Original Article

Development and evaluation of pulsatile drug delivery system of pantoprazole sodium for the management of nocturnal acid breakthrough

Daisy Arora*, Bharat Khurana, Sukhbir Kaur

Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India

Correspondence:
Daisy Arora, Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab, India.
Phone: +91-9992222427.
E-mail: daisyarora86@gmail.com

How to cite this article: Arora D, Khurana B, Kaur S. Development and evaluation of pulsatile drug delivery system of pantoprazole sodium for the management of nocturnal acid breakthrough. Pharmaspire 2019;11(1):29-33.

Source of Support: Nil,

Conflicts of Interest: None declared.

ABSTRACT

Background: The aim of the present investigation was to develop a pulsatile drug delivery system of pantoprazole sodium for the management of peptic ulcer (PU) due to nocturnal acid breakthrough. PU disease is a group of disorders characterized by the presence of ulcers in any portion of the gastrointestinal tract exposed to acid in sufficient concentration and duration. Press-coated tablets were prepared by first preparing the inner core tablets using the direct compression method and then recompressing the core tablet with the coating layer. The type and concentration of disintegrant in the core tablet were varied in different formulations to optimize the best tablets in terms of immediate release and quick disintegration. **Methods:** Press-coated tablets were prepared with varying concentration of coating material, i.e., hydroxypropyl methylcellulose (HPMC) K4 M and ethyl cellulose to optimize the lag time. **Results:** The blend of HPMC and ethyl cellulose in a ratio of 40:60 showed the desired lag time of approximately 3 h and then burst immediate release with the highest dissolution rate as compared to other ratios. **Conclusion:** The chrono delivery of pantoprazole sodium could be achieved by formulating the tablet by compression or press-coating technique.

Keywords: Pantoprazole sodium, peptic ulcer, pulsatile drug delivery, press-coated tablets; dissolution

INTRODUCTION

Peptic ulcer (PU) disease presents worldwide health problems for over a century and has been proved one of the leading causes of gastrointestinal surgery because of its high morbidity and mortality.[1,2] Nocturnal acid breakthrough (NAB) is defined as the state in which intragastric pH goes far below <2 during the overnight period for at least 60 continuous minutes, and clinical consequences are more in patients with complicated gastroesophageal reflux disease. The most effective suppressors of gastric acid secretion are the gastric H^+, K^+-ATPase proton-pump inhibitors like pantoprazole sodium. NAB follows the circadian rhythm with an intensity of peak is more between 2 a.m. and 4 a.m. in the early morning.[3] Despite the remarkable achievements in various management strategies, few issues associated with this disease still remain unaddressed.[1,4]

These limitations can be overcome by the chronotherapeutic approach, in which drug releases after predetermined lag time and we can achieve synchrony between plasma concentration of drug and peak symptoms associated with NAB.[5,6] Nocturnal acid suppression affords effective ulcer healing in the majority of patients with uncomplicated gastric and duodenal ulcers.[7,8] Hence, all the agents may be administered once daily at bedtime for acute, uncomplicated ulcers.

Thus, in the present work, pantoprazole sodium-loaded pulsatile drug delivery system, i.e., immediate release core tablet compressed within the press-coated tablet is envisaged. Consequently, the administration of pantoprazole formulated in such a delivery system, when taken at bedtime with a programmed start of drug release in early morning hours, could offer more effective therapy for the treatment of NAB.

Access this article online	
Website: www.isfcppharmaspire.com	**P-ISSN:** 2321-4732 **E-ISSN:** XXXX-XXXX

MATERIALS AND METHODS

Materials

Pantoprazole sodium was obtained from Cure Quick Pharmaceuticals, Karnal (Haryana), as a gift sample. Hydroxypropyl methylcellulose (HPMC) K15 M, lactose, microcrystalline cellulose, starch, sodium carbonate, citric acid, croscarmellose sodium, magnesium stearate, talc, ethyl cellulose, n-hexane, acetone, and n-Octanol were procured from S.D. Fine Chemicals, India. All reagents used in the present investigation were of analytical grade.

