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Development of a gastroretentive pulsatile drug delivery platform

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Keywords
chronotherapy; floating drug delivery; gastroretention; lag-time; pulsatile drug delivery

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Abstract

Objectives To develop a novel gastroretentive pulsatile drug delivery platform by combining the advantages of floating dosage forms for the stomach and pulsatile drug delivery systems.

Methods A gastric fluid impermeable capsule body was used as a vessel to contain one or more drug layer(s) as well as one or more lag-time controlling layer(s). A controlled amount of air was sealed in the innermost portion of the capsule body to reduce the overall density of the drug delivery platform, enabling gastric floatation. An optimal mass fill inside the gastric fluid impermeable capsule body enabled buoyancy in a vertical orientation to provide a constant surface area for controlled erosion of the lag-time controlling layer. The lag-time controlling layer consisted of a swellable polymer, which rapidly formed a gel to seal the mouth of capsule body and act as a barrier to gastric fluid ingress.

Key findings By varying the composition of the lag-time controlling layer, it was possible to selectively program the onset of the pulsatile delivery of a drug.

Conclusions This new delivery platform offers a new method of delivery for a variety of suitable drugs targeted in chronopharmaceutical therapy. This strategy could ultimately improve drug efficacy and patient compliance, and reduce harmful side effects by scaling back doses of drug administered.

Introduction

It is now well established that maintaining a relatively constant plasma drug level throughout the dosage interval is not optimum in many conditions. Relationships between drug presence, duration of action and safety may be influenced by, among other factors, circadian rhythms. Varying drug concentrations in the biosystem may be more effective if coinciding with, and being capable of managing, peak manifestations of the clinical condition. Pulsed, rather than persistent delivery may also alleviate or eliminate side effects.[1] Targeting a specific rhythm of a disease could reduce dosage, thereby reducing drug exposure and some unwanted side effects. Targeting rhythms may also prevent drug interactions, providing wider treatment options for patients suffering from multiple ailments. Consequently, the concept of chronotherapeutics has emerged and is based on time-dependent variations in the risk or symptoms of diseases as well as in the pharmacokinetics and pharmacodynamics, efficacy and toxicity of drugs.[2–4]

With recently improved understanding in chronopharmacology, oral pulsatile drug delivery systems to match the circadian pathophysiology, following a pre-determined lag-time, have the potential to achieve optimal clinical outcomes.[3,5] For example, blood pressure and heart rate in patients with hypertension rapidly increase after awakening from the night time, this coincides with the risk period of adverse cardiovascular events such as angina, myocardial infarction, sudden cardiac death and thrombotic and haemorrhagic stroke.[6–10] A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. The same could be true for preventing the symptoms of rheumatoid arthritis, allergic and infectious rhinitis and migraine headache in the morning.[11]

However, transit times of dosage forms in the gastrointestinal tract may become a challenge, particularly for drugs that are preferentially absorbed from the upper gastrointestinal tract. The transit times of many oral dosage forms across the stomach and small intestine can be approximately 4–6 h.[12] Pulsatile delivery systems may release drug at the correct time as programmed from the system, but drug may be released into a region of the gastrointestinal tract where it is only

poorly absorbed or, worse, not absorbed at all. These considerations led to the development of oral pulsatile release dosage forms possessing gastric retention capabilities that allow the systems to remain above or within the window of absorption, and extend the period of absorption of drugs exhibiting limited window of absorption in the upper gastrointestinal tract.[13–20] It is hoped that targeting this window of absorption will lead to an improvement of pharmacokinetic profiles, bioavailability and subsequent therapeutic outcomes.

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems,[21–24] bioadhesive systems,[25,26] swelling and expanding systems[27,28] and high-density systems.[29,30] With many simplified practical approaches to increased gastric residency through inherent buoyancy, floating dosage forms are widely used for pulsatile delivery. A combination of floating and pulsatile principles offers an advantage that the system can achieve long residence time in the stomach, sufficient for delivering an adequate amount of drug at the right time, particularly in diseases requiring medication during sleeping and awakening.[13,15–20]

To accomplish drug delivery, a floating dosage form must maintain structural integrity and overall bulk density lower than that of gastric contents (reported as ~1.004 g/ml[31]) until complete drug delivery from the systems. However, the reported gastric retention times of previous floating drug delivery systems range from 3 h to 10 h, even though they floated in the dissolution medium more than 24 h.[21–23,32] This might result from loss of integrity and/or buoyancy of the system before attaining complete drug release.

Since multiparticulate systems could be distributed over the length of the gastrointestinal tract due to requiring floating lag-time and then the drug could be released at different locations, single unit systems might be more favourable because of the large size of the dosage forms, which restricts rapid passage through the gastric pylorus.[33]

This study focused on developing a novel gastroretentive pulsatile drug delivery platform for oral drug delivery that maintains sufficient structural integrity and overall density below that of the gastric content (i.e. <1 g/ml) until complete drug release occurs. The development of a gastric fluid impermeable capsule body that floats in a vertical orientation to deliver a payload of drug at pre-determined lag-time intervals is described.

Materials and Methods

Materials

Silicified microcrystalline cellulose (Prosolv SMCC 90) was provided by JRS Pharma (Patterson, NY, USA). Lactose monohydrate (FlowLac 100) was from Mutchler Inc. (Harrington Park, NJ, USA). Capsugel (Greenwood, SC, USA) provided hard gelatin capsules size 0. Dow Chemical (Dow Chemical Company, Midland, MI, USA) provided ethylcellulose (EC; Ethocel Standard 100 Premium, viscosity 90–110 cP in 2% w/v), hydroxypropyl methylcellulose (HPMC; Methocel K 100 Premium LV, viscosity 80–120 cP in 2% w/v and E50 Premium LV, viscosity 40–60 cP in 2% w/v) and polyethylene oxide (PEO; Polyox WSR N-750, M_W 0.3×10^6, viscosity 600–1200 cP in 5% w/v and WSR 205, MW 0.6×10^6, viscosity 4500–8800 cP in 5% w/v). Triethyl citrate (TEC) was provided by Vertellus (Greensboro, NC, USA). Other materials were purchased from various suppliers: acetone (VWR International, Inc., Suwanee, GA, USA), isopropanol (Thermo Fisher Scientific Inc., Fair Lawn, NJ, USA), litmus indicator (powder) Acros Organics (Geel, Belgium), theophylline anhydrous (powder, USP), croscarmellose sodium and magnesium stearate (MgSt) (Spectrum Chemicals, Gardena, CA, USA).

