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A novel system for three-pulse drug release based on "tablets in capsule" device

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Abstract

The objective of the present study was to obtain programmed drug delivery from a novel system, which contains a water-soluble cap, impermeable capsule body, and two multi-layered tablets. Types of materials for the modulating barrier and its weight can significantly affect the lag time (defined as the time when drug released 8% of the single pulse dosage). We chose sodium alginate and hydroxy-propyl methyl cellulose (HPMC E5) as the candidate modulating barrier material. Through adjusting ratio of sodium alginate and lactose, lag time was controllable between the first two pulsatile release. Linear relationship was observed between the ratio and the lag time. Through adjusting the ratio of HPMC E5/lactose, lag time between the second and the third pulse can be successfully modulated. In further studies, drug release rate of the second pulsatile dose can be improved by adding a separating layer between the third and the modulating barrier layer in the three-layered tablet. To evaluate contribution of bulking agent to drug release rate, lactose, sodium chloride, and effervescent blend were investigated. No superiority was found using sodium chloride and effervescent blend. However, lactose favored it. The results reveal that programmed drug delivery to achieve pulsatile drug release for three times daily can be obtained from these tablets in capsule system by systemic formulation approach.
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Keywords: Pulsatile; Sodium alginate; Multi-layered tablets

1. Introduction

Assuming that physiological processes and biological functions display constancy over time, much effort had been devoted in the past in developing the drug delivery systems that maintain a flatter plasma level for an extended period of time. However, chronobiological studies belie this concept. Along with many applications in local and systemic delivery of drugs, pulsatile release system would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. So by developing the pulsatile device, plasma peak is obtained at an optimal time, number of doses per day can be reduced; saturable first pass metabolism and tolerance development can also be avoided. Pulsatile drug release system, which allows the release of active pharmaceutical material in single or successive pulses at precise and well controlled time periods, is a recently developed drug delivery system (Bussemer et al., 2003). As close attention is paid to chronopharmacology (Lemmer, 2000), though it is in its infancy, great progress has been made in pulsatile tablets (Fan et al., 2001; Sungthongjeen and Puttipipatkhachorna, 2004), pulsatile microspheres (Makino et al., 2000), pulsatile capsules (Mohamad and Dashevsky, 2006; Sutch et al., 2003; Bussemer and Bodmeier, 2003). Recently, other systems, pulsatile implants (Gusea et al., 2006) as an example, in this field have been successfully studied. However most of these studies focus on single-pulse drug release system. Drugs are usually encapsulated in one way or another within a barrier material, which is composed of an erodible or biodegradable polymer. Depending on the barrier material structure and thickness, different release lag times can be achieved. After the barrier material is dissolved, eroded or degraded, drugs are rapidly released from the inner reservoir core.

Based on the concept that a formulation given once a time daily, a three-pulse drug release system proposed for oral administration was designed, for achieving the selective delivery of

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drugs at appropriate time, which is a chronopharmaceutical approach for the better treatment of disease with circadian rhythms.

This novel system is a so-called "tablets in capsule device" (impermeable cylinder Zou and Jiang, 2007, tablet-in-capsule system Liang-Kan et al., 2005). The designed capsule device consists of an impermeable capsule body and a soluble cap. The multi-layered tablets formulation prepared is filled within the capsule body and sealed with the water-soluble cap. A three-layered tablet (Abdul and Poddar, 2004; Conte and Maggi, 2000), which serves as the first two pulses, a two-layered tablet or in powder forms, which forms the third pulsatile drug release. Both multi-layer tablets are inserted into an impermeable capsule body with a water-soluble cap, lactose filled in the bottom. On reaching body fluid, the cap dissolved and the first pulse released, following which the modulating barrier swelling and eroded which cause a lag phase preceding the onset of release of the second pulse. The modulating barrier of the bi-layered tablet performs the same role. Tag time can be successfully controlled by adjusting the ratio of barrier materials and lactose. To accelerate the release rate of the second pulse, a separating layer is added between the quick release layer and the modulating barrier layer in the three-layered tablet. The significance of factors, such as types of barrier materials, weight of barrier layer, tablets hardness, location of tablets in capsule, and bulking agent, were investigated in order to characterize the lag time and the drug release profiles.

Diclofenac sodium was chosen as a model active pharmaceutical material.