Formulation of pantoprazole sodium-loaded pulsatile drug delivery system, i.e., press-coated tablets

Press-coated tablets were prepared by first preparing the inner core tablets using the direct compression method and then recompressing the core tablet with the coating layer.[9] The type and concentration of disintegrant in the core tablet were varied in different formulations to optimize the best tablets in terms of immediate release and quick disintegration. Press-coated tablets were prepared with varying concentration of coating material, i.e., HPMC K4 M and ethyl cellulose to optimize the lag time.[10] The direct compression method was used because it is a simple method and also produces tablets with low disintegration time.[11] The formula for preparing tablets is shown in Table 1.

Formulation of the powder blend

Powder mixtures of pantoprazole sodium, microcrystalline cellulose (MCC, Avicel PH-102), citric acid, sodium bicarbonate, lactose, and croscarmellose sodium (Ac-Di-Sol) were dry mixed for 20 min, followed by the addition of magnesium stearate and talc as a lubricant. The mixtures were then further blended for 10 min. The powder mixture thus prepared was then characterized for pre-compression parameters.[12]

Pre-compression characterization

Bulk density (BD) and tapped density (TD)

BD was determined by filling powder into a pre-weighed 50 ml volumetric cylinder to the volume and the density was calculated by the formula:

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$

Table 1: Formulation design of inner core tablet

Ingredients	Formulation code		
	ICT1	ICT2	ICT3
Drug (pantoprazole sodium) (mg)	40	40	40
Microcrystalline cellulose (mg)	50	50	-
Sodium carbonate:citric acid (1:1) (mg)	50	-	50
Croscarmellose sodium (mg)	6	6	6
Lactose (mg)	50	100	100
Magnesium stearate (mg)	2	2	2
Talc (mg)	2	2	2
Total weight of tablet (mg)	200	200	200

TD was determined by tapping repeatedly the same powder filled cylinder on a hard surface until no more volume reduction occurred.

Angle of repose

The angle of repose was determined by a funnel method. A glass funnel was fixed on a stand in its upright position at a known height above a white paper.[13] Powder blends were poured slowly in the funnel and allowed to flow through to the paper until they just touched the tip of the funnel. The angle of repose was calculated from the following equation:

$$\text{Tan}\,\theta = h / r$$

Where, h and r are the height and radius of the granule cone, respectively.

Carr's compressibility index (CCI)

CCI was determined using the values of volumes taken in the determination of loose and tapped bulk densities with the help of CCI formula:

$$\text{CCI}(\%) = \frac{(\text{TD} - \text{BD})}{\text{TD}} \times 100$$

Compression of powder blend to form inner core tablet

Inner core tablets were prepared by direct compression method as per the formula given in Table 1. The uniform powder blend was compressed to form the tablets using the 8 mm, circular, flat-faced punch on the rotary tablet punching machine (Fluidpack, India). The total weight of tablets was kept constant at 200 mg. The tablet press setting was kept constant across all formulations.[14]

Formulation of the mixed blend for the coating layer

The various formulation compositions containing HPMC K4 M and ethyl cellulose as coating layer in different compositions were weighed and dry blended for about 10 min. About 1% magnesium stearate was used as a lubricant and blend used as press-coating material to prepare press-coated pulsatile tablets by direct compression method.[15] The composition of the coating layer is given in Table 2.

Formulation of press-coated tablets

The core tablets were press coated with 200 mg of a mixed blend using different weight ratios of water-soluble polymer HPMC and water-insoluble polymer ethyl cellulose in different weight ratios, as given in Table 2. A 100 mg of coating layer material was weighed

Table 2: Formulation of the mixed blend for the coating layer

Ingredients	Formulation code						
	PCT1	PCT2	PCT3	PCT4	PCT5	PCT6	PCT7
HPMC K4 M:ethyl cellulose (%ratio) (mg)	100:0	80:20	60:40	50:50	40:60	20:80	0:100
Magnesium stearate (mg)	1%	1%	1%	1%	1%	1%	1%
Total weight of blend for each tablet (mg)	200	200	200	200	200	200	200

and transferred into a 9 mm die then the core tablet was placed manually at the center.[9] The remaining 100 mg of the barrier layer material was added into the die and compressed using a rotary tablet punching machine (Fluidpack, India). The weight of each tablet was adjusted up to 400 mg.