Preparation of gastric fluid impermeable capsule bodies

Gastric fluid impermeable capsule bodies (size 0) were prepared using a laboratory-scale dipping process. The gelatin capsule bodies were separated from the cap and dipped into the coating solution, which contained Ethocel Standard 100 Premium and TEC (ratio 95 : 5) as 8%, 9% and 10% w/v solutions in a 50 : 50 v/v mixture of acetone and isopropanol for 10 s per dipping cycle, with a periodicity of 10 min (to allow for evaporation) in the fume hood. The capsule bodies were then dried in the oven at 40°C. The drying time was optimized to remove all the solvent. The resultant capsule bodies were then further processed by simply immersing in water to remove the gelatin layer, yielding a completely impermeable capsule body.

Acid/water permeability evaluation

Gastric fluid impermeable capsule bodies were filled with litmus indicator powder. Individual impermeable capsule bodies ($n = 6$) were placed into beakers containing 0.1 N HCl buffer solution (40 ml) with the temperature maintained at 37 ± 2°C. A colour change observed in the litmus indicator as well as the visual migration of the dissolved indicator into the capsule wall were considered to be failures in acid/water permeability resistance.

Buoyancy and optimal loading capacity

EC capsule bodies manufactured with an average weight of 56 mg were selected to house 13 different HPMC/lactose tablet weights of 100, 200, 300, 400, 450, 460, 500, 600, 645, 650, 655, 660 and 665 mg. The mixture of HPMC/lactose was comprised of 80% w/w Methocel K 100 Premium LV, 19.5% w/w FlowLac 100 and 0.5% w/w MgSt. All powdered

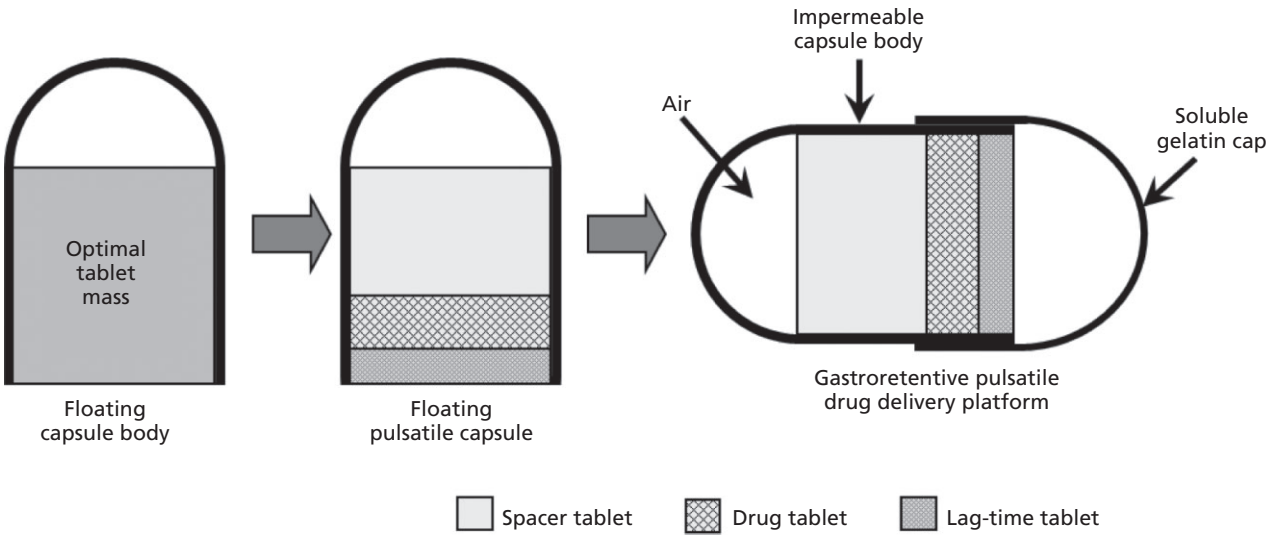


Figure 1 Configuration of the novel gastroretentive pulsatile drug delivery platform.

ingredients were passed through a 600 μm sieve before use to deagglomerate. Methocel and FlowLac 100 were tumble mixed for 15 min. MgSt was then added and tumbled mixed for a further 5 min. The dry powder blend was compressed manually to the die of a Model F single punch tableting machine (F.J. Stokes Machine Company, Philadelphia, PA, USA) equipped with a 7-mm diameter flat-faced punch (Natoli Engineering Company, Inc., St Charles, USA).

Each tablet was positioned flush to the open end of a capsule body – this sealed air in the innermost portion of the capsule body (Figure 1). A loading capacity test was performed by using a horizontal shaker method. A beaker containing 900 ml 0.1 N HCl buffer solution was placed on a Lab-Line Orbit Environ-Shaker (Lab-Line Instruments, Inc., Melrose Park, IL, USA) and each device was dropped into the beaker. During shaking at 100 rpm for 2 min, the floating behaviour was evaluated. This included an assessment of floating orientation of assembled capsules, using a visual ranking scheme. The ranking scheme was classified as: partially submerged, inclined or vertically oriented. The theoretical metacentric height, or *GM* distance (Figure 1), was also calculated using Equation 4 below and compared with the visual stability evaluation. Additionally, the bulk density of each assembled capsule was also determined. Experiments were performed in triplicate ($n = 3$) for each different HPMC/lactose tablet weights in each case.

