix composition. Finally, the outer matrix was composed of Precirol®, as a lipidic binder/sustained release agent and sodium bicarbonate, as a gas-generating agent to improve the immediate floatation of the pellets.

Preliminary orientation tests have shown that the incorporation of higher molecular weight polymers such as Methocel K4 M or Methocel K15 M in the inner part of matrix pellets caused a rapid pellet disintegration in contact with acidic media. On the other hand, in order to reduce the lag time before buoyancy, the use of Methocel® K100 was also envisaged in the outer pellets coating layer. However, such pellets showed a higher tendency to agglomeration. The benefit to have sodium bicarbonate on the surface of pellets seems to be evident, if we consider the floating mechanism of pellets. Upon arrival in the acidic environment of the stomach, an exchange between chloride and bicarbonate ions localised on the surface of pellets took place. As a result, CO_2 was rapidly released, causing an immediate floating of the pellets, then the acidic medium entered into the inner matrix where CO_2 was released further and entrapped in the gelled medium formed by Methocel® K100. In this way, pellets floated immediately after being in contact with an acidic

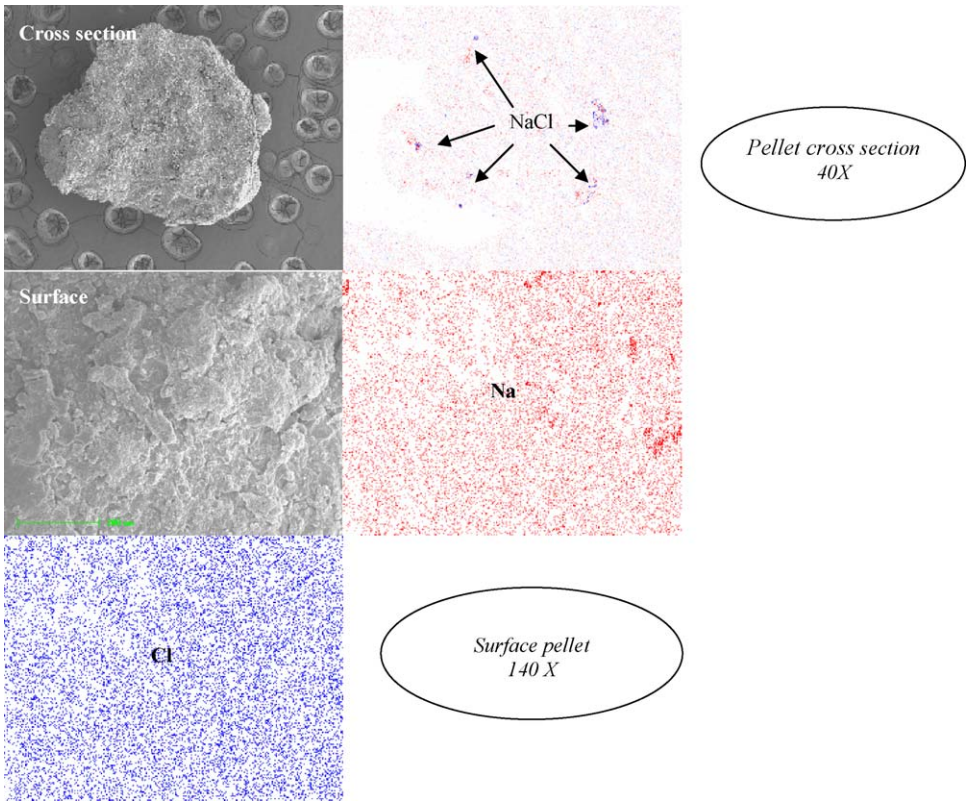

Fig. 3. Chemical composition determined at the surface and cross-section structures of placebo pellets by mapping X-ray microscopy technique.