Characterization of inner core tablets and press-coated tablets

Drug content

Twenty tablets were crushed to a very fine powder. A quantity of powder equivalent to 40 mg of drug was weighed and assayed as described in USP 24.

Hardness and thickness

Hardness and thickness were determined using 10 tablets for each test and mean was taken. For each formulation, the hardness of tablets was determined using the Pfizer hardness tester. The thicknesses of the tablets were determined using a Vernier caliper.

Friability

Twenty tablets were carefully weighed and loaded into the drum of a Roche's friabilator and operated for 4 min at 25 rpm. Then, tablets were collected, dedusted between tissue towels, and reweighed. Percentage friability was calculated as follows:

$$\text{Friability}(\%) = \frac{(\text{Wi} - \text{Wf})}{\text{Wi}} \times 100$$

Table 3: Physical properties of powder blend for preparing inner core tablet

Formulation code	Powder blend properties		
	Bulk density (g/cm^3)	Carr's index	Angle of repose
ICT1	0.871±0.54	12.4±1.19	24.5±0.84
ICT2	0.965±1.23	14.3±0.76	25.9±0.75
ICT3	0.923±0.941	15.2±0.32	27.3±0.88

All values are expressed as mean±SD, n=6

Where, W_i and W_f are the mass of the tablets before and after the test, respectively.

Weight variation

For each of the formulations, the weight variation test was performed according to USP XVII. The test results were found to be within pharmacopoeial limits. From each batch, 20 tablets were individually weighed and the mean was calculated.

Disintegration time

The disintegration time of the tablet was measured in distilled water at 37 ± 2°C according to USP disintegration test apparatus. Three trials for each batch were performed.

In vitro dissolution studies

In vitro drug release studies were conducted to assess the pulsatile behavior of the press-coated formulation. *In vitro* dissolution studies of core tablet were carried out using USP Type II apparatus (Labindia, DS 8000). pH 6.8 phosphate buffer was used as a dissolution medium. The test was conducted with a paddle speed of 100 rpm and 37 ± 0.5°C. In each vessel, 900 ml of the dissolution medium was added.[16,17] One tablet was added to each vessel and the vessels were covered with lids. Samples were collected at predetermined time intervals. The dissolution medium was replaced with fresh supply after each sampling run. Each sample of 5 ml was filtered through a filter paper set on a funnel. The filtrate was suitably diluted and an absorbance reading was taken at 289.5 nm.

In vitro dissolution studies of press-coated tablets were carried out using USP XXIII Type II (basket method) apparatus (Labindia, DS 8000). To simulate the pH changes along with the gastrointestinal tract, dissolution media with 0.1 N HCl and phosphate buffer (pH 6.8) were sequentially used. When performing the experiment, 0.1 N HCl medium was used for 2 h (since the average gastric emptying time is 2 h) then removed and fresh phosphate buffer (pH 6.8) was added for subsequent hours. A 900 mL of the dissolution medium was used at each time and

Table 4: Evaluation parameters of various batches of inner core tablets

Formulation code	Tablet properties				
	Friability (%)	Hardness (kg/cm^2)	Weight (mg)	Drug content (%)	Disintegration time (seconds)
ICT1	0.53±0.09	4.5±0.76	199.3±1.09	99.7±0.21	54±3
ICT2	0.65±0.11	4.7±1.01	201.4±1.84	101.1±1.12	145±4
ICT3	0.71±0.10	4.6±0.24	201.5±1.01	99.5±0.76	154±3