In the hydrostatic principles from the study of the 'stability of a floating body',[34] the *GM* distance is a parameter used to evaluate the stability of floating body and it can be applied to a floating capsule body in this study. The *GM* distance can be calculated by knowing the mass and dimensions of the capsule body and tablet components, and by applying Equation 1.[34]

$$GM = \left(\frac{R^2}{4\left(\frac{m_c + m_t}{\pi R^2 d_f} \right)} \right) - \left(\frac{OG_c m_c + OG_t m_t}{m_c + m_t} \right) + \left(\frac{\frac{m_c + m_t}{\pi R^2 d_f}}{2} \right) \quad (1)$$

Where, G_c and G_t are centres of gravity of the capsule body and tablet, respectively and the distances of OG_c and OG_t can be calculated using Equation 2 and Equation 3, respectively.[35]

$$OG_c = \frac{4R^2 + 3\pi R(L-R) + 6(L-R)^2}{3\pi R + 12(L-R)} \quad (2)$$

$$OG_c = \frac{h_t}{2} \quad (3)$$

Therefore, Equation 1 can be expressed as Equation 4.

$$GM = \left(\frac{R^2}{4\left(\frac{m_c + m_t}{\pi R^2 d_f} \right)} \right) - \left(\frac{\left(\frac{4R^2 + 3\pi R(L-R) + 6(L-R)^2}{3\pi R + 12(L-R)} \right) m_c + \left(\frac{h_t}{2} \right) m_t}{m_c + m_t} \right) + \left(\frac{\frac{m_c + m_t}{\pi R^2 d_f}}{2} \right) \quad (4)$$

Table 1 Formulations of lag-time tablets

	Composition						
Formula	Polyox WSR N-750	Polyox WSR 205	Methocel E50 LV	Methocel K100 LV	FlowLac 100	MgSt	Total
F1	40.0	–	–	–	59.5	0.5	100.0
F2	60.0	–	–	–	39.5	0.5	100.0
F3	80.0	–	–	–	19.5	0.5	100.0
F4	–	40.0	–	–	59.5	0.5	100.0
F5	–	60.0	–	–	39.5	0.5	100.0
F6	–	80.0	–	–	19.5	0.5	100.0
F7	–	–	20.0	–	79.5	0.5	100.0
F8	–	–	40.0	–	59.5	0.5	100.0
F9	–	–	60.0	–	39.5	0.5	100.0
F10	–	–	–	20.0	79.5	0.5	100.0
F11	–	–	–	40.0	59.5	0.5	100.0
F12	–	–	–	60.0	39.5	0.5	100.0

All the amounts are shown as milligrams. MgSt, magnesium stearate.

Where, d_f is the density of fluid or medium (mg/ml), m_c is the mass of impermeable capsule body (mg), m_t is the mass of tablet (mg), R is the radius of impermeable capsule body (cm), L is the length of impermeable capsule body (cm) and h_t is the height/thickness of tablet (cm). The dimensions of the floating device that maintains a vertically stable position are shown in Figure 1. For stability, the *GM* distance indicated in Equation 4 must be positive and the stability (restoring force) increases with increasing *GM* distance.[34]

Manufacture of gastroretentive pulsatile capsules

Preparation of model theophylline tablets

A theophylline tablet was composed of 5% w/w theophylline anhydrous, 71.5% w/w FlowLac 100, 20% w/w Prosolv SMCC 90, 3% w/w croscarmellose sodium and 0.5% w/w MgSt.

All powdered ingredients (except for the MgSt) were passed through a 600 μm sieve before use for deagglomeration before tumble mixing for 15 min. MgSt was added and tumbled mixed with the blend for a further 5 min. The powder blend (100 mg) was fed manually into a Model F single punch tableting machine equipped with a 7-mm diameter non-beveled flat faced punch (Natoli Engineering Company, Inc., St Charles, MO, USA) and compressed to a tablet with mean hardness of 7 kilopond (kp) and mean height of 1.9 mm.

Preparation of lag-time control tablets

Lag-time control tablets were prepared by selecting one of four polymers (Polyox WSR N-750, Polyox WSR 205, Methocel E50 LV or Methocel K100 LV). The selected polymer was blended with FlowLac 100 and MgSt as shown in Table 1, using the same procedure as described for the theophylline tablet with mean height of 1.9 mm. Importantly in this study, the thickness of the lag-time tablet was controlled to be at a constant value. This was because the relative tablet thickness had a direct impact on increasing distance of the tablet from the exit point of the floating capsule body (mouth), directly affecting the water ingression and subsequent dissolution profile.

Preparation of spacer tablets

Powder blends comprising 76.5% w/w FlowLac 100, 20% w/w Prosolv SMCC 90, 3% w/w croscarmellose sodium and 0.5% w/w MgSt were prepared by sieving all powdered ingredients (except for the MgSt) through a 600 μm sieve and tumble mixing for 15 min. MgSt was added and tumbled mixed with the blend for a further 5 min. The powder blend was pressed as a spacer tablet with an average weight of 400 mg and mean height of 7.5 mm using a 7-mm diameter non-beveled flat faced punch and compressing to a 20 kp hardness.

Assembly of gastroretentive pulsatile capsule

The capsule was assembled as follows: (i) a spacer tablet was filled into the impermeable capsule body; (ii) a theophylline tablet was placed next to the spacer tablet; (iii) a lag-time tablet was inserted into the mouth of the impermeable capsule body and positioned flush with the end of the impermeable capsule body and finally covered with a gelatin cap (Figure 1). A relatively airtight seal was created in the innermost portion of the impermeable capsule body.

Dissolution of gastroretentive pulsatile capsules

The release rates of the theophylline-containing capsules ($n = 6$) were determined using a USP II Hanson SR-Plus Dissolution Test Station (Hanson Research Corporation, Chatsworth, CA, USA) at a paddle speed of 50 rpm in 500 ml of a 0.1 N HCl buffer solution (pH 1.2) at 37 ± 0.5°C. The theophylline concentration from the dissolution test was automatically measured at 270 nm by UV/VIS spectrophotometer (Agilent Technologies, Inc., Santa Clara, USA) every 10 min. The dissolution data obtained were plotted as percent cumulative drug released versus time. The time of 50% drug release of pulse release ($T_{50\%}$) was also calculated by extrapolation on the time axis of each individual release curve.

Floating characteristics

The floating characteristics of the gastroretentive pulsatile capsules were evaluated during the dissolution study ($n = 6$). The time between the introduction of the whole capsule and its buoyancy on the medium until the floating pulsatile capsule floated in a vertical orientation were observed. The time during which the device remained buoyant (floating duration) was also examined. After the gelatin cap dissolved, the floating orientation of the floating pulsatile capsule on the medium was also assessed using the same visual ranking scheme as in the buoyancy methods section above. Additionally, the *GM* distance was also calculated using Equation 4 and compared with the visual stability evaluation. In addition, the structural integrity of the devices during the study was visually monitored.

Statistical analysis

All data were shown as mean ± standard deviation (SD). $T_{50\%}$ was determined to compare the pulsatile release of all formulations ($n = 6$). In addition, the statistical differences in drug release and $T_{50\%}$ among the investigated formulations were determined using a one-way analysis of variance (JMP 7 software; SAS Institute Inc., Cary, USA). $P < 0.05$ was considered statistically significant.

