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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