IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
August 2018 Vol.:13, Issue:1

Development and Evaluation of Multiparticulate Drug Delivery System for Colon Targeting

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Pallavi M. Chaudhari*[1], Bhavana P. Kapse[2]

[1]Dr. D. Y. Patil College of Pharmacy, Akurdi, Pune - 411044

[2]Dr. D.Y. Patil Institute of Pharmacy, Akurdi, Pune-411044

Submission: 19 July 2018
Accepted: 27 July 2018
Published: 30 August 2018

Keywords: Multiparticulate, Colon Targeting, Pellets, Eudragit L-30 D-55, Eudragit S 100 Polyvinyl pyrrolidone K-30, Korsmeyer peppas

ABSTRACT

In the present research work, pellets of proton pump inhibitor drug that is Omeprazole used in the treatment of peptic ulcer has been utilized as a model drug and different approaches were tried to get a delayed release site-specific and stable formulation using Eudragit L-30 D-55, S 100 polymers. For this purpose, nonpareil seeds were used, where initial drug layer was loaded on it, then with an intermediate coat and finally a functional coating was done using R & D Coater. The drug layer consists of a combination of drug and polymers of hydroxyl propyl methyl cellulose/ hydroxyl propyl cellulose. The intermediate layer was composed of Polyvinylpyrrolidone K-30. And finally, the functional coating contained pH dependent Eudragit polymers to have delivery of the drug to the colon. After formulation of the batches, pellets were further evaluated for different parameters like flow properties, particle size, friability, assay, dissolution etc. Batch B6 was the optimized formulation. It followed the Korsmeyer peppas kinetic model. Dissolution and assay studies conducted on all other formulations showed similar release profile and a promising approach, for colon targeting.

INTRODUCTION

Since last 20 decades, the lot of interest has been developed, for site-specific formulations to the colon1. This colonic drug delivery system is also called as "*SMART SYSTEM*", due to their property of triggering mechanism, responding only to the true physiological conditions, particularly to colon[2]. The colon is a site where both local and systemic drug delivery can be adminsitered[3]. A number of other serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs are targeted to the colon. For treatment of gastro-duodenal ulcers and symptomatic gastroesophageal reflux, Omeprazole a proton pump inhibitor has a short biological half-life, is widely used. This drug is available in powder form, having pKa1 4.2 and pKa2.9 respectively, indicating low stability at lower pH values. This drug is available in tablet form. Pelletization is an attractive approach to formulate multiparticulate dosage form due to several advantages over single unit dosage forms[4,5.] The use of pellets helps in preventing drug release in stomach, and irritation in the stomach. With this pellets also offer a greater flexibility, as compared to the solid dosage form. They flow freely, pack easily, leading to uniform and reproducible fill weights of the capsules and tablets. Thus, the main aim of this study was to formulate a multiparticulate drug delivery system for colon targeting, using Eudragits.

MATERIALS AND METHODS

MATERIALS:

Nonpareil seeds were procured from Micropellets, Nashik. Omeprazole from Wockhardt Pharmaceuticals Ltd, Eudragit L-30 D-55, (Rohm Pharma GmbH, Darmstadt, Germany). Hydroxypropyl methylcellulose E-5, Hydroxypropyl cellulose EF Polyvinyl Pyrrolidine K-30

METHODS:

Preparation of pellets of Omeprazole

The pellets were prepared by coating on the nonpareil seeds, previously layered with the drug. Three successive coats were given to the drug layered pellets, as mentioned below.

Initial Coat: Hydroxypropyl Methylcellulose E-5 or Hydroxypropyl Cellulose was dissolved in water with continuous stirring followed by sodium citrate. Tween 80 was added to the

solution and then the drug was added with continuous stirring and the process was continued for 30 minutes. The obtained pellets were dried till the moisture content was NMT 2% W/W. The parameters set for this were as inlet temperature of 50°C, product temperature was between 38-42° C, and Solution Dispensing rate was 0.5 ml/min.

