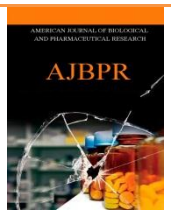
e-ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr



DESIGN AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM CONTAINING PANTOPRAZOLE SODIUM

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Article Info

Received 24/05/2016
Revised 30/05/2016
Accepted 09/06/2016

Key words: - Pulsatile drug delivery system, Lag time, Circadian rhythm, Pantoprazole sodium.

ABSTRACT

The basic design of the pulsatile system consisted of rapid release of drug from core tablets after a lag time of 5hr. The objective of the present study was to develop and evaluate an oral pulsatile drug delivery system containing pantoprazole sodium to mimic the circadian rhythm of the peptic ulcer by releasing the drug with a distinct predetermined lag time of 5h. Totally six formulations were developed using different concentration of cross carmellose sodium and sodium starch glycolate. The prepared blend and core tablets were evaluated for FTIR, Micromeritics study, hardness, friability, weight variation, drug content, disintegration time, and dissolution study. The best formulation was selected for Eudragit S 100 coating and evaluated for dissolution. The result of the study indicates that the drug was released after lag time of 5 hrs. And thus the dosage form can be taken at bed time. So the content was released in morning hours. i.e. the time of symptoms.

INTRODUCTION

Pulsatile delivery is the rapid and transient release of certain amounts of drug molecules within a short time period immediately after a predetermined off release period, i.e., lag time. These deliver the drug at the right time and at the right place and in the right amount thus increasing patient compliance [1].

Usually the symptoms of peptic ulcer occur in the morning and it has rhythmic variations. Pantoprazole sodium is a synthetic proton pump inhibitor i.e mainly used for the treatment of duodenal ulcer, gastric ulcer moderate and severe oesophagitis, Zollinger Ellison syndrome and it is available in formulation for oral intake, and injections. The drug has biological half-life of 1.9hour and 40% of drug administered dose undergoes first pass metabolism. Absorption of the Pantoprazole sodium more in colon when compared to the stomach and small intestine. Hence the design of Pulsatile delivery system is desirable [2].

Pulsatile release systems are formulated to undergo a lag time of predetermined span of time of no release, followed by a rapid and complete release of loaded drugs. The approach is based on the principle of delaying the time of drug release until the system transmits from mouth to colon. A lag time of 5 hours is usually considered sufficient since small intestine transit is about 3-4 hours, which is relatively constant and hardly affected by the nature of formulation administered [3-5].

MATERIALS AND METHODS

Pantoprazole sodium, Microcrystalline cellulose, Cross carmellose sodium, sodium starch glycolate, Aerosil, Eudragit S100 was obtained from Yarrow chem products, Mumbai, Magnesium stearate from lobe chemie Pvt Ltd, Mumbai. All the materials and reagents were of analytical grade.

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Precompression Parameters

The FTIR, bulk density, tapped density, Carr's Index, Angle of repose and Hausner's ratio were determined for all the formulation powder blend. Table 1[6,7].

Formulation of Pulsatile pantoprazole core tablet

The core tablets containing 100 mg of the drug were prepared by direct compress method and the various formulae used in the study are shown in Table 1. The drug, diluents, superdisintegrant, was passed through sieve No 40. All the above ingredients were properly mixed together. Talc and Magnesium stearate were passed through sieve No 80, mixed and blended with initial mix. The powder blend was compressed into tablets on a ten station rotary punch tablet machine using 8 mm convex punch [8].

Evaluation of core tablets

The core tablets were evaluated for hardness, weight variation, friability, and invitro dissolution behavior according to standard Pharmacopoeial procedures. The hardness of the tablets were determined by the Monsanto hardness tester. 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%) [9,10].

Friability test was carried out using 20 tablets. The tablets were pre-weighed and placed in a Roche friabilator operated for 100 revolutions. Tablets were then dedusted and reweighed. The difference in weights was used to calculate the friability [11] Table 2.