Results and Discussion

Preparation of impermeable capsule bodies

Many kinds of devices to house pulsatile doses have been discussed previously in the literature, the most extensively described device being a coated gelatin capsule. EC is an insoluble and water-impermeable polymer and it has been used to coat the gelatin capsule in the Pulsincap device[36] and alternative versions of Pulsincap.[37,38] Cellulose acetate has also been used to coat the gelatin capsule in the Port system due to its semi-permeable property.[39] However, the critical areas of coating are around the open mouth of the capsule and the region of the uncoated gelatin inside the capsule. These areas appear to be the easiest point of entry for water into the capsule body, making the gelatin capsule hydrate and lose its structural integrity, eventually resulting in premature release of the drug.[40] To overcome this problem, a dipping process (modified hard gelatin capsule dipping process), followed by removal of gelatin by dissolution was introduced in this study.

Gastric fluid impermeable capsule bodies were prepared with incremental coating thicknesses by varying dipping cycle periodicities, or dipping in different concentrations of coating solutions as presented in Table 2. In general, increasing the body weight of the impermeable capsule also increased the wall thickness of the impermeable capsule thereby increasing the structural integrity. However, it was noted that the dipping process for one cycle in coating solutions with concentration of 8%, 9% and 10% w/v, yielded coatings that were too thin for the capsules to be adequately manipulated for further study.

Since no decrease in weight was found after drying in the oven at 40°C for 12 h, we assumed that the optimal time for curing the polymer and removing all the solvent should be at least 12 h in this study.

Some limitations for the dipping process were also observed and are described as follows. Firstly, the solvent comprising acetone and isopropanol easily vaporizes at room temperature (24–26°C). This results in the precipitation of EC as a white colour on the film during drying after one dipping cycle of the gelatin capsule body in the coating solution with concentration below 8% w/v. However, this problem can be overcome by increasing the number of dipping cycles or using a more concentrated solution of EC (while maintaining the same ratio of EC to TEC at 95 : 5). Secondly, at high concentrations of EC, the coating solution is very viscous resulting in more variation of capsule body weight as shown in Table 2. When dipping into 8%, 9% and 10% w/v EC coating solutions, most weight variability was demonstrated when using the 10% w/v coating solution. Therefore, the viscosity of coating solution also is a concern for the whole coating process.

Acid/water permeability evaluation

In our study, the floating capsule body was designed to restrict water ingress for dissolution/erosion of the tablet content at the single exposed tablet face only. Hence, an acid/water permeability test was conducted to provide assurance that the device was able to resist acid/water permeability until complete drug release had occurred. The ability of the capsule body to resist acid/water uptake was evaluated. Impermeable capsule bodies obtained from more than one dipping cycle

Table 2 Impermeable capsule body weight and resistance time from acid/water uptake

Coating solution (% w/v)	Dipping cycle	Capsule body weight (mg)					Resistance time (hours)
			Coated capsule body after drying at 40°C				
		Gelatin	10 h	11 h	12 h	Impermeable capsule body	
8%	1	56.4 ± 0.9	63.6 ± 1.0	63.7 ± 1.0	63.8 ± 1.0	9.6 ± 0.3	NT
	2	56.4 ± 0.5	78.6 ± 0.3	78.4 ± 0.5	78.4 ± 0.5	24.3 ± 0.3	9
	3	57.0 ± 0.8	93.9 ± 0.7	93.8 ± 0.6	93.7 ± 0.7	38.9 ± 0.7	16
	4	57.1 ± 0.5	111.6 ± 1.2	111.5 ± 1.3	111.6 ± 1.3	56.2 ± 1.4	24
	5	56.7 ± 0.2	127.1 ± 0.6	127.0 ± 0.8	126.8 ± 0.7	71.5 ± 0.7	36
	6	56.6 ± 0.8	142.2 ± 3.3	141.9 ± 3.3	141.8 ± 3.4	85.4 ± 2.4	48
9%	1	57.6 ± 0.4	66.4 ± 0.5	111.6 ± 1.2	66.8 ± 0.3	11.0 ± 0.5	NT
	2	56.8 ± 0.4	82.3 ± 1.2	127.1 ± 0.6	82.5 ± 1.5	27.7 ± 1.3	9
	3	57.0 ± 0.2	99.5 ± 0.6	142.2 ± 3.3	99.5 ± 0.7	44.5 ± 0.9	16
	4	57.0 ± 0.5	116.8 ± 0.6	116.8 ± 0.6	117.1 ± 0.7	62.1 ± 0.4	28
	5	56.6 ± 0.6	136.9 ± 0.3	136.6 ± 0.3	136.8 ± 0.5	81.1 ± 1.0	48
10%	1	57.0 ± 0.7	73.4 ± 1.5	73.6 ± 1.4	73.5 ± 1.4	17.5 ± 1.4	NT
	2	56.8 ± 1.0	94.6 ± 2.5	94.6 ± 2.5	94.9 ± 2.6	38.5 ± 2.2	12
	3	56.9 ± 0.5	121.4 ± 5.9	121.2 ± 5.9	121.3 ± 5.8	63.8 ± 5.1	24

NT, no test required due to very thin wall of EC capsule body. Data are means ± SD, $n = 6$.

were able to resist the acid uptake for more than 24 h, as seen from the lack of indicator colour change. However, moisture or water could still traverse the wall of EC, and subsequently we observed that the unchanged litmus indicator permeated inside of the capsule wall. Therefore, the resistance time of impermeable capsule body could be limited by water uptake resistance failure (Table 2).

After dipping into 8% w/v coating solution for two, three and four cycles, impermeable capsule bodies with average weight of 24, 38 and 56 mg showed good resistance to acid or water uptake for 9, 16 and 24 h, respectively. In addition, the impermeable capsule bodies with average weight of 71 and 85 mg from the dipping process for five and six cycles showed excellent resistant times greater than 24 h.

The impermeable capsule bodies prepared by dipping in 9% w/v and 10% w/v coating solution also showed excellent resistance to acid or water uptake as shown in Table 2. Based on a desired gastroretention time of the device, the resistance time of the impermeable capsule body to acid/water permeability could be used to select an appropriate impermeable capsule body for use as a vessel to contain tablet contents.

