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Formulation and evaluation of pulsatile drug delivery system for chronobiological disorder: Asthma

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Abstract

The objective of the present study was to develop and evaluate an oral pulsatile drug delivery system to mimic the circadian rhythm of the disease by releasing the drug with a distinct predetermined lag time of 6 h (± 0.25 h). The basic design of the system consisted of a rapid release tableted core and a controlled release tableted coat. A combination of Isopropyl Alcohol (70%) and Acetone (30%) was used as solvent for Eudragit S100 coating. An in vitro dissolution study of the prepared tablet was conducted initially for 2 h in simulated gastric fluid and after that medium was changed to intestinal fluid pH 7.4.

Keywords: Pulsatile drug delivery system, Lag time, Circadian rhythm, Eudragit S100.

Introduction

Oral control drug delivery offers a number of advantages over conventional immediate release preparations. These systems are designed to deliver the drug at controlled and predetermined rate thus maintaining their therapeutic effective concentration in systemic circulation for prolonged periods. On the other hand, for certain therapies a pulsatile drug release pattern, where the drug is released after well-defined lag time [1]. It is well documented that most of the body functions display circadian rhythms, e.g. heart rate, stroke volume, blood pressure, blood flow, body temperature, gastric- pH. Moreover, in a number of organs their functions vary with the time of the day. It is increasingly recognized that there are rhythmic and temporal patterns in the manifestation of many disease states. Traditionally drugs are released in an immediate or extended pattern. However in recent year's pulsatile release systems are gaining growing interest, where the drug is released rapidly after a well defined lag time, could be adventitious for many drugs or therapies. Pulsatile drug delivery is one that releases a therapeutic agent at a rhythm that ideally matches biological requirement of a given disease therapy [2]. Diseases where constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems". Disease like Asthma results in increased airway responsiveness & worsening of lung function. These symptoms typically occur between midnight & especially around 4 am. Thus this study attempts to design & evaluate a chronomodulated drug delivery system of Theophylline, a bronchodilator for the treatment of asthma. It was aimed to have a lag time of 6h. i.e. the system is taken at the bed time and expected to release the drug after a period of 6h. i.e. at the 4 am when the asthma attacks are more prevalent. Such time controlled pulsatile delivery can be achieved mainly with drug containing cores. Which are covered with release controlling layers. The core serves as reservoir and the release-controlling layer protect the core from the environment e.g. water, acidic pH and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve,

rupture or alter their permeability at the required time [3].

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time [4, 5]. Such systems are also called time-controlled as the drug released is independent of the environment. Pulsatile drug delivery systems are gaining a lot of interest and attention these days.

These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon and cases where night time dosing is required.

Advantages of pulsatile drug delivery: [6]

1. Extended daytime or nighttime activity.
2. Reduced side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fever dosage units are required by the patient in therapy.
7. Drug targeting to specific sites like colon.
8. Protection of mucosa from irritating drugs.
9. Drug loss is prevented from first pass effect.

Materials and method

Material

Theophylline was obtained as a gift sample from Kores Pharmaceuticals Pvt. India. Eudragit S 100 obtained as a gift sample from Wockhardt Research Centre, Aurangabad. Microcrystalline cellulose, Magnessium stearate, Acetone and Potassium dihydrogen phosphate were purchased from local authorized dealer.

The core tablets were prepared by direct compression method. An accurately weighed 250 mg of drug and other ingredients like sodium starch glycolate, lactose and magnesium stearate were mixed by triturating in glass mortal-pestle. The blend was directly compressed at weight of 312 mg using 10 mm punch on ten-station rotary tablet machine (Karnavati Engg. Ltd., India. Model: Rimek Minipress 2D). The compositions of the formulation batches are given in Table 1.

