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In vitro and in vivo evaluation of floating riboflavin pellets developed using the melt pelletization process

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Abstract

Floating pellets were prepared using the melt pelletization process in a Mi-Pro® high shear mixer (Pro-C-epT, Belgium). Formulations were based on a mixture of Compritol® and Precirol® as meltable binders and on the use of sodium bicarbonate and tartaric acid as gas-generating agents. Good floating abilities were obtained by using the gas-generating agents in both the inner matrix and the outer coating layer of the pellets. In vitro evaluation of floating capability was performed both by using the resultant weight apparatus and by counting floating pellets at the surface of beakers containing 0.1N HCl solution, in vivo evaluation of floating pellets capabilities was also performed. Riboflavin-containing floating pellets (FRF) were administered orally to nine healthy volunteers versus non-floating pellets (NFRF). Volunteers were divided in two groups, fasted group ($n=4$) 729 kcal and fed group ($n=5$) 1634 kcal as the total calorie intake on the testing day. An increase of urinary excretion of riboflavin was observed when the volunteers were dosed with the floating pellets, especially after feeding. As riboflavin has a narrow window of absorption in the upper part of small intestine, this phenomenon could be attributable to the gastric retention of floating pellets.

Keywords: Melt pelletization; Controlled-release; Floating pellets; Riboflavin; Urinary excretion

1. Introduction

Oral floating dosage forms are developed in order to be retained in the stomach and the upper part of small intestine, assuring a slow delivery of drug above the absorption site. Gastro-retentive devices may be useful for the delivery of many different kind of drugs, especially for optimum delivery of drugs that act locally in the stomach, e.g. misoprostol (Oth et al., 1992), and for stomach-specific antibiotic drug delivery used in the treatment of *Helicobacter pylori* (Burton et al., 1995; Patel and Amiji, 1996; Whitehead et al., 2000).

In this regard, the present work aims to assess the intragastric behaviour in humans of a new multiple unit system produced by the melt pelletization process (Hamdani et al., in press). Riboflavin (RF) was therefore chosen as the drug tracer because its absorption occurs mainly in the proximal small intestine. Moreover, it undergoes very little metabolism and its pharmacokinetics can be investigated by analysis of the urinary excretion following oral administration in humans (Sato et al., 2003, 2004). In this evaluation, riboflavin was used in its sodium salt form: sodium riboflavin 5′-phosphate (RF5′PNa). This Vitamin B_2 derivative is more water-soluble than riboflavin itself but is subject to the same absorption and transport mechanisms. Furthermore, it is excreted in the urine as RF and also has absorption sites mainly limited to the upper region of the small intestine. This allows indirect demonstration of an increase in the residence time of the dosage form above the absorption area: any increase in the gastric transit time of the dosage form increases the quantities of absorbed and eliminated riboflavin (Ingani et al., 1987b).

A previous investigation that included formulation, dissolution and buoyancy tests had shown good in vitro floating capabilities for comparable placebo, tetracycline and theophylline formulations (Hamdani et al., in press). But in order to evaluate the real floating capabilities of floating RF5′PNa pellets on the gastric content and their usefulness in achieving an extended gastric transit, these pellets were compared with non-floating RF5′PNa pellets (control). The in vivo behaviour of RF5′PNa

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dosage forms was evaluated by means of RF urinary excretion measurements among fasted and fed healthy volunteers.

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. Sodium bicarbonate and tartaric acid (Federa, Belgium) were used as gas-generating agents. Sodium riboflavin 5′-phosphate (Certa, Belgium) was used as a model drug. 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.

2.2. Methods

2.2.1. Pellet manufacture

Floating (FRF) and non-floating (NFRF) pellets were prepared in a vertical small-laboratory-scale high-shear mixer (Mi-Pro®, Pro-C-epT, Belgium). The production conditions have been discussed in previous works (Hamdani et al., 2002, in press). Formulations and manufacturing conditions are shown in Table 1. The temperature of the heating jacket was kept constant throughout the whole process (45 °C). The product temperature, the torque, the impeller speed (IS) and chopper speed (CS) were monitored during pellet manufacture. In order to avoid excessive particle-size increase and/or agglomeration during the pelletization step, the product temperature was carefully controlled and ensured by flowing cooling air (2–3 m^3/h) through the bowl lid. Finally, a very short (2 min) "coating step" completed the process. For this step, the machine was stopped in order to add the coating mix (Precirol® and gas-generating agents) to the pellets, then the process was restarted with the heating jacket temperature, IS, CS and the cooling air flow kept identical to the experimental conditions used during the massing/pelletization step. The duration of the whole pellet manufacturing process was around 40 min.

Table 1
Formulation and manufacturing conditions of riboflavin floating and non-floating pellets

Formulation (%, w/w)		Manufacturing conditions
FRF		
Matrix (250 g)		*Granulation*
Sodium riboflavin 5′-phosphate	12	IS: 1800 rpm
Precirol®	15	CS: 130 rpm
Compritol®	53	Heating jacket: 45 °C
$NaHCO_3$	8	*Pelletization*
Tartaric acid	7	IS: 800 rpm
Methocel K100	5	CS: 4000 rpm
Coating (70 g)		MT: 18 min
Precirol®	71	Heating jacket: 45 °C
$NaHCO_3$	18	*Coating*
Tartaric acid	11	IS: 800 rpm
		CS: 4000 rpm
		CT: 5 min
		Heating jacket: 45 °C
NFRF		
Matrix (250 g)		*Granulation*
Sodium riboflavin 5′-phosphate	12	IS: 1800 rpm
Precirol®	15	CS: 130 rpm
Compritol®	15	Heating jacket: 45 °C
Lactose450 Me ad	100	*Pelletization*
		IS: 800 rpm
		CS: 4000 rpm
		MT: 25 min
		Heating jacket: 45 °C

2.2.2. In vitro evaluation of floating capabilities

Only pellets with size fractions in the range of 1250–2000 μm (sieve analysis) were considered for the in vitro floating evaluation studies.

2.2.2.1. Counting method. The method has been described by Ichikawa et al. (1991). Briefly, a precise number, between 100 and 150, of pellets was immersed in 70.0 ml of 0.1N 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 for 23 h. The liquid surface of the beaker was then checked for floating pellets submerged beneath other pellets. When such undesirable phenomena were observed, the beaker was gently shaken in order to gain monolayer of floating pellets on the liquid surface. The number of floating pellets was then estimated by photographing the liquid surface in the beaker and counting the number of floating pellets on the picture. Experiments were performed in triplicate and the percentage of floating pellets was calculated by Eq. (1):

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

2.2.2.2. Resultant weight method. The resultant weight (RW) of the pellets was measured at known time intervals using the apparatus and method of Timmermans and Moës (1990a,b). The medium was 0.1N HCl containing 0.05% (w/v) of Polysorbate 20. Experiments were performed in triplicate at 37 °C. The pellets were placed in a basket which acted as a sample holder and which was attached to the resultant-weight apparatus (Fig. 1). As described by Timmermans and Moës (1990a,b), the resultant-weight apparatus enables in vitro monitoring of 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 capabilities. As described by Eq. (2), 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 acting on the object.

$$F = F_{buoy} - F_{grav} = d_f g V - d_s g V = (d_f - d_s) g V = (d_f - M/V) g V \quad (2)$$