Buoyancy and optimal loading capacity

The gastroretentive performance of floating drug delivery systems was evaluated for floating duration as well as buoyancy performance by using a USP type II dissolution apparatus.

Theoretically, a device can float when the buoyancy force exerted by the fluid is more than the opposite force from gravity (as a function of the overall mass of the assembled capsule) (Figure 2) or the device floats when the total force, F, acting vertically on the device is positive (Equation 5).[41]

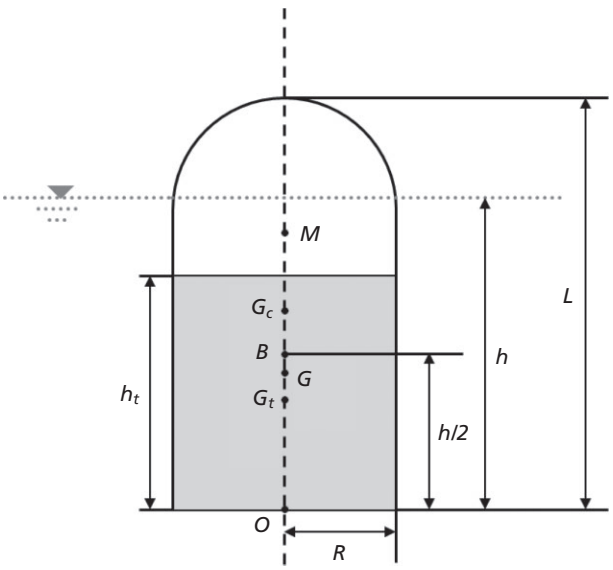


Figure 2 Stable position (vertical orientation) relative to water line (round dots) of floating capsule body containing tablet insides: *B*, centre of buoyancy; *G*, centre of gravity; *M*, metacentre; G_c, centre of gravity of impermeable capsule body; G_t, centre of gravity of tablet; *h*, depth of immersion; *R*, radius of impermeable capsule body; *L*, length of impermeable capsule body; h_t, height of tablet. (modified from IIHR-Hydroscience & Engineering (1999), Edwards & Penny (2002)[34,35]).

$$F = F_{Buoyancy} - F_{Gravity} \tag{5}$$

Equation 2 can also be written as follows:[42]

$$F = (d_f - d_s)gV = \left(d_f - \frac{W}{V}\right)gV \tag{6}$$

Where, d_f is the density of the fluid or medium (mg/ml), d_s is the density of the solid object or device (mg/ml), g is the acceleration due to gravity (m/s^2), V is the volume of the device (ml) and W is the mass (weight) of the device (mg).

For buoyancy, the term of $\left(d_f - \frac{W}{V}\right)$ has to be a positive value. Hence:

$$W < d_f V \tag{7}$$

In the floating capsule body, W is a total mass of m_c and m_t assuming the mass of air inside the device is negligible, so Equation 7 can be expressed as follows:

$$(m_c + m_t) < d_f V \tag{8}$$

Equation 8 can be rearranged to determine maximum weight of tablet (m_t) as follows:

$$m_t < (d_f V) - m_c \tag{9}$$

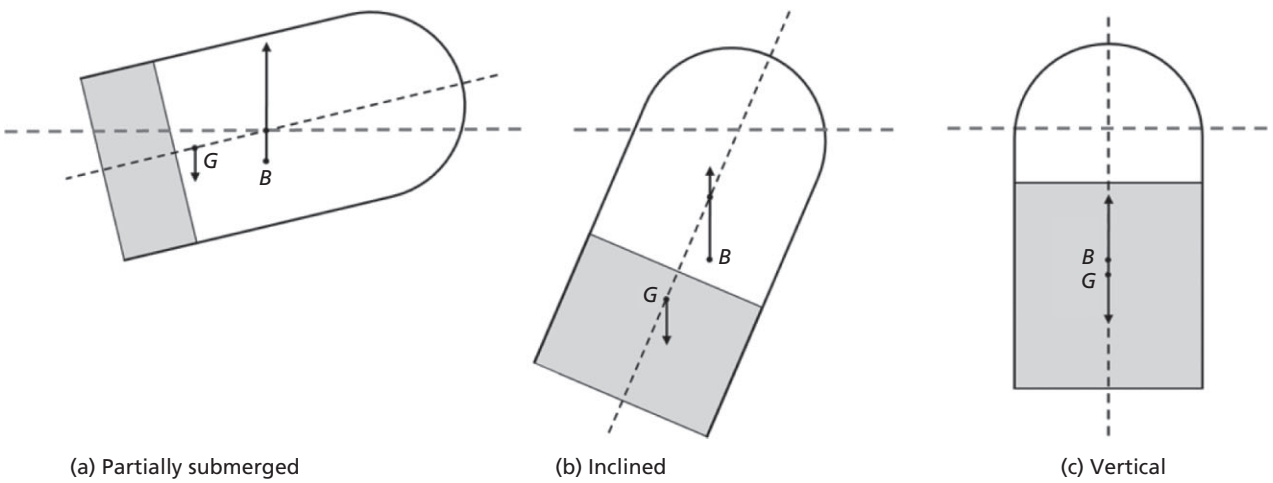
We can calculate the volume of the capsule body by measuring its dimensions. We also know the approximate density of the medium or the gastric contents (~1 g/ml). Therefore, we can calculate the maximum weight of tablet (m_t) contained inside the capsule body that can enable the maintenance of buoyancy in the medium using Equation 9.

In general, the floating device should be less dense than the stomach contents and thus remain in the fundus region of the stomach, where mixing of the stomach contents occurs to a lesser extent.[43] Critically, the floating position in the fluid could be partially submerged, inclined or vertically orientated by increasing the tablet mass inside the capsule body, respectively as shown in Figure 3. Since dissolution/erosion occurs only at the exposed side of tablet facing the medium, the vertical floating position will promote the maintenance of a constant surface area for dissolution or erosion of tablet inside the floating device.[18,40,44]

However, peristaltic contraction in the stomach will act on the capsule and potentially force the capsule to sink or, worse still, be ejected from the stomach before the drug release is accomplished. With the potential for external forces to act on the capsule, the buoyancy test in the USP type II apparatus was not considered to be sufficient to determine the floating status or stability of floating devices in the gastric fluids. So, to compliment this test the theory of gravitational metacentric (GM) distance was applied to theoretically determine the optimal loading capacity of the capsule body (Figure 4).