All values are expressed as mean±SD, n=6

Table 5: Evaluation parameters of various batches of press-coated tablets

Formulation code	Properties of press-coated tablets				
	Friability (%)	Hardness (kg/cm^2)	Weight (mg)	Drug content (%)	Thickness (mm)
PCT 1	0.12±0.07	5.8±0.76	400±4.09	97.7±0.92	3.29±0.32
PCT 2	0.45±0.01	6.2±1.01	401.4±6.74	96.23±1.22	3.21±0.46
PCT 3	0.34±0.02	6.3±0.24	401.9±3.01	98.5±0.76	3.45±0.32
PCT 4	0.45±0.04	6.6±0.12	399.2±5.89	94.34±1.23	3.54±0.38
PCT 5	0.49±0.03	6.9±0.27	404±4.19	95.12±2.34	3.25±0.76
PCT 6	0.57±0.09	6.9±0.31	402±3.21	93.21±3.78	3.17±0.15
PCT 7	0.38±0.10	6.9±0.20	398.9±2.23	96.32±3.2	3.21±0.62

All values are expressed as mean±SD, n=6

stirred at 50 rpm at 37±0.5°C. A 5 mL of dissolution media was withdrawn at a predetermined time interval and fresh dissolution media were replaced.[9,16,18] The withdrawn samples were analyzed at 289.5 nm using a ultraviolet spectrophotometer.

RESULTS AND DISCUSSION

Characterization of the pre-compression powder blend

The results of various characterization parameters of the powder blend are summarized in Table 3. The blend prepared for core tablets was evaluated for their flow properties. BD varied between 0.871 and 0.965 g/cm^3 Carr's index was found to be 12.4, 14.3, and 15.2 for powders of different formulations. The angle of repose was found to be 24.5, 25.9, and 27.3. These values indicated that the prepared powers exhibited good to fair flow properties.

Evaluation of inner core tablet

Inner core tablets were prepared by direct compression method as per the formula. The uniform powder blend was compressed to form the tablets and evaluated. The results of various characterization parameters of inner core tablets are summarized in Table 4. The hardness for different formulations was lies between 4.5 and 4.7 kg/cm^2 and it indicates that all the formulations were having satisfactory mechanical strength. The average weight of the core tablets was found to be 199.3, 201.4, and 201.5 mg, respectively, for different batches, which are well within the desirable limit and indicating uniform in mass and thickness. The friability ranged from 0.53% to 0.71% for different formulations and it was below 1%, which represents good mechanical resistance of the tablets. The drug content was also within limits in different formulations, showed favorable drug loading efficiency. Based on the disintegration time, formulation ICT1 was selected as the best formulation for the further press coating and other evaluation studies such as physicochemical properties and *in vitro* drug release studies.

Table 6: *In vitro* release profile of pantoprazole sodium from the optimized batch of inner core tablet

Time (min)	% cumulative drug release
5	32.46±2.65
10	49.46±3.55
15	70.56±4.87
20	85.26±3.78
25	97.04±5.63
30	98.54±1.77

All values are expressed as mean±SD, n=6

Formulation and evaluation of press-coated tablets

On the basis of the above optimization and characterization results, formulation ICT1 was selected for further press coating. The core tablets were press coated with 200 mg of a mixed blend using different weight ratios of water-soluble polymer HPMC and water-insoluble polymer ethyl cellulose. The press-coated tablets were further evaluated for various parameters, as summarized in Table 5. All the formulations showed almost uniform size, shape, and appearance. Furthermore, all the parameters were within limits and acceptable.

In vitro dissolution studies of core tablet

In vitro dissolution studies of core tablets were carried out using USP Type II apparatus. pH 6.8 phosphate buffer was used as a dissolution medium. The drug release profiles of optimized core tablet formulation as a function of time is given in Table 6. The core tablets of pantoprazole sodium were found to be fast disintegrating. When the tablet comes in contact with the dissolution medium, it gets rapidly disintegrated. Thus, it shows 85% of drug release within 20 min upon contact with the dissolution medium. In the present study, croscarmellose sodium used in core tablets formulation and it gave immediate release and quicker disintegration of tablets.