2. Experimental

2.1. Instrument and materials

752C UV spectrophotometer (The Third Analytical Apparatus, Shanghai, China), ZRS-4 Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China), single punch press (TDP type; First Pharmacy Machine, Shanghai, China), 78X-2 hardness tester (Huanghai Pharmacy Machine, Shanghai, China).

Diclofenac sodium (DS, Tiande Pharmacy, Tieling, China), hydroxy-propyl methyl cellulose (HPMC, Methocel® E5, E15, E50, Colorcon, Shanghai, China, METOLOSE® SR 2208 100CP, Shin-Etsu Chemical Co., Ltd.), low-substituted hydroxypropyl cellulose (L-HPC, NF LH-B1, Shin-Etsu Chemical Co., Ltd.), ethylcellulose (EC, ETHOCEL® 45CP, Colorcon, Shanghai, China), crospovidone (PPVP, POLYPLASDONE® XL, International Special Product, Shanghai, China), microcrystalline cellulose (MCC, Celldone® 102 CG), lactose (Yi Yang Biochemical, Hunan, China), sodium alginate (Keltone® HVCP, International Special Product), polyvinylpyrrolidone (Kollidon® 30, BASF, Ludwigshafen, Germany), carbopol (CARBOPOL® 940 NF, NOVEON, US), carboxymethyl starch (CMS-Na, JRS, Germany), dimethylphthalate (DMT, Chemical Agent, Shanghai, China), dichlormethane (DCM, Chemical Agent, Nanjing, China), citric acid (Chemical Agent, HeFei University of Technology, China), sodium bicarbonate (Chemical Agent), sodium chloride (Chemical Agent), capsule (0#, CAPSUGEL, Suzhou, China).

2.2. Preparation of impermeable capsule body

The impermeable capsule body is constituted of EC (ETHOCEL® 45CP). 10% EC dichloromethane solution, with 0.5% DMT as plasticizer, was prepared before filling into the 0# gelatin capsule body. Then the solvent was evaporated overnight at 4 °C in refrigerator. Afterwards, the capsule body and the untreated soluble cap were stored in desiccators for further use. During the experimental time, the EC capsule body shows no water permeability and the capsule body can be used in this study for daily administration.

2.3. Preparing of three-layered tablets

Powders of both modulating barrier and rapidly release layer (DS:PPVP:lactose 1:1:1), with 0.5% magnesium stearate added as lubricant were sieved through an 80 mesh sieve, respectively. Then the three-layered tablets were prepared by progressively filling the die of a single-punch tableting machine by hand with weighed amounts of a homogeneous mixture of the respective powders followed by compression.

2.4. Fabrication of bipulsed capsule

The three-layered tablet was inserted into the capsule body with a soluble cap. 250 mg lactose was added to assure the upper surface of the tablet flushed with the open end of the capsule body. The tablet (75 mg, diameter 7 mm) fitted snuggly with the wall of the capsule. The whole device is shown in Fig. 1 (without tablet B, which was substituted by lactose).

2.5. Studies of modulating barrier

To select appropriate materials for the modulating barrier, HPMC (E5, E15, E50, 100CP), sodium alginate, carbopol (940 NF), CMS-Na were chosen as candidates, which were commonly used materials for controlled or sustained release.

2.5.1. Studies of weight of modulating barrier influence on drug release

To characterize the influence of modulating barrier weight, three-layered tablets of different modulating barrier weight (100,

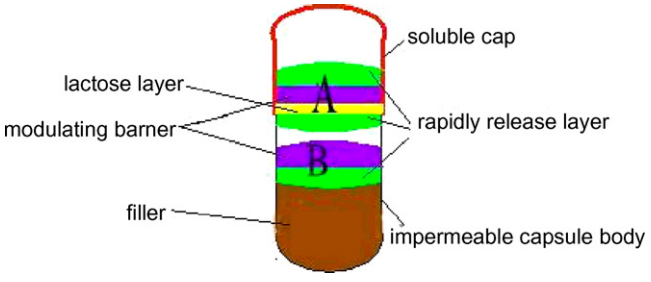

Fig. 1. Conceptual diagram for three-pulse capsule device. A: Three-layered tablet with a additional lactose layer. B: Bi-layer tablet.