Table 1: Formulation of Core Tablet

Ingredient	CR 1	CR 2	CR3	CR 4	CR 5	CR 6	CR7	CR 8	CR 9	CR 10	CR 11	CR 12
Theophylline (mg.)	250	250	250	250	250	250	250	250	250	250	250	250
Lactose (mg.)	50	50	50	50	50	50	-	-	-	-	-	-
MCC (mg.)	-	-	-	-	-	-	50	50	50	50	50	50
SSG (%)	1	2	3	4	5	6	1	2	3	4	5	6
Mg. Stearate (%)	1	1	1	1	1	1	1	1	1	1	1	1

Methods

Formulation of core tablet

The core tablets were prepared by using two different diluents in 12 different formulations to impart burst effect so as to rupture the coating and immediate release of the drug [7].

Evaluation of Core Tablet

Core tablets were evaluated for hardness, weight variation, friability and in vitro dissolution behavior according to standard pharmacopoeial procedures. The hardness of the tablets was determined by the Monsanto hardness tester (Spacelab, India. Model: 13-1). To calculate weight variation, 20 tablets were weighed individually and the average was calculated. Individual weight was then compared to the average weight. Weight variation was found to fall within the USP limit (± 0.5%) [8, 9]. Friability test was carried out using 20 tablets. The tablets were pre-weighed and placed in a Roche friabilator (Electrolab, India. Model: EF 1W) operated for 100 revolutions. Tablets were then dedusted and reweighed. The difference in weights was used to calculate the friability [10].

Formulation of Coated Tablet

The core tablets were coated with a Polymethacrylate copolymer (12.5%) to release the drug in the lower part of the small intestine where the pH is around 7 [11]. The Polymethacrylate copolymer Eudragit S100 having solubility at pH 7 will dissolve in the intestinal pH. As the intestinal fluid will penetrate in the core tablet, the superdisintegrant will cause the tablet to release the drug by rupturing the coating.

Di-butyl phthalate was used as plasticizer to make the coating more pliable [12]. The coating solutions were prepared using (70:30) ratio of IPA: Acetone solution in 100 % extra quantity to overcome the handling waste [13].

In vitro Drug Release Study for Coated Tablet:

The In-Vitro dissolution studies of the pulsatile tablet formulation of Theophylline were carried out using dissolution test apparatus USP-II paddle type. The dissolution medium consisted of 900 ml of standard buffer of pH 1.2 for the first 2 h followed by pH 7.4 for the remaining time period upto 8 to 10 h. The temperature of the medium was maintained at 37 ± 0.5^0C. The speed of rotation of the basket was kept at 100 rpm. Aliquots of 1 ml were withdrawn after every half hour. These samples were diluted to make up the volume of 10 ml with pH 1.2 buffer for first 2 hours and then by pH 7.4 buffer. The samples so withdrawn were replaced with the fresh dissolution medium equilibrated at the same temperature. The drug released at the different time intervals from the dosage form is measured by UV visible spectrophotometer, by measuring the absorbance for the samples solutions at 272 nm.

Table 2: Formulation of Coated Tablet

Formulations	CTD 1	CTD 2	CTD 3	CTD 4	CTD 5	CTD 6	CTD 7	CTD 8
Eudragit S100 (%)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Avg.% Wt Gain	1	1	1	1.5	1.5	1.5	2	2
Di-butyl phthalate (%)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
IPA:Acetone (70:30)	100	100	100	100	100	100	100	100

Factorial Design [14]
In this study, A 3^2 randomized full factorial design was used where two factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of superdisintegrant (SSG) and weight gain after coating were selected as independent variables. Table 3 summarizes dependent and independent variables and the resulted formulations are listed in table 3.

Table 3: Experimental design: Factors and Responses.

Coded Factor	Level	Factor 1 SSG (%)	Factor 2 Wt. Gain (%)
-1	Low	2	1
0	Intermediate	4	1.5
1	High	6	2

Stability Studies [15]
The stability studies were carried out on the optimized formulations, at 40^0C/ 75% RH for a period of one month. The sample tablets were wrapped in the laminated aluminum foils and were placed in the accelerated stability chamber at 40^0C/75% RH for a period of one month. Sampling was done at a predetermined time intervals of 0, 7, 14, 21 and 28 days. The tablets were evaluated for physical appearance, assay, % release of the drug and lag time.