Dissolution for Core tablet

The dissolution studies for the pantoprazole sodium core tablets were carried out using dissolution test apparatus USP II paddle type. The dissolution medium consisted of 900 ml of phosphate buffer of pH 6.8 for 60 min. The temperature of the medium was maintained at 37±0.5°C. The speed of rotation of the paddle was kept at 50 rpm. Aliquots of 5ml were withdrawn after every 15 minutes. These samples were diluted to make up the volume of 50ml with pH 6.8 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 sample solutions at 289nm. Figure 3 - 4

Formulation of Pulsatile Pantoprazole coated tablets

The coating solution was developed by dissolving Eudragit S 100 (20%) inacetone and isopropyl alcohol mix solvents and then Polyethylene glycol (2%), Titanium dioxide (5%) was added and stirring . The resulting solution was adjusted with aceton and isolpropyl alcohol mixed solvents. The core tablets were coated using dipping and drying method and increase in weight percent after coating was determined as the coating level.

Dissolution study for coated tablet

The dissolution studies of the pulsatile tablets containing pantoprazole sodium was carried out using 900 ml of 0.1N HCl for 2h followed by pH 6.8 phosphate buffer solution. The set condition was 37±0.5°C, 50 rpm, and paddle type USP XX111 apparatus. Aliquots withdrawn for every one hour intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable diluents were assessed spectrophotometrically at 289nm. Figure 5

RESULTS AND DISCUSSION

Pulsatile drug delivery systems for Pantoprazole sodium were prepared with a view to release the pantoprazole sodium at 5am from the administered dosage form for effective treatment of peptic ulcer. Pulsatile drug delivery systems were designed with dipping and drying coating technique and the results are reported here.

The flow property of the powder mixture are important for the uniformity of mass of the tablet, The flow property of powder mixture was analyzed before compression of tablets Low Hausner's ratio, compressibility index and angle of repose values indicated a fairly good flowability of powder mixture. As the tablet powder mixture was free flowing, tablets produced were of uniform weight with acceptable weight variation. Hardness (3-4kg/cm^2) and friability loss (0.49-0.82%) indicated that tablets had a good mechanical resistance.

Drug Excipients Compatibility Study

The IR spectrums (Fig 1-2) were obtained using FTIR Spectrophotometer. The FTIR spectra of the pure Pantoprazole sodium and physical mixture of drug-polymer were recorded to check interaction between drug and polymers. The characteristic peak due to pure Pantoprazole sodium has appeared in the spectra without any markable change in the position. It indicates that there was no chemical interaction between Pantoprazole sodium and polymers [12-15].

Evaluation of core Tablets

Hardness and Friability

The tablets showed hardness value ranged from 3-4 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.

Weight Uniformity

The Pharmacopoeial limits for deviation for tablets of more than 80 mg but less than 250 mg are±7.5% and more than 250 mg are ± 5%. The values are found between 238 and 264. 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.

Uniformity of drug content

Good uniformity in drug content was found within and among the different types of tablet formulations. The values ranged from 75.82 to 95.17% of labelled 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 cross carmellose sodium give disintegration time from 120 to 124 second, whereas the tablets prepared by using sodium starch glycolate shows disintegration time from 120- 117 seconds. The studies showed that tablets prepared by sodium starch glycolate gives best disintegration results.

***Invitro* drug release study for core tablet**

The tablets prepared by using cross carmellose sodium shows % drug release as 75.82, 79.42, 83.02 for F1, F2, F3 formulations. The formulations containing sodium starch glycolate shows % drug release as 91.57, 95.17, and 92.25 for F4, F5, F6 formulations.

From the above study F5 formulation was considered as a best formulation based on evaluation parameters. In this batch F5 show satisfactory hardness, maximum drug release and disintegrated within 2 minute. A pulsatile drug release, where the drug is released rapidly after a well-defined lag time. Here the core tablet F5 show maximum drug release. So F5 formulation is susceptible for coating**.**

***Invitro* drug release study for coated tablet**

The dissolution studies on F5 formulation were conducted in 0.1N HCl for 2hrs, 6.8 pH phosphate buffer for 2-5hrs. The dissolution profile was showed in Fig 6. Eudragit S 100 maintained a lag time of 5hrs and the drug was released after 5hrs.