In hydrostatic principles, a floating body in the vertical position is also said to be stable to resist a small disturbance because there is sufficient restoring force for it to correct itself to its vertical position again after tilting.[34,45,46] The restoring force can be determined from the GM distance using Equation 4; a higher GM distance indicates a greater restoring force of the device.

Indeed, the buoyancy force acts through the centre of buoyancy, B, and it depends on the shape of the submerged volume. At the most stable position (vertical), the buoyancy force acts through the centre of gravity, G. In this stable position, the floating device can correct itself back after tilting due to an external force. After tilting, the original water surface (OO) is moved to the new water line ($O'O'$) (Figure 4). G remains in the same position relative to the overall mass of the floating device, but B moves from B to B' because the shape of the submerged volume has changed. The intersection point of the action lines of the buoyancy force before and after tilting is called the metacentre (M). For stability of floating devices,



(a) Partially submerged (b) Inclined (c) Vertical

Figure 3 Three possible floating orientations of the floating capsule body relative to the water line (horizontally dashed line). *B*, centre of buoyancy; *G*, centre of gravity.

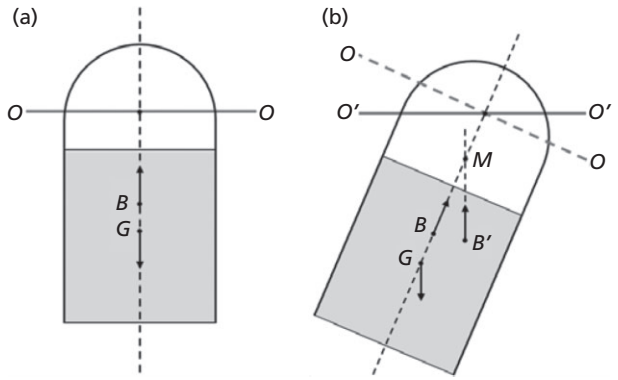


Figure 4 Metacentric height (*GM* distance) of a floating capsule body composed of an impermeable capsule body, an HPMC/lactose tablet positioned flush with the end of the impermeable capsule body and an air seal in the innermost portion of the impermeable capsule body. (a) Vertical position. (b) After tilting.

M must be above *G* or the distance of *GM* must be a positive value because a higher *GM* distance results in a greater restoring force for the floating device to correct itself to its stable position. This also represents greater stability of the floating device to resist the disturbance from sinking.

To investigate the stability of the floating device we set up the loading capacity test using a horizontal shaker method. Each device was horizontally shaken at 100 rpm for 2 min, which was enough time to determine whether each differing bulk density could float in vertical orientation or not. Different bulk densities of the devices were achieved by varying inserted tablet masses to evaluate the optimal loading range for the vertical floating orientation.

The results of the stabilized buoyancy and loading capacity test are shown in Table 3. Increased tablet weights incorporated into the capsule bodies resulted in an increased overall density, and the assembled capsule bodies sank above the critical density of the medium (approximately 1 g/ml). Interestingly, some capsule bodies sank while they were horizontally shaken at 100 rpm even though their densities were below the medium's density. This indicates that stabilized buoyancy is the important factor and must be evaluated early on in formulation design of these gastroretentive drug delivery systems. It was found that devices were able to float on the surface of the medium in a vertical orientation when their densities were approximately 0.71–0.98 g/ml, corresponding to an optimal loading capacity of 450–645 mg. The *GM* distance increased with increasing tablet weight inside the capsule body; this corresponded in practical terms to increasing vertical buoyancy with more stable buoyancy of devices.

Manufacture of gastroretentive pulsatile capsules

In this work, EC capsule bodies manufactured with an average weight of 56 mg were selected to house the pulsatile dose because their resistance time for acid and water uptake (up to 24 h) and the optimal loading capacity were determined in the previous section.

The data from Table 3 was used to design the optimal loading capacity of floating capsule bodies for maintaining buoyancy in a good vertical stable orientation. For this propose, a spacer tablet was chosen to adjust the mass inside the floating capsule body. Therefore, the optimal tablet mass was divided into three parts, including a lag-time tablet, a drug tablet and a spacer tablet, as outlined in Figure 2.

In this study all tablets were compressed with a 7-mm diameter non-bevelled flat-faced punch that fitted tightly inside the impermeable capsule shell. Also, the outer surface of the lag-time tablet was pushed flush with the open end of the impermeable capsule body. The tight fit between the lag-time tablet and the impermeable capsule shell plays an important role in preventing fluid penetration to the capsule content and drug release before complete erosion of the lag-time tablet.[18]

Dissolution of gastroretentive pulsatile capsules

An important aspect of the design is related to control of drug release by an eroding lag-time layer. Erosion materials must be carefully selected to provide the most reproducible and predictable drug release time. To select appropriate materials for the lag-time tablet, PEO and HPMC were chosen as candidates. Both polymers have been widely used for controlled or sustained-release formulations.[12,18,47,48] In addition, these polymers generally dissolve uniformly irrespective of pH, so they would be suitable for use in the stomach, which has a natural variation of pH during the day.[49,50] Theophylline was selected as a model drug due to it having mid-range solubility and being an easily detectable chromophore. This is applicable with the dissolution apparatus assembled in-line with a UV detector for automated analysis over long periods.

Upon contact with medium, following the rapid dissolution of the gelatin cap, all selected polymers in the study were able to form a gel layer that rapidly sealed the mouth of the capsule body. This gel seal acts as a barrier to water ingression, allowing lag-time control to be imparted. After the predetermined lag-time, governed by the dissolution/erosion of the lag-time tablet, the drug was released in a pulsatile pattern.