medium and no pellet disintegration or agglomeration could be observed. This statement could be confirmed only if the sodium bicarbonate was wide spread on the outer surface of the pellets. In order to establish the aptitude of the high shear mixer to form a homogeneous coating around the pellets and thus to prove the external distribution of the coating mix, placebo pellets were prepared by addition of 5% (w/w) NaCl to the coating mix. Then, the chemical composition analysis of the surface and the pellet cross-section was determined by scanning electron microscopy combined with X-ray image analysis (distribution of the chemical elements Cl, C and O). As shown in Fig. 3, a homogeneous distribution of Cl is observed at the surface of pellets and no chlorides were present in the inner part of the matrix pellet. Furthermore, this analysis did not show any new granule formation during the coating step, certainly thanks to the shortness (2 min) of this step. This indicates that only a deposition of the coating mixture on the surface of the pre-existent pellets occurred during the coating step.

The assessment of the floatability by both the resultant-weight and counting methods demonstrated that, except for ciprofloxacin pellets, all of the formulations shown in Table 1 produced pellets with good floating abilities. The resultant-weight values for ciprofloxacin pellets fall on negative values, as shown in Fig. 4, thus indicating that the pellets go sinking. Furthermore, Fig. 5 confirms the superior floating ability (floating pellets in %) of the placebo pellets in comparison to the ciprofloxacin pellets. The percentage of the floating placebo pellets was around 80% after 1 h and still greater than 75% after 23 h. Fig. 4 also shows that the RW values for the placebo

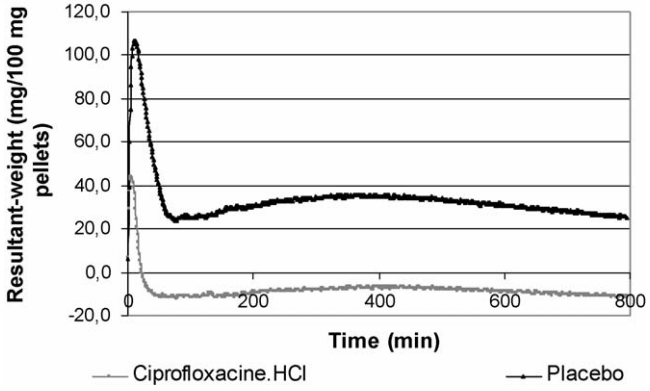

Fig. 4. Resultant weight values of ciprofloxacin and placebo pellets.

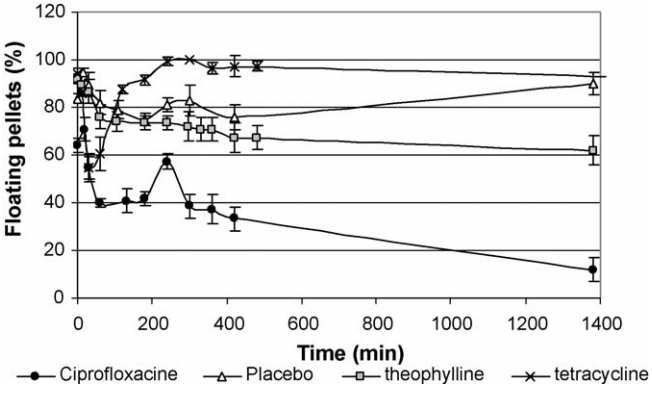

Fig. 5. Floating ability comparison (counting method) between placebo pellets, ciprofloxacin, tetracycline and theophylline pellets (% floating pellets).