In vitro dissolution studies of press-coated tablets

The drug release profiles of press-coated tablet formulations as a function of time are given in Table 7 and Figure 1. The pulsatile press-coated tablets were prepared using different weight ratios of water-soluble polymer HPMC and water-insoluble polymer ethyl cellulose. When water-soluble polymer HPMC alone used as an outer coating polymer (in PCT1 formulation), it has shown the least lag time and released the drug approximately after 1.5 h. However, slow disintegration and thus slow drug release were found in this formulation. Hence, HPMC alone cannot be used as an outer coating polymer to achieve lag time. In contrast, ethyl cellulose alone used in PCT7 formulation as an outer coating polymer which shows good lag

Table 7: *In vitro* release profile of pantoprazole sodium from various press-coated tablets

Time (h)	% cumulative drug release						
	PCT1	PCT2	PCT3	PCT4	PCT5	PCT6	PCT7
0.5	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
1.5	0	0	0	0	0	0	0
2	12.34±1.43	0	0	0	0	0	0
2.5	23.67±1.65	41.23±3.77	0	0	0	0	0
3	27.46±1.98	59.67±2.71	32.49±2.65	40.27±3.21	0	0	0
3.5	38.45±2.7	71.23±6.87	49.42±4.12	57.65±3.76	63.23±5.77	51.23±4.87	47.65±2.65
4	54.27±3.34	83.45±5.98	67.44±4.76	73.29±6.87	91.34±5.14	67.45±2.76	58.78±4.12
4.5	69.69±4.76	89.9±6.12	72.47±5.06	89.55±5.98	97.44±3.76	79.76±4.86	71.90±3.76
5	85.76±3.43	93.64±5.28	87.54±6.21	94.56±5.81	98.89±2.81	85.67±3.91	82.35±2.76

All values are expressed as mean±SD, n=6

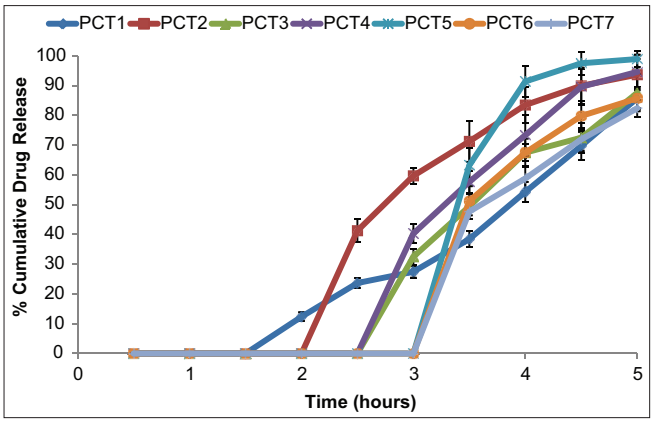

Figure 1: *In vitro* release profile of pantoprazole sodium from various press-coated tablets (Batch PCT1 to PCT7)

time up to 3 h, but the dissolution rate was quite low due to the high content of the water-insoluble polymer.

The blend of HPMC and ethyl cellulose was used in a different ratio to achieve the desired lag time. Among all ratios, 40:60 ratios (used in batch PCT5) showed desired lag time of approximately 3 h and then burst immediate release with the highest dissolution rate as compared to other ratio use, as shown in 1. It has shown a longer lag time. Thus, the combination of HPMC and ethyl cellulose in the ratio of 40:60 found to be the best possible combination for achieving desired lag time.

CONCLUSION

From the above study, it can be concluded that the system was found to be satisfactory in terms of release of the drug after a predetermined lag time when the greatest need of drugs in the early morning to treat the disease. One of the promising formulations demanded pulsatile drug delivery system with specific lag time approximately 3 h hence with the existing drug molecule, the chronotherapeutic management of PU has opened a "new lease of life." Further, *in vivo* studies are required to completely assess the potential of pulsatile drug delivery systems in real sense.