150, and 200 mg, sodium alginate/lactose 3:7) were prepared. Capsules were packed as described in Section 2.4. Then in vitro dissolution was carried out ($n = 3$). A total of 900 ml dissolution medium (deionized water) was filled into the standard USP 26 type I dissolution apparatus. The capsules were placed in the basket and the speed was adjusted to 100 rpm. Temperature of the medium was maintained at 37 °C to simulate body temperature. 5 ml of samples were withdrawn at appropriate time intervals, with the same volume of fresh medium supplemented to maintain a constant volume of 900 ml. The aliquots were suitably diluted by corresponding dissolution media and analyzed for drug content using 752C UV spectrophotometer ($\lambda = 276$ nm).

The concentration of Diclofenac sodium (C_n) at a certain time is determined by standard curve and the actual concentration (c) is calculated from $c = C_n + \sum_{i=1}^{n-1} C_i \times 5/900$ (n is the time of sampling corresponding to C_n). According to $v = [\mathrm{d}((100c/c_\infty)/\mathrm{d}t][\%/h]$, where t is defined as the midpoint time of two next sampling points corresponding to v, velocity–time ($v - t$) curve is plotted.

2.5.2. Studies of in vitro behavior with different sodium alginate/lactose ratio as barrier

To characterize the influence of sodium alginate ratio (with lactose as moderator) on the in vitro dissolution profiles, three-layered tablets of various alginate ratios were prepared (20, 30, 35, 40, 50 and 60%), 250 mg lactose served as filler at the bottom of capsule body ($n = 3$).

2.5.3. Influence of tablets hardness

To establish the impact of tablets hardness on the lag time of this device, three-layered tablets of different rigidity (3.4, 7.5, and 13 kg/mm) was prepared. Hardness of tablets was determined by 78X-2 hardness tester. To assure the upper surface of the tablet flushed with the open end of the capsule body, amount of lactose which served as filler was adjusted ($n = 3$).

2.6. Influence of separating layer on drug release rate

As the results revealed (Fig. 5), though same formulation of the rapidly release layer in three-layered tablets, drug in the second pulse released more slowly. However, when peeling off every layer of tablets, gomphosis (or adherence) existed between layers, especially between the third and the second. A separating layer was added between the bottom layer and the second. Lactose, for its excellent water solubility, was chosen as the right material. Then the so-called three-layered tablets were constituted of four layers.

2.7. Evaluation of bulking agent efficiency on drug release rate

The gas generated may push drug out after lag time, so effervescent blend as bulking agent may accelerate drug release and sodium chloride is widely used in osmotic pump system as osmotic agent (Liu and Che, 2006). To establish bulking agent efficiency on drug release rate, we chose lactose, effervescent blend (citric acid/sodium bicarbonate 2:1), sodium chloride (high osmotic pressure) as candidate fillers. Two kinds of three-layered tablets were prepared, named tablets A and B. In tablet A, the rapidly release layers were prepared according to Section 2.3, and the modulating layer was formed by compressing 100 mg sodium alginate/lactose (40:60). The upper two layers of tablet B were coincident with tablet A, while the formulation of the bottom layer is shown as follows: Diclofenac sodium:citric acid:sodium bicarbonate:crospovidone 2.5:2.33:1.17:1.5. Tablets A were packed into capsules with lactose, effervescent blend, sodium chloride filled at the bottom, respectively, while tablet B with lactose ($n = 3$).

2.8. Studies of the third pulse lag time

Bi-layered tablets (sodium alginate/lactose 20:80 as modulating barrier) were prepared to establish influence of tablets location in capsule body. The tablets were inserted into the capsules with upper-layer (the barrier layer) flushed with the open end, 1/3, 2/3 of the capsule body. 325, 200, and 150 mg lactose was filled, respectively ($n = 3$), so that precise location could be assured. However, tablets would slide and could not hold its position in dissolution apparatus. To assure that it would not slide, the tablets were treated with 10% polyvinyl pyrrolidone (PVP) ethanol solution. Tablets brushed with PVP solution around its surrounding surfaces would stick to the capsule body and would not glide when handling. And as revealed in this study, it would not influence the dissolution behavior.