Table 1. Composition of Pantoprazole Sodium Core Tablets

Sl.no	Ingredients(mg)	F1	F2	F3	F4	F5	F6
1	Pantoprazole sodium	40	40	40	40	40	40
2	Avicel	200	200	200	200	200	200
3	Cross carmellose sodium	1	1.5	2	-	-	-
4	Sodium starch glycolate	-	-	-	1	1.5	2
5	Magnesium stearate	2	2	2	2	2	2
6	Aerosil	2	1.5	1	2	1.5	1
7	Total weight	245	245	245	245	245	245

Table 2. Micromeritic Properties of drug.

Sl.no	Parameters	F1	F2	F3	F4	F5	F6
1	Bulk density(g/cm^3)	0.61	0.57	0.62	0.75	0.57	0.65
2	Tapped density(g/cm^3)	0.70	0.65	0.70	0.89	0.63	0.72
3	Carrs Index (%)	12.8	12.3	11.4	15.7	9.52	9.72
4	Hausner's ratio	1.14	1.14	1.12	1.18	1.10	1.10
5	Angle of repose	31.12	30.02	29.18	32.34	33.28	35.14

Table 3. Post Compression Parameters for Pulsatile Pantoprazole Core Tablets

S.no	Parameters	F1	F2	F3	F4	F5	F6
1	Weight variation(mg)	246±0.41	247±2.02	252±1.58	252±0.5	248±1.51	254±3.15
2	Hardness(kg/cm^2)	2.3±2	3.3±2	2.3±2	3.5±5	3.3±2	3.8±2
3	Friability (%)	0.76	0.82	0.56	0.58	0.49	0.78
4	Drug Content (%)	75.82	79.42	83.02	91.57	95.17	92.25
5	Disintegration time (sec)	120	122	124	120	117	118
6	Dissolution (%)	75.82	79.42	83.02	91.57	95.17	92.25