ACKNOWLEDGMENT

Authors are thankful to Cure Quick Pharmaceuticals for providing gift sample of pantoprazole sodium.

REFERENCES

1. Khurana B, Arora D, Narang R. Topical delivery of nanoemulsion for antipsoriatic drugs. J Drug Deliv Ther 2018;8:1-11.
2. Kaur A, Singh R, Sharma R, Sunil K. Peptic ulcer: A review on etiology and pathogenesis. Int Res J Pharm 2012;3:34-8.
3. Rao NG, Soumya P, Revathi K, Nayak BS. A review on pulsatile drug delivery system. Int Res J Pharm 2013;4:31-44.
4. Khurana B, Goyal AK, Budhiraja A, Aora D, Vyas SP. Lipoplexes versus nanoparticles: PDNA/siRNA delivery. Drug Deliv 2013;20:57-64.
5. Singh A, Dubey H, Shukla I, Singh DP. Pulsatile drug delivery system: An approach of medication according to circadian rhythm. J Appl Pharm Sci 2012;2:166-76.
6. Prasanth VV, Modi MP, Mathew ST, Abraham A. Formulation and evaluation of enteric coated time release press coated tablets of theophylline for chronopharmacotherapy. Pharm Lett 2012;4:599-606.
7. Tuorkey MJ, Abdul-aziz KK. Gastric ulcer's diseases pathogenesis, complications and strategies for prevention. Webmedcentral Gastroenterol 2011;2:1-24.
8. Arora D, Khurana B, Narang RK, Nanda S. Quality by design (QbD) approach for optimization and development of nano drug delivery systems. Trends Drug Deliv 2016;3:23-32.
9. Khadabadi SS, Chishti NH, Khan FM, Tadvee AA. Formulation and evaluation of press coated tablet of ketoprofen-a chronotherapeutic approach. Int J Pharm Pharm Sci 2013;5:733-40.
10. Domala R, Eedara BB, Dhurke RK. Development of pulsatile drug delivery system using novel solubilizers for antihypertensive drug. Int J Pharm Pharm Sci 2014;6:659-64.
11. Kamalakkannan V, Kannan C, Jaganathan K, Kumaran KS, Kumar RS. Formulation and *in vitro* evaluation of aceclofenac pulsatile tablets as a oral-time controlled drug delivery system. Arch Appl Sci Res 2013;5:121-31.
12. Arora D, Nanda S. Quality by design driven development of resveratrol loaded ethosomal hydrogel for improved dermatological benefits via enhanced skin permeation and retention. Int J Pharm 2019;567:118448.
13. Arya RK, Juyal V, Singh R. Development and evaluation of gastroresistant microspheres of pantoprazole. Int J Pharm Pharm Sci 2010;2:112-6.
14. Mogal RT, Galgatte UC, Chaudhari PD. Floating pulsatile drug delivery of ranitidine hydrochloride for nocturnal acid breakthrough: Design, optimization, *in vitro* and *in vivo* evaluation. Int J Pharm Pharm Sci 2013;5:722-7.
15. Pahwa R, Kumar V, Kohli K. Clinical manifestations, causes and management strategies of peptic ulcer disease. Int J Pharm Sci Drug Res 2010;2:99-106.
16. Pahal S, Arora D, Kumar MS, Mahadevan N. Development of paclitaxel loaded immunonanoparticles for HER-2 positive breast cancer cells. Int J Recent Adv Pharm Res 2011;1:25-39.
17. Arora D, Khurana B, Kumar MS, Vyas SP. Oral immunization against hepatitis B virus using. Int J Recent Adv Pharm Res 2011;1:45-51.
18. Sirisha VN, Namrata M, Sruthi B, Harika I, Kirankumar P, Kiran Y, *et al*. Pulsatile drug delivery system-a review. Int J Pharm Res Allied Sci 2012;1:13-23.