Intermediate Coat: PVP K-30 was added to purified water so as to get a solution of 10% w/w. The obtained pellets were dried till the moisture content was nmt 2% w/w. The parameters set for this were as inlet temperature of 50°C, product temperature was between 35-40° C, and Solution Dispensing rate was 0.7 ml/min.

Functional Coat: PEG 400 was dissolved in water. Talc and titanium oxide were added to the solution with continuous stirring. The resulting mixture was poured in the Eudragit L-30 D-55 solution with continuous stirring. The obtained pellets were dried till the moisture content was NMT 2% w/w. The parameters set for this were as inlet temperature of 50°C, product temperature was between 36-40°C and Solution Dispensing rate was 1.0 ml/min. Details are shown in Table 1.

EVALUATION OF PELLETS

Fourier transform infrared spectroscopy

The infrared (IR) spectrum of pure drug and prepared formulation was done. The formulations IR was compared with that of the pure drug to confirm the chemical integrity of the drug in the formulations developed. The samples were powdered and mixed with dry powdered potassium bromide. The powdered mixture was taken in a sampler and scanned in FTIR spectrophotometer (Jasco, FT/IR 4100).

Flow properties:

The flow properties of the Omeprazole pellets were characterized for the angle of pellets were poured through a funnel, fixed at a position at a height of exactly 2.0 cm above the hard surface. The pellets were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the height of the pile/ radius of its base gave the angle of repose[6]. The pellets were also characterized for bulk density, tapped density also. The prepared pellets exhibited good flow properties, as shown in Table 2.

Friability study

The friability study was performed on the pellets to ensure their mechanical strength. Pellets of known weight were placed in a Roche Friability tester and subjected to impact at 25 rpm for 4 min. The friability was calculated using the following equation;

Friability (%) = {1- initial weight/ weight retained after 100 rotations] X 100

The friability of the pellets was found to be in the range of 0.12± 0.03% to 0.13± 0.054 which indicated the good mechanical strength of pellets in the term of fragmenting or powdering during filling operation into a capsule shell. The results are shown in Table 2.

Drug content

Required pellets were ground into fine powder and all the powder was transferred into 100 ml volumetric flask and dissolved in 100 ml methanol. Samples were taken, filtered, diluted suitably and assayed spectrophotometrically at 301 nm[7]. The experiment was performed in triplicate and mean values were taken and results shown in Table 2.

***In vitro* drug release studies**

The dissolution of the capsule was performed using USP XXIII dissolution apparatus type II (paddle method) initially using 300 ml of 0.1 N HCl acid (pH 1.2) as the dissolution medium, which was maintained at $37^0C \pm 2^0C$ and stirred at 50 rpm. Aliquots of 5ml of samples were withdrawn with a bulb pipette at different time intervals and replaced with equal volume of 0.1 N HCl acid and the aliquots were filtered using Whatman Filter Paper No.1. Filtered aliquots were analyzed spectrophotometrically at 301 nm and the percentage drug released at various time intervals was calculated. This test was done in triplicates.

Drug release models

To describe the kinetics of the drug release from the controlled release pellets, mathematical models such as zero-order, first-order, Higuchi, Hixon-Crowell, Korsmeyer-peppas models were used[8]. The release data were evaluated by model dependent (curve fitting) method using PCP Disso ver. 2.08 software.

Stability study

Stability study of the optimized batch was carried out by packing the pellets into a suitable packaging and subjected for an accelerated stability study at 40°C, 75% RH conditions as per ICH guidelines for a period of 3 months.

RESULTS AND DISCUSSION:

EVALUATION OF PELLETS

FT-IR analysis:

FT-IR spectra of Omeprazole, excipients, and prepared samples were recorded as described above. The drug showed aromatic C-H stretch at 3059.10 cm^{-1}, N-H Stretch at 3566.38 cm^{-1}, C=C Stretch at 1631.78 $cm^{-1.}$ All the peaks of the drug appeared in the physical mixture as well as pellets, which showed that there was no interaction between drug and excipients used, as shown in Figure 1 & 2.