Fig 1. FTIR Spectra Of Pure Drug Pantoprazole Sodium

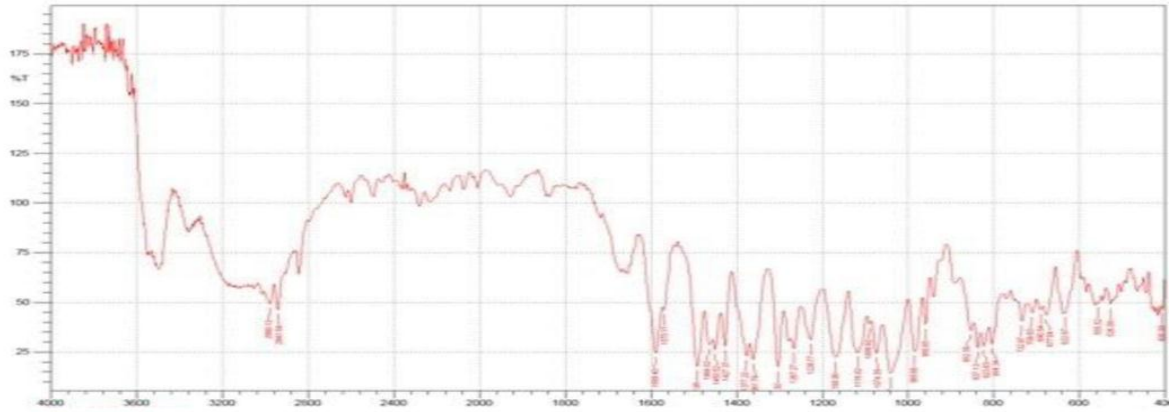


Fig 2. FTIR Spectra of Pure Drug Pantoprazole Sodium And Excipients

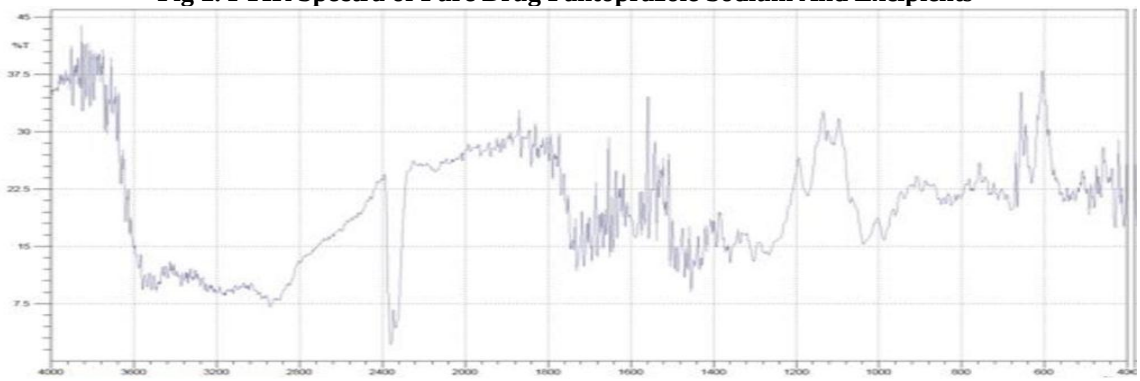


Fig 3. Dissolution profiles of Core tablets of Formulations Containing Cross carmellose Sodium

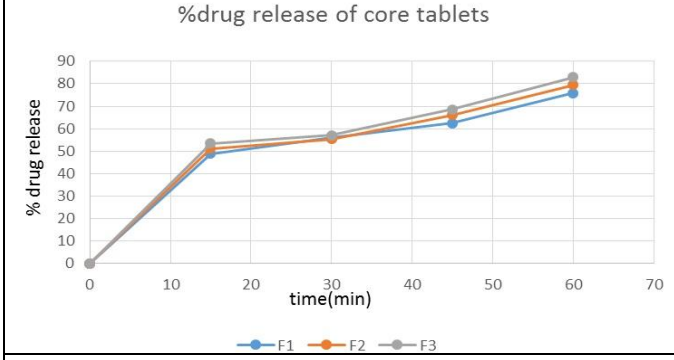


Fig 4. Dissolution Profiles of Core Tablets of Formulations Containing Sodium StarchGlycolate

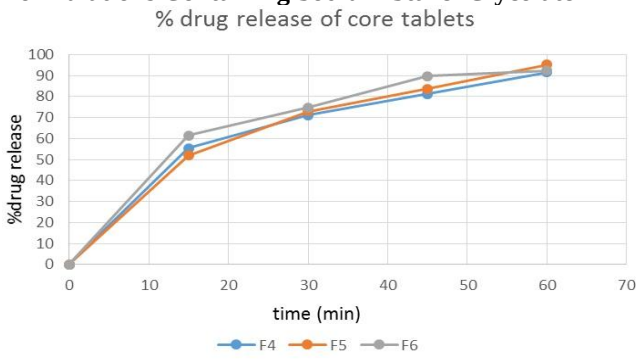
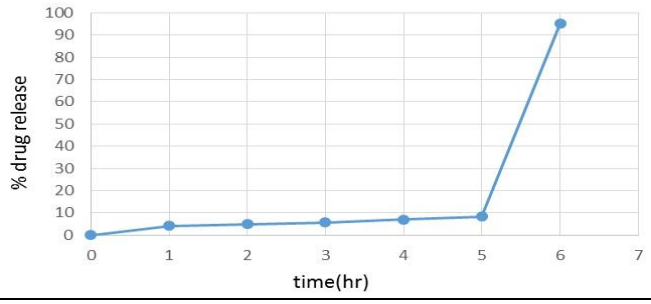


Fig 5. Dissolution Profile of Coated Tablets



CONCLUSION

The release rate after lag time can be adjusted as pulsatile release pattern using the Eudragit S 100 type of polymer and immediate release pattern using the superdisintegrants. From the above study F5 formulation was considered as a best formulation based on evaluation parameters.

ACKNOWLEDGEMENT

The authors are grateful to Management of Grace College of Pharmacy, Palakkad to provide facilities to carry out the research article.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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