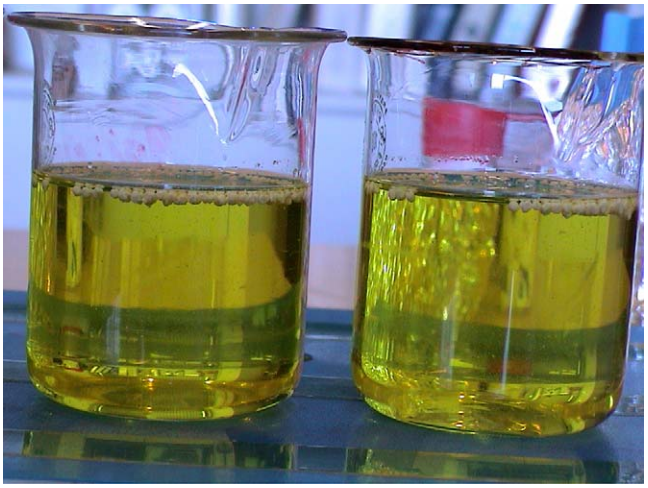

Fig. 6. Tetracycline pellets floating at the surface of the test fluid after 7 h.

pellets increase sharply, immediately after their contact with the acidic medium thanks to the CO_2 generated from sodium bicarbonate present in the coating. Peak RW values up to about 100 mg/100 mg pellets were observed for the placebo pellets. However, the RW peak values decreased quite rapidly when the entire CO_2 from the coating bicarbonate layer was released, but the RW values are still positive, thanks to a more progressive CO_2 generation from the inner matrix composition (sodium bicarbonate and Methocel® K100). The RW values for placebo pellets, which are in accordance with their good floatability, were still positive up to 800 min after their contact with the acidic medium.

In order to enlarge the manufacturing process of floating pellets, tetracycline hydrochloride and theophylline were also tested as model drugs. It was observed that both tetracycline and theophylline formulations displayed good floating properties, as more than 60% of pellets floated up to 8 h, as described in Fig. 5. Accordingly, as shown in Fig. 6, tetracycline pellets appeared still floating at the surface of the test fluid for 7 h. It is also important to notice that the shape of RW curves and the RW values obtained for the theophylline and tetracycline pellets are comparable to those obtained for the placebo pellets (data not shown).

The weak floating abilities of the ciprofloxacin pellets may be correlated with the smaller particle size of this drug ($D(4.3) = 9.4\ \mu m$) in comparison with lactose 450 mesh ($D(4.3) = 21.4\ \mu m$), tetracycline·HCl ($D(4.3) = 56.4\ \mu m$) and theophylline ($D(4.3) = 109.8\ \mu m$). The small ciprofloxacin particles' size may increase the number of particle bonds during the granulation process, then increasing the densification of pellets. Consequently, less floating abilities were observed for ciprofloxacin pellets in comparison with all the other formulations (Table 1). Fig. 7 shows SEM microphotographs of the cross-sections of the ciprofloxacin and placebo (lactose) pellets. It was clearly observed that the ciprofloxacin pellets were denser than the placebo pellets. Furthermore, as shown in Fig. 8, SEM microphotographs of cross-sections of the theophylline and tetracycline pellets, revealed a comparable pellets surface structure than the placebo pellets thanks to their large particle size. Nevertheless, it is still necessary to perform appropriate porosity and density evaluations in order to evaluate mass densification during the pelletization process and to discriminate the floating pellets containing different drugs.

Finally, the ability of the different floating pellets formulations to obtain sustained drug release properties was evaluated through in vitro dissolution tests. As it can be observed in Fig. 9, the presence of lipidic binders in both the inner part and the coating of the pellets permitted the obtaining of effective controlled-release properties for the three model drugs evaluated. The highest drug release profiles obtained for tetracycline pellets can be explained by his higher water solubility (known as a freely soluble drug with a water solubility of 100 mg/ml at 22 °C) in comparison with the other drugs. As the mechanism of drug release from lipidic Gelucires matrix systems, with very low HLB values (next to 1) like Compritol® and Precirol®, is mainly controlled by diffusion (Aïnaoui et al., 1997; Aïnaoui and Vergnaud, 1998), thus the drug release from such pellets depends mainly on the drug solubility. This also explains the important burst effect observed for tetracycline·HCl release in comparison with pellets containing theophylline and ciprofloxacin.