Result and discussion

Drug Excipients Compatibility Study
The IR spectrums were obtained using FTIR Spectrophotometer. The FT-IR spectra of the pure Theophylline and physical mixture of drug–polymer were recorded to check interaction between drug and polymers. The characteristic peak due to pure Theophylline has appeared in the spectra without any markable change in the position. It indicates that there was no chemical interaction between Theophylline and polymers [16-19].

Evaluation of core tablets:
Hardness and friability: [20]
The tablets showed hardness values ranging from 4 to 5 kg/cm^2. Another measure of a tablets strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In present study, the friability values for all the tablet formulations were found to be <1%, indicating that the friability is within the prescribed limits.

Table 4: Evaluation of core tablets

Formulations	Hardness (kg/cm^2)	Weight Uniformity (mg) ± SD	Friability (%)	Thickness	Uniformity of content	Disintegration time (sec.)
CR 1	4.8	307± 1.70	0.621	2.8±0.3	100±1.02	673
CR 2	4.9	308±1.67	0.554	2.8±0.3	101±1.12	532
CR 3	4.8	310±2.34	0.741	2.8±0.4	101±1.04	379
CR4	4.5	313±2.9	0.358	2.9±0.5	98±0.98	298
CR 5	4 .6	320±2.88	0.558	8±0.5	99±0.94	247
CR6	4 .3	323±2.93	0.658	3±0.4	102±1.26	191
CR 7	4 .7	306±1.89	0.554	2.7±0.4	100±1.01	221
CR 8	4 .4	309±2.01	0.741	2.7±0.5	101±1.02	153
CR 9	4 .3	313±2.22	0.358	2.8±0.4	97±1.12	71
CR 10	3.9	317±2.78	0.558	3±0.5	98±0.99	10- 15
CR 11	4.00	320±2.56	0.658	2.9±0.3	100±0.81	10- 15
CR12	4 .2	322±2.56	0.554	3±0.5	99±1.07	10- 15

Values as mean ± SD, n=5.

Table 5: Lag time (t_{10}) of CTD 1 –CTD 8

Formulation	lag time (t_{10}) in minutes
CTD 1	147
CTD 2	172
CTD 3	207
CTD 4	254
CTD 5	312
CTD 6	346
CTD 7	377
CTD 8	438

Weight Uniformity:
The pharmacopoeial limits for deviation for tablets of more than 250 mg are ± 5%. The values are found between 306±1.89 and 323±2.93. The average percentage deviation for all tablet formulations was found to be within the specified limits and hence all formulations complied with the test for weight variation.

Thickness:
Tablets from all batches showed thickness values in the range of 2.7±0.3 to 3±0.5 mm.

Uniformity of drug content:
Good uniformity in drug content was found within and among the different types of tablet formulations. The values ranged from 97±1.12 % to 101±1.023 % of labeled amount. Hence the tablet prepared passes the pharmacopoeial limit.

Disintegration time:
As per the requirements of pulsatile tablets the core tablet should give rapid and transient release. The tablets prepared by using lactose as diluents give disintegration time from 191 to 663 second, where as the tablets prepared by using microcrystalline cellulose shows disintegration time between 221 to 10-15 second. Where Sodium starch glycolate was used as superdisintegrant in both case. The studies showed that the tablet hardness affects the disintegration time, harder the tablet more the disintegration time. Hardness from 4 to 5 gives best disintegration results being in its own limits.

Evaluation of Coated tablet:
Determination of lag time (t_{10}):
The dissolution profile of all 8 batches shows increase in the lag time with increase in the percent weight gain. The weight gain directly increases the coating thickness so the lag time too. The aim of the study was to develop a tablet which will be protected from gastric environment and will release the drug rapidly in the intestine after 5-6 hours of administration. So the above batches showed increase in lag time from 147 to 438 minutes with respect to their coating level.
The lag time was determined while performing the dissolution test and the values are shown in Table 5 and Figure 1 and 2.