The effects of polymer content on controlling lag-time period and drug release for each polymer were studied and data is shown in Figures 5–8. In general, increasing the polymer concentration caused an increase in lag-time period before pulse release of the drug. Also, the higher viscosity grade of polymer resulted in longer lag-times. The time of 50% drug release of each formulation ($T_{50\%}$) was calculated as

Table 3 Buoyancy parameters of investigated floating capsule bodies

m_{total} (mg)	m_c (mg)	L (cm)	R (cm)	m_t (mg)	h_t (cm)	GM (cm)	Floating behaviour	Bulk density (g/ml)
157.1 ± 0.8	56.9 ± 0.8	1.80 ± 0.01	0.37 ± 0.00	100.3 ± 0.6	0.19 ± 0.00	-0.10 ± 0.00	Partially submerged	0.22 ± 0.00
257.4 ± 0.2	56.8 ± 0.7	1.79 ± 0.01	0.37 ± 0.00	200.7 ± 0.5	0.38 ± 0.00	0.02 ± 0.00	Partially submerged	0.36 ± 0.00
356.1 ± 0.6	56.0 ± 0.6	1.79 ± 0.01	0.37 ± 0.00	300.2 ± 0.8	0.57 ± 0.01	0.09 ± 0.00	Inclined	0.50 ± 0.00
458.3 ± 1.3	56.5 ± 0.5	1.80 ± 0.00	0.37 ± 0.00	402.0 ± 1.9	0.76 ± 0.01	0.13 ± 0.00	Inclined	0.65 ± 0.01
510.2 ± 2.0	57.2 ± 0.4	1.80 ± 0.01	0.37 ± 0.00	453.3 ± 2.1	0.84 ± 0.00	0.16 ± 0.00	Vertical	0.71 ± 0.01
516.7 ± 1.2	56.8 ± 0.2	1.80 ± 0.01	0.37 ± 0.00	460.1 ± 1.5	0.86 ± 0.01	0.16 ± 0.00	Vertical	0.72 ± 0.00
558.4 ± 0.9	57.3 ± 0.3	1.80 ± 0.01	0.37 ± 0.00	501.1 ± 0.6	0.95 ± 0.02	0.17 ± 0.00	Vertical	0.79 ± 0.01
657.9 ± 0.3	56.7 ± 1.0	1.80 ± 0.00	0.37 ± 0.00	601.3 ± 0.9	1.12 ± 0.01	0.21 ± 0.00	Vertical	0.92 ± 0.01
700.6 ± 0.5	55.5 ± 0.4	1.80 ± 0.01	0.37 ± 0.00	645.2 ± 0.5	1.20 ± 0.01	0.22 ± 0.00	Vertical	0.98 ± 0.01
706.1 ± 0.7	56.6 ± 0.8	1.80 ± 0.01	0.37 ± 0.00	649.7 ± 1.2	1.21 ± 0.01	–	Sink	0.99 ± 0.00
710.4 ± 0.4	55.8 ± 0.5	1.79 ± 0.01	0.37 ± 0.00	654.7 ± 0.5	1.22 ± 0.01	–	Sink	1.00 ± 0.00
715.3 ± 0.2	56.6 ± 0.5	1.80 ± 0.00	0.37 ± 0.00	659.1 ± 0.5	1.22 ± 0.01	–	Sink	1.00 ± 0.00
722.0 ± 0.9	57.0 ± 0.4	1.81 ± 0.00	0.37 ± 0.00	665.1 ± 0.5	1.24 ± 0.01	–	Sink	1.00 ± 0.00

All the values are shown as mean ± SD, n = 3. Testing condition: horizontally shaking at 100 rpm in 0.1 N HCl buffer solution 900 ml.

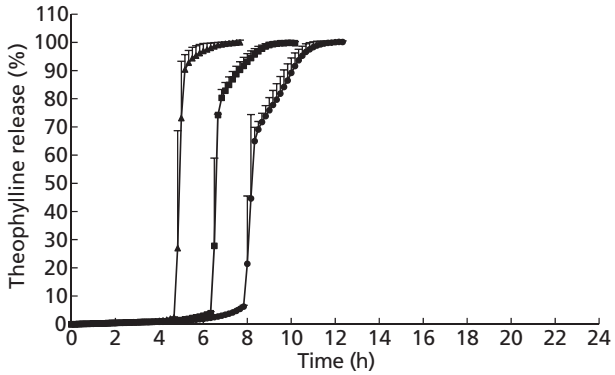


Figure 5 Dissolution profiles of the platform fitted with 100 mg lag-time tablet containing 40% (▲), 60% (■) and 80% (●) Polyox WSR N-750 (n = 6, error bars represent the standard deviation).

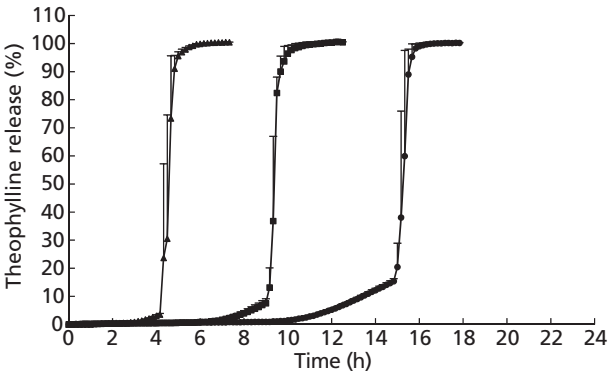


Figure 7 Dissolution profiles of the platform fitted with 100 mg lag-time tablet containing 20% (▲), 40% (■) and 60% (●) Methocel E50 LV (n = 6, error bars represent the standard deviation).

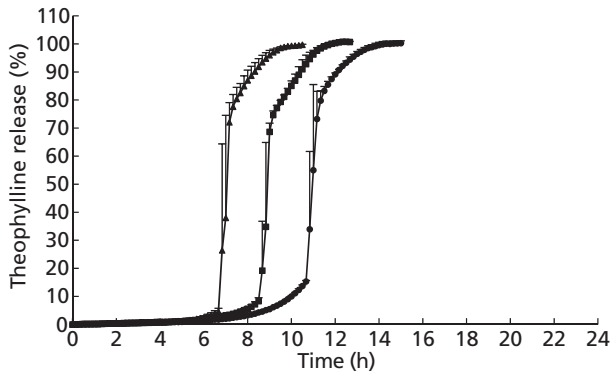


Figure 6 Dissolution profiles of the platform fitted with 100 mg lag-time tablet containing 40% (▲), 60% (■) and 80% (●) Polyox WSR 205 (n = 6, error bars represent the standard deviation).