Since upper-layer of the bi-layered tablets (the barrier layer) would be flush with 2/3 of the capsule body in the final device, blank rapidly disintegrating tablets without drug were prepared, whose formulation is same to the rapidly release layer with equal amount of drug substituted by microcrystalline cellulose (MCC). Weight of these blank tablets equals to the three-layered tablets.

2.9. Fabricating of capsule device for three pulses drug release

2.9.1. Fabricating of capsule device for three pulses drug release with bi-layered tablets served as the third pulse

To achieve three pulses drug release, a novel system was designed. The system consists of a water-soluble cap, impermeable capsule body, and two multi-layered tablets (shown in Fig. 1).

Lactose was filled into the capsule body to assuring that the upper surface of the three-layered tablet flushed with the open end of the capsule body.

2.9.2. Fabricating of capsule device for three pulses drug release with multi-layered powders served as the third pulse

The device is similar to the one shown in Fig. 1. The bi-layered tablet is substituted by two powder layers with a lactose layer between; one served as the modulating barrier and the other the rapidly release layer.

3. Results and discussion

It was shown that HPMC of any type selected established barrier behavior. Further studies show that lag time using HPMC of hyper viscosity (100 cp) is too long (>8 h) even in low ratio to lactose. The other types show low reproduction quality. But HPMC E5 can be used as the third pulse modulating barrier materials as shown in the following studies. CMS-Na shows no barrier ability. Carbopol behaves as the HPMC of hyper viscosity. Fortunately, sodium alginate was found attractive due to its frequent use as suitable materials to achieve delays in drug release.

3.1. Influence of modulating barrier weight on lag time

In Mukesh C. Gohel's study (Gohel and Manhapra Sumitra, 2002), drug release was found to be inversely proportional to the weight of the plug. However, they designed their system by ejecting the plug after lag time using an effervescent blend as driving force.

In our studies, corrosion of the modulating barrier contributes most to the onset of drug release. Data shown in Fig. 2 reveals that modulating barrier weight can significantly affect lag time. Further studies show that increasing the amount of modulating barrier can cause trouble during inserting into the capsule (increased tablets thickness). We chose 100 mg as the favorite amount for modulating barrier.

3.2. Influence of sodium alginate ratio on drug release lag time

The naturally occurring alginate polymer has long been used in food and beverage industries as thickening, gel-forming and colloidal stabilizing agents. In addition to being a widely used food additive, alginate possesses several characteristics that make it a potential biopolymer suitable for the development of controlled-release systems (Liew et al., 2006). Primary studies show that sodium alginate can be used as a modulating barrier material for its high gel-forming ability. Through adjusting sodium alginate ratio in the modulating barrier, we got lag time controllable drug pulsatile release. The results are shown in Fig. 3. Linear relationship was observed between ratio of sodium alginate/lactose and lag time. ($y = 10.367x + 0.6061$, $R^2 = 0.9681$).

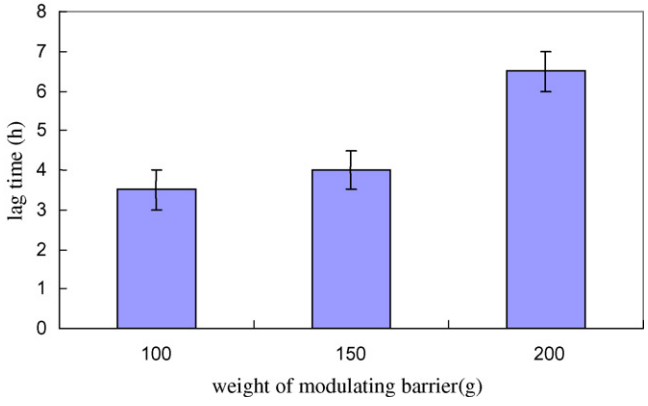

Fig. 2. Influence of modulating barrier (sodium alginate/lactose 3:7) weight on the lag time (mean ± S.D., $n = 3$).