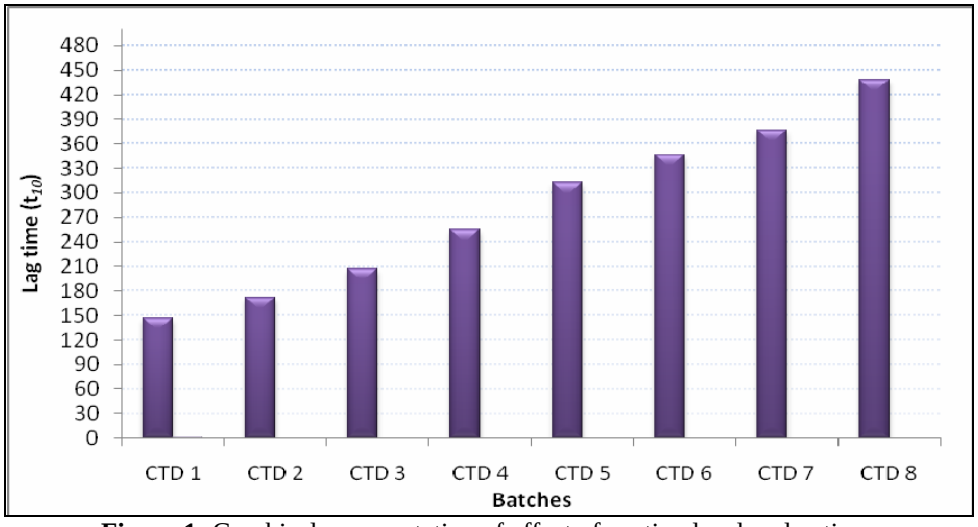

Figure 1: Graphical representation of effect of coating level on lag time.

Table 6: Weight uniformity, Thickness and Disintegration time of PT 1 to PT 9

Formulation	Weight uniformity (mg) ± SD	Thickness	Disintegration time (min)
PT 1	322±1.3	2.8±0.02	198
PT 2	328±1.21	2.9±0.02	187
PT 3	332±1.65	3.0±0.04	181
PT 4	327±0.06	2.9±0.03	293
PT 5	332±1.47	3.0±0.03	287
PT 6	340±1.11	3.1±0.05	279
PT 7	334±1.53	3.0±0.03	384
PT 8	338±0.97	3.2±0.05	382
PT 9	346±1.05	3.3±0.02	279

Values for thickness are expressed as mean ± SD, n=5.

In vitro Dissolution studies:

In Vitro Dissolution profile for formulations CTD 1 to CTD 8 shown in Figure 2.

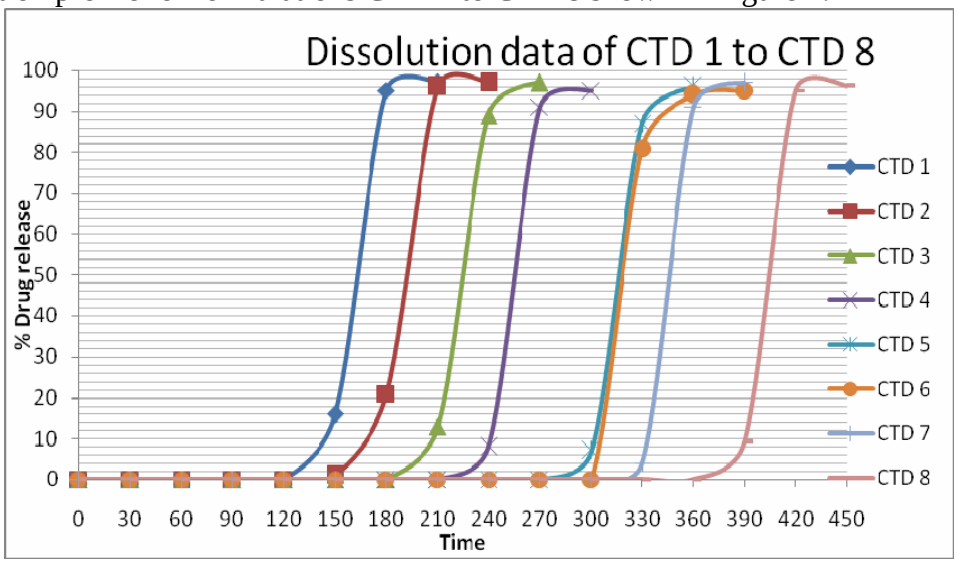

Figure 2: Common Dissolution Profile of CTD 1 to CTD 8

Table 7: Determination of lag time of PT 1 to PT 9:

Formulation	lag time (t_{10}) in minutes
PT 1	262
PT 2	256
PT 3	251
PT 4	361
PT 5	359
PT 6	352
PT 7	454
PT 8	453
PT 9	451

Table 8: Stability studies of 1 month

Stability (40 ±2^{0}C, 75 ±5% RH)	Physical appearance	Assay	Drug Release (%)	Lag Time (t_{10})
0 day	√	99.45	97.43	359
1 Week	√	98.97	96.79	357
2 Week	√	98.45	96.25	353
3 Week	√	98.12	95.87	349
4 Week	√	97.91	95.56	345

Evaluation of pulsatile tablet prepared by applying factorial

Design:

Weight variation:

The pharmacopoeial limits for deviation for tablets of more than 250 mg are ± 5%. The values are found between 322±1.3 and 346±1.05. The average percentage deviation for all tablet formulations was found to be within the specified limits and hence all formulations complied with the test for weight variation.

Thickness

Tablets from all batches showed thickness values in the range of 2.7±0.3 to 3±0.5 mm.

Disintegration time:

After coating with impermeable anionic polymer i.e. Eudragit S100 the disintegration time of the tablet was increased. The disintegration time increased with increase of percentage level of coating with polymer and decreased with increase of concentration of sodium starch glycolate. The tablet didn't disintegrated, or showed any crack on it in simulated gastric fluid for 1h after that it showed increase in the disintegration time from 181 to 384 minutes.