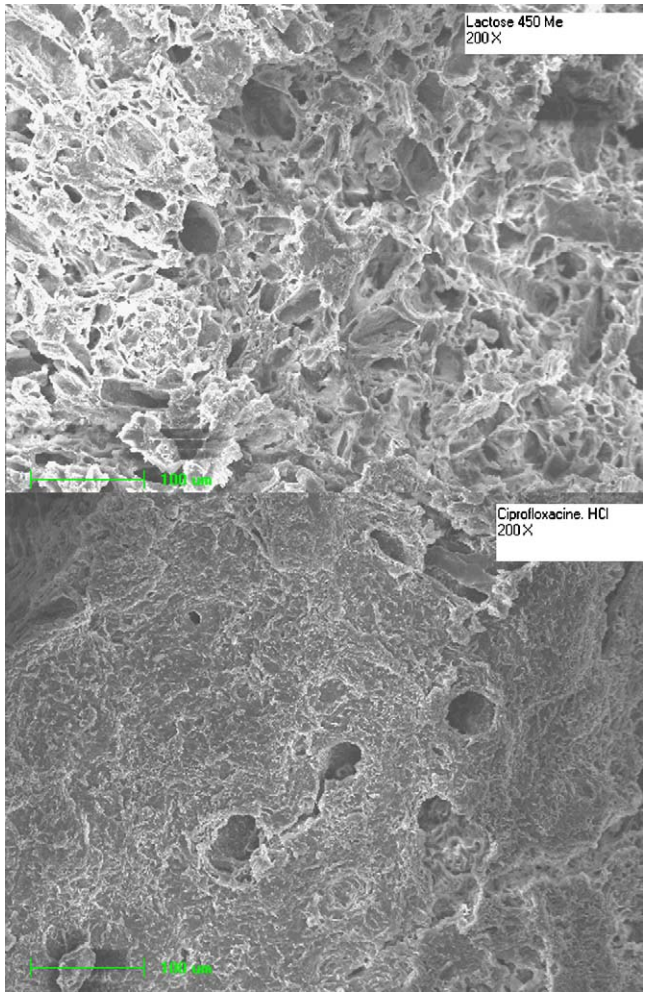

Fig. 7. SEM photographs of the cross-section of placebo (lactose 450 Me) and ciprofloxacin pellets (pellets were analysed after 22 h agitation in acid medium from the counting method).