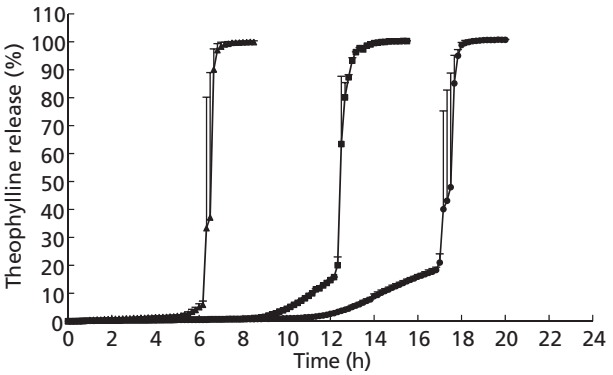


Figure 8 Dissolution profiles of the platform fitted with 100 mg lag-time tablet containing 20% (▲), 40% (■) and 60% (●) Methocel K100 LV (n = 6, error bars represent the standard deviation).

Table 4 Effect of polymer type and concentration in the lag-time tablet on the time of 50% drug release ($T_{50\%}$)

	$T_{50\%}$ (h)			
	Polymer concentration (%)			
Polymer type	20	40	60	80
Polyox WSR N-750	–	4.9 ± 0.1	6.6 ± 0.1	8.1 ± 0.1
Polyox WSR 205	–	7.0 ± 0.2	8.9 ± 0.1	10.9 ± 0.2
Methocel E50 LV	4.5 ± 0.2	9.4 ± 0.1	15.3 ± 0.2	–
Methocel K100 LV	6.5 ± 0.3	12.5 ± 0.1	17.4 ± 0.3	–

T50, time of 50% drug release. All the values are shown as mean ± SD, $n = 6$. Significant difference: $P < 0.05$.

shown in Table 4. Increasing the polymer content in the lag-time tablet was found extend $T_{50\%}$.

Higher polymer content in the lag-time tablets was shown to increase the incidence of premature drug release. This might be a result of faster diffusion of soluble drug through the gel layer than actual polymer erosion. The basic principle of hydrophilic polymer erosion involves water ingress followed by polymer dissolution.[51] In this study, the lag-time tablet surface wets and the polymer starts to partially hydrate and form a gel layer after being exposed to the medium. The medium continues to penetrate through the tablet and on into the capsule device through the gel layer; thereby the soluble drug can diffuse through this gel layer and results in the premature release of drug before the lag-time tablet has completely eroded.

Additionally, when considering a single pulsed release from the floating device, only the outermost erosion layer is of importance. Therefore, it is essential that the lag-time layer, comprising polymer which rapidly hydrates and forms gel to seal the mouth of capsule body, acts as a barrier to water ingression for controlling lag-time and preventing premature drug release. This has previously been shown to be important to prevent premature drug release from erosion controlled capsules.[38] Also, the hydrophilicity of lactose possibly enhances the surface wetting of the polymer in the lag-time tablet, promoting rapid dissolution.[48,52]

Apparent retardation of drug was seen once drug release was initiated in the PEO-containing formulations and this has a profound effect at the higher content of PEO in the lag-time tablet. However, no retardation of drug was observed for the HPMC-containing formulations. The PEO-containing formulations present a higher constant gel layer thickness compared with the HPMC-containing formulations at an equivalent time period,[53] thus allowing more time for complete erosion of the lag-time tablet and also the dissolution process of the drug tablet is slowed down. Gel layer formation in the HPMC-containing formulations is slower than that in the PEO-containing formulations due to a more rapid erosion process.

Table 5 Buoyancy parameters of the floating pulsatile capsules for all formulations of gastroretentive pulsatile drug delivery platforms

Parameters	
m_{total} (mg)	657.25 ± 1.49
m_c (mg)	56.20 ± 0.60
L (cm)	1.79 ± 0.01
R (cm)	0.37 ± 0.00
m_t (mg)	600.90 ± 0.38
h_t (cm)	1.13 ± 0.01
CM (cm)	0.20 ± 0.01
Overall density (g/ml)	0.93 ± 0.02
Floating behaviour	Vertical orientation

m_{total}, total mass of floating pulsatile capsule; m_c, mass of impermeable capsule body; L, length of impermeable capsule body; R, radius of impermeable capsule body; m_t, mass of tablet; h_t, height/thickness of tablet; GM, theoretical metacentric height. All the values are shown as mean ± SD, $n = 72$.

Floating characteristics

All devices floated immediately (no observable delay was noted) after being dropped into the medium. After the gelatin cap dissolved, the floating pulsatile capsule instantly floated in a good vertical orientation relative to the medium until the drug tablet was released completely. In the vertical orientation, the floating pulsatile capsule would have a constant surface area of the lag-time tablet facing with the medium or gastric fluid for dissolution/erosion, providing the best control of pulsatile release compared with the partially submerged or inclined oriented positions. The bulk density of the floating capsule bodies was about 0.93 g/ml, lower than that of the gastric contents. Also, the GM distances within the floating pulsatile capsules were determined as positive values, representing a good vertically stable orientation of the assembled floating pulsatile capsules (Table 5). Furthermore, all assembled floating pulsatile capsules showed excellent structural integrity during the dissolution study. These properties are necessary for gastroretentive delivery systems to prevent destruction and/or relocation of the device into the lower parts of the gastrointestinal tract during peristaltic contraction.[54]

In general, the buoyancy of a device is dependent on its overall density, which should be below 1 g/ml (the approximate density of gastric fluid), until such a time as complete drug release has occurred. In this study, the novel device maintained buoyancy efficiently due to its excellent integrity over the experimental period. Only the tablet inside the floating pulsatile capsule was dissolved and/or eroded by the medium. Although the medium occupied the empty area of dissolved or eroded tablet mass instead, the overall density of devices was maintained below 1 g/ml. Since the medium's density is usually less than that of the tablet, the medium mass inside the capsule body was lower than the part of the

dissolved or eroded tablet mass. Furthermore, air content in the devices was maintained throughout, and this was enough to keep buoyancy during dissolution study.

Conclusions

A new gastroretentive pulsatile drug delivery platform has been developed. The floatability of the platform could be well controlled by having the air compartment in the innermost portion of the impermeable capsule body and adding the optimal loading capacity in order to reduce the overall density of the device. The optimal tablet mass could be adjusted by adding the internal spacer tablet. Additionally, a gravitational metacentric height (or *GM* distance) of the floating device was observed to be a good predictor of overall floating stability in a critical vertical orientation. Importantly, manipulation of the amount or specific grade of water soluble polymer in the lag-time tablet enables control of specific pulsatile lag-time. This novel gastroretentive pulsatile device could easily be adapted for oral administration with a variety of drugs, and could be especially useful for targeted chronopharmaceutical therapy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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