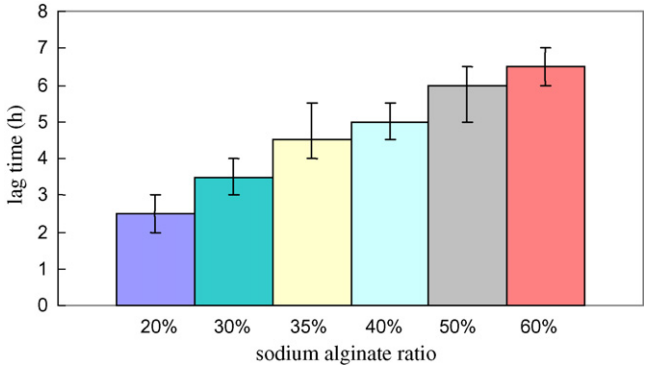

Fig. 3. Influence of sodium alginate ratio on drug release lag time (mean ± S.D., $n = 3$).

3.3. Influence of tablets hardness

As the multi-layered tablets will be inserted into the capsule body, it will be mechanically stable. However, increased hardness may cause high tableting energy. Fortunately, the hardness of multi-layered tablets has no influence on drug release behavior (Fig. 4). To get a mechanically stable tablet, we chose a higher pressure during tableting process (hardness of tablets: 10–13 kg/mm).

3.4. Influence of separating layer on drug release rate

Gomphosis might be formed when multi-layered tablets were prepared. Increased prepressing pressure could weaken gomphosis, which attenuated affinity between layers and caused fissure. As the first pulse released rapidly when the cap was dissolved, gomphosis did not cause significant influence on drug release rate. Lactose is a water-soluble material and in this novel system, it serves as filler at bottom of capsule body. Also it can significantly accelerate drug release without affect lag time, when added (even small amount, 20 mg) between the third and the second layer of the three-layered tablet (Fig. 5).

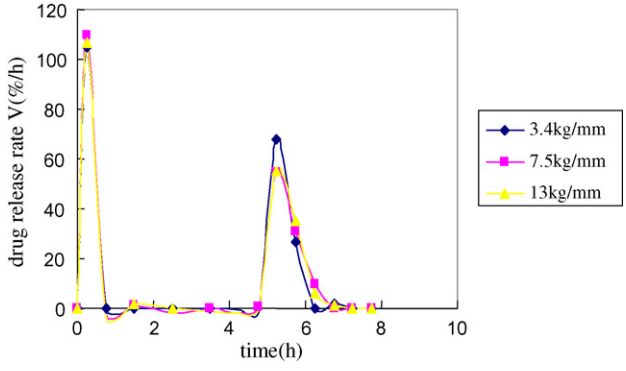

Fig. 4. Influence of tablets hardness on drug release (100 mg sodium alginate/lactose 2:3 as modulating barrier).

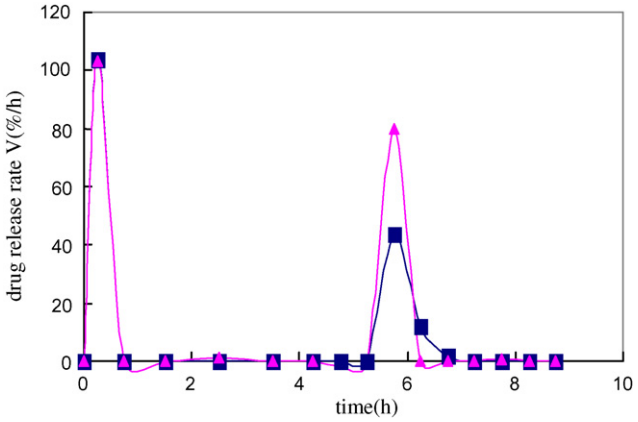

Fig. 5. Influence of separating layer on drug release rate, 100 mg sodium alginate/lactose 2:3 served as modulating barrier, (▲) with separating layer, (■) without separating layer.

3.5. Evaluation of bulking agent efficiency on drug release rate

Theoretically, when water permeated into capsule body through modulating layer and contacted with effervescent blend, carbon dioxide generated would accelerate drug release. However, as indicated in the experiment, the dissolution profiles revealed sustained release and decurtated lag time. As water penetrated before modulating layer completely eroded, drug released in bubbles breaking through self-amendable gel layer. Tablet B performed in the same way. Also sodium chloride shows no superiority, whereas lactose favored drug release.