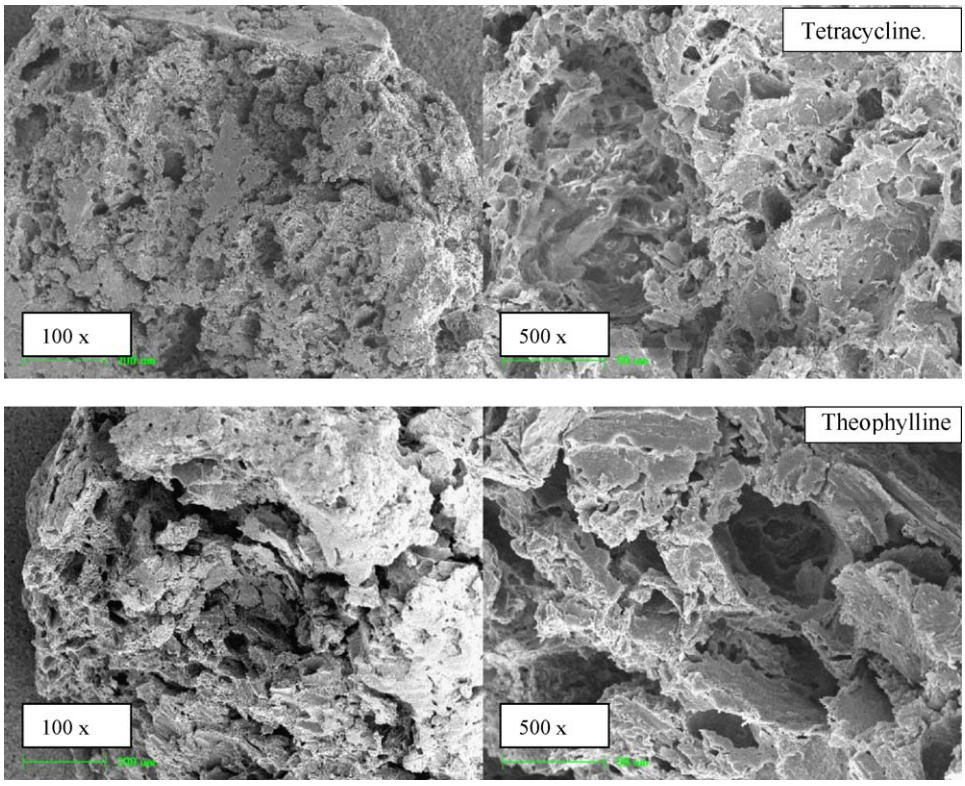

Fig. 8. SEM photographs of the cross-section of theophylline and tetracycline pellets (pellets were analysed after 22 h agitation in acid medium from the counting method).

One can conclude that, good floating capacities were obtained for formulations based on the use of an effervescent agent in both the inner matrix and the outer coating layer of pellets. Floating oral multiple unit dosage forms with high drug content (more than 40%, w/w) had been developed by using a very short and ecological process. However, due to the high drug content in formulations combined with the specific granulation process used for the preparation of pellets, drugs characteristics, i.e. particle size, and particle size distribution may have an influence on the floating properties.

Preliminary scaling up evaluation conduced on a 25 l high shear mixer, Ultima® (GEA-Niro, Denmark) has shown the feasibility of pellets fabrication process on a higher scale machine. This equipment was used by adapting the standard conditions described before to the size increase (e.g. IS and Chopper speeds of 420 and 1500 rpm, and 160 and 1500 rpm, during the mixing and the granulation steps, respectively). More over, an arrival of ambient air was added in the boll to keep the mass temperature as stable as possible during the pelletization step. This preliminary scaling up evaluation might be confirmed on several batches and results will be presented in a future paper.

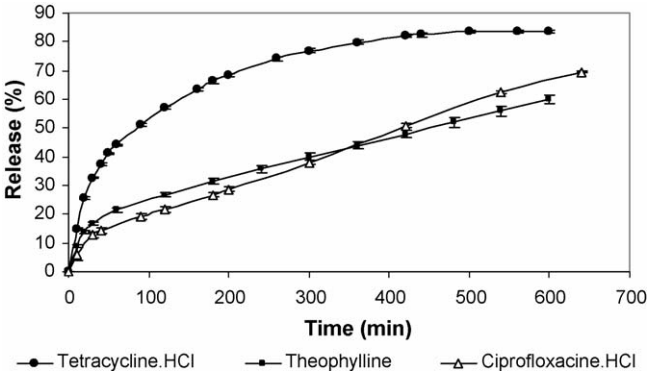

Fig. 9. Drug release (HCl 0.1 N, 0.05% (w/v) Polysorbate 20) from ciprofloxacin, tetracycline and theophylline pellets. Mean ($n = 5$, mean ± S.D.).

4. Conclusion

Floating multiple-unit pellet formulations were developed as a new potential application for the melt pelletization process. Pellets have shown excellent immediate and lasting buoyancies in an acidic medium (HCl 0.1 N, Polysorbate 20). The presence of a gas-generating agent (sodium bicarbonate) in both the inner matrix and the outer coating layer of pellets have permitted to obtain rapid and continuous buoyancy. Floating abilities were combined with sustained release properties due to the lipophilic character of Compritol® and Precirol® used as binders during the fabrication process.

In order to investigate the actual floating ability of the formulations described on the gastric content and their usefulness in extending gastric residence time, such formulations will selected for an in vivo evaluation.

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