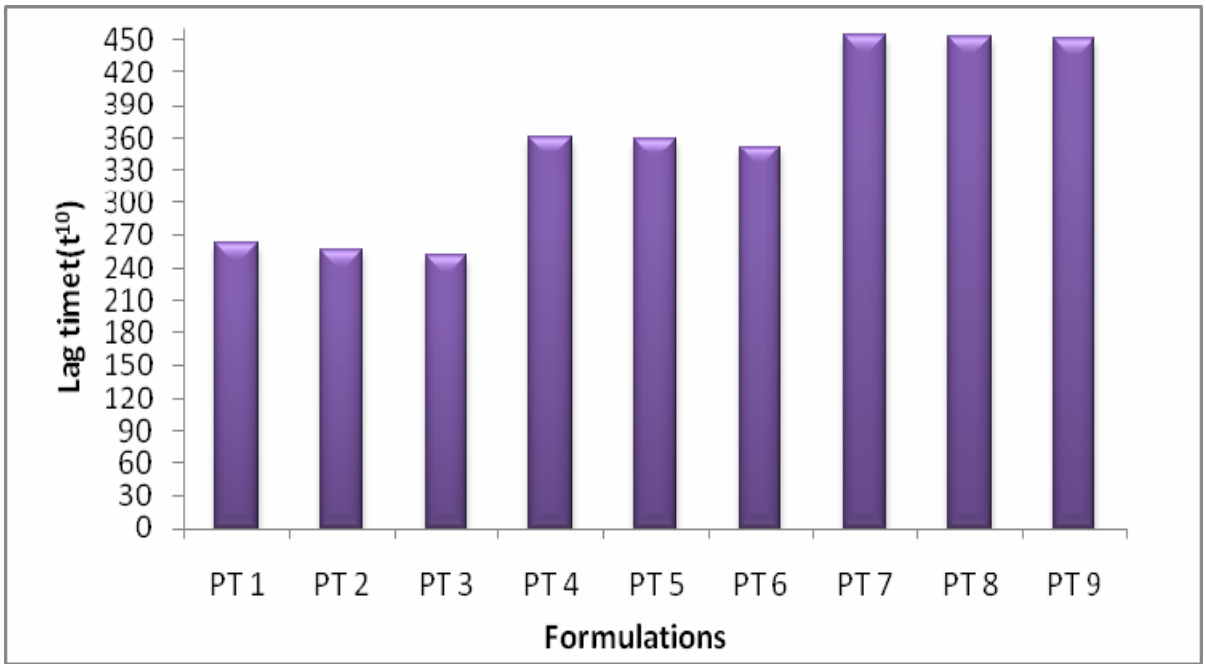

Figure 3: Lag time of PT 1 – PT 9

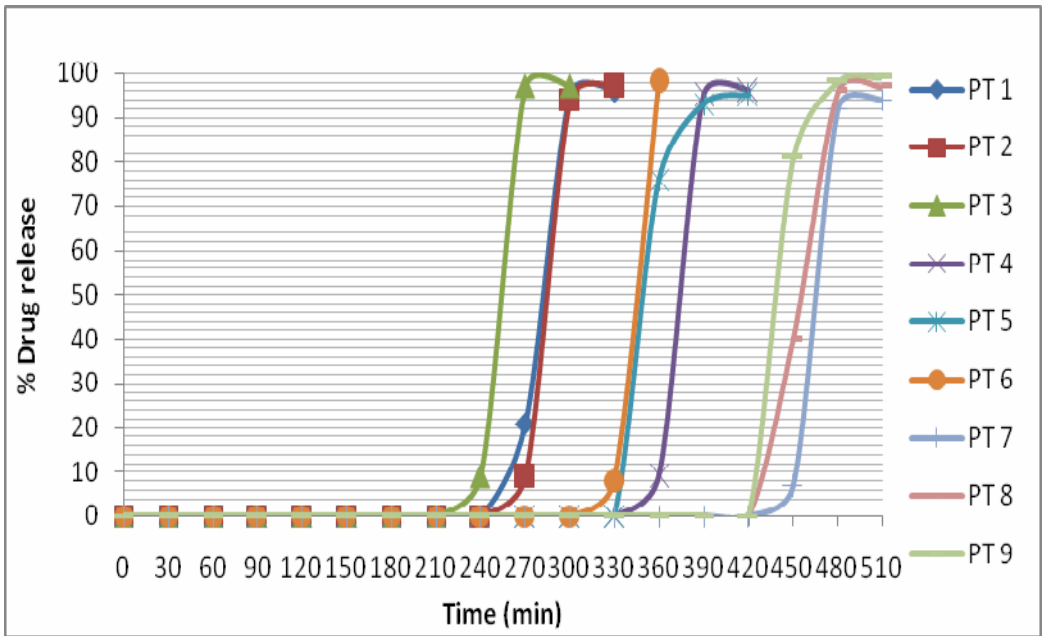

Figure 4: Common dissolution profile of PT 1 - PT 9

Determination of lag time

After coating with impermeable anionic polymer i.e. Eudragit S100 the lag time of the tablet was increased. The lag time increased with increase of percentage level of coating with polymer and decreased with increase of concentration of sodium starch glycolate. The lag time was found between the range of 251 to 454 minutes.

In vitro dissolution test:

The In- vitro drug release studies revealed that the release of Theophylline from different formulations varies with concentration of superdisintegrants and percent weight gain of pH soluble polymers (Eudragit S100).

Sodium starch glycolate have superdisintegrant property as well as swelling property. It not only plays role of disintegration but it also help to rupture the polymer coating. Increase in the level of sodium starch glycolate reduces the lag time whereas increase in the coating level increases the lag time. In vitro dissolution data of all PT 1-PT 9 batches showing comparative release pattern.

Stability Studies

The stability studies of optimum formulation revealed that there is no significant reduction in the assay, drug release and lag time (t_{10}) of the active drug was observed and physical appearance of the formulation was not altered over a period of one month.

Conclusion

A coated PDDS for Theophylline to mimic the circadian rhythm of the disease by releasing the drug at appropriate time (At the time of symptoms). The system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 6 h and thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms. The release of drug was rapid and complete after the lag time. Lag time can be controlled by adjusting the percent weight gain as well as the superdisintegrant concentration.

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Declaration of interest

The authors report no conflicts of interest.

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