3.6. Investigation of three pulses drug release

In order to develop and evaluate the third pulsatile drug release, we chose HPMC (E5) as barrier material (lactose to adjust lag time). Difference in lag time was found when tablets were inserted into capsule to various locations (Fig. 6). To analogue the three-pulse device, blank tablets were used to maintain precise location of the bi-layered tablets in capsule. Also the third lag time can be conveniently studied by this facility. Controllable lag time was achieved by adjusting ratio of HPMC/lactose (Fig. 7).

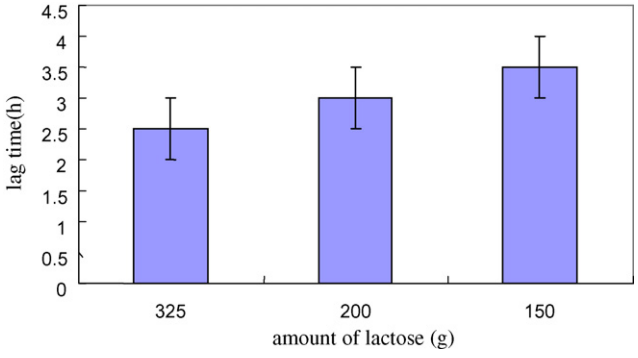

Fig. 6. Influence of tablets location in capsule on drug release lag time, sodium alginate/lactose 1:4 as modulating barrier (mean ± S.D., $n = 3$).

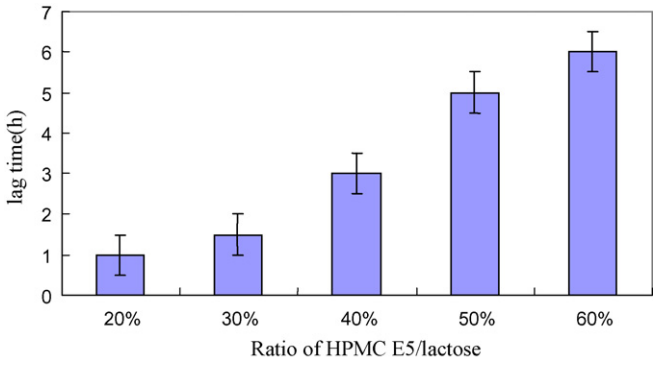

Fig. 7. Influence of ratio of HPMC E5/lactose on lag time (mean ± S.D., $n = 3$).

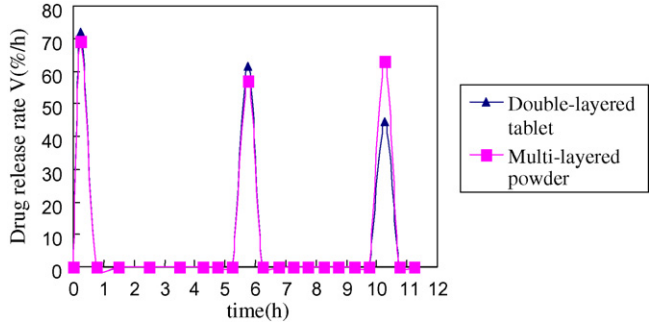

Fig. 8. In vitro release profiles of the three-pulse drug release system, sodium alginate/lactose 2:3 as modulating barrier for the second pulse, HPMC E5/lactose 1:1 served as the third pulse modulating barrier.

For further studies, three-layered tablets (100 mg 40% sodium alginate/lactose as barrier), bi-layered tablets (100 mg 40%, 50% HPMC E5/lactose play the modulating barrier role, respectively) were packed to form the novel system describe above. In vitro dissolution showed satisfied three pulses release profiles. Contrast to bi-layered tablets as the third barrier material, substituted multi-layer powders could also achieve valid three pulses drug release in vitro (Fig. 8).

Drug release lag time shows precise coincidence with the results displayed in Fig. 7. Then we can use the simple device to evaluate the third pulse lag time in relatively short time.

4. Conclusions

In conclusion, an EC impermeable capsule (a soluble cap included) system based on tablets in capsule device with controllable drug release lag time was developed. The system can be used for daily programmed drug delivery for three pulses. The proposed device was manufactured using currently applicable pharmaceutical technologies and materials recognized as safe. Modulating barrier layer (without drug) and rapidly release layer could be studied and prepared, respectively, as multi-layered tablets were employed. In the present study, each part of the novel system can be prepared separately and fabricated in the final step, which profited industrialization. It can be considered as one of the promising formulation technique for preparing pulsatile drug release system.

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