***In-vitro* Drug release study:**

The enteric coated pellets B4 batch showed a 6.78% drug release, whereas B5 batch showed 4.63% and F6 batch showed 3.75 % drug release in 0.1HCL. The enteric coated pellets B4 batch showed 85.02 % drug release, whereas B5 batch showed 81.39% and B6 batch showed 78.44 % drug release in phosphate buffer, pH 6.8.

In-vitro dissolution studies indicate that when HPMC Acetate Succinate was introduced into the formulation and as well as the functional coat was of Eudragit L-30 D-55 and Eudragit S-100 it showed a maximum release of nearly 80-86 % release in 30 minutes as compared to the other formulation where the functional coat is of HPMCA succinate respectively.

In all the three formulations, the maximum amount of the drug was released only when exposed to the colonic environment and within 20-30 minutes. When the two polymers were added in equal amounts the drug release was found to be maximum.

Kinetic analysis of optimized batch

Model fitting was applied to formulations using PCP software. Zero order, First order, Higuchi, Korsmeyer-Peppas, Hixon Crowell model were tested. The results are shown

in Table 3. The best-fitted kinetic model for the drug release was determined by studying the parameter R^2 value, and F-value (Fischer ratio) for given models. A higher value of R^2, as well as the lower value of F, gives the best-fitted model for drug release.

Accordingly, the kinetic data for drug release was best fitted to the Korsmeyer-Peppas model. Also, the *n* value (release coefficient or x-variable) in Korsmeyer-Peppas model for optimized formulation was found to be 0.3376. So mechanism of drug release was found to be Anomalous transport. The mechanism of release of Omeprazole pellets from the formulated batch was by anamolous non- Fickian diffusion i.e., diffusion coupled with erosion.

Stability study of the optimized formulation

Stability study was carried out for the optimized formulation, as per accelerated stability study. The dissolution profile after stability study was similar compared to samples soon after the preparation.

Table 1: Formulation of the coated pellets prepared

Contents	B1	B2	B3	B4	B5	B6
	Amount (gm)					
Initial Coating						
Non-pareil seeds	48.98	48.98	48.98	48.98	48.96	48.98
Omeprazole	10.21	10.21	10.21	10.21	10.21	10.21
Sodium Citrate	2.83	3.83	4.83	4.83	4.47	4.83
Tween 80	-	-	-	0.97	1.02	0.97
HPMCE5	-	4.65	6.65	9.65	2.68	-
HPC	-	2.68	-	-	2.68	9.65
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Intermediate coating						
PVP K-30	2.83	3.83	4.83	4.83	4.47	4.83
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Functional coating						
HPMC	-	-	-	-	8	-
Eudragit L-30 D-55	33.3	33.3	33.3	-	-	-
Eudragit S-100	-	-	-	33.3	-	33.3
Talc	1	1	1	2.1	-	2.1
Titanium oxide	2.3	2.3	4.15	4.15	-	4.15
Propylene glycol 400	-	-	-	0.56	1	0.56
Acetone	-	-	-	-	q.s.	-
Ethanol	-	-	-	-	q.s.	-
Purified Water	q.s.	q.s.	q.s.	q.s.	-	q.s.

Table 2: Flow properties, drug content and friability of coated pellets

Batches	Evaluation parameters for coated pellets						
	The angle of repose ($^{\theta}$)	**Bulk density (gm/cm^3)**	**Tapped density (gm/cm^3)**	**Hausner's ratio**	**Carr's index (%)**	**Drug content (%)**	**Friability (%)**
B1	25.50± 0.20	0.54± 0.011	0.58± 0.013	1.02± 0.01	2.71± 0.07	81.35 ± 0.093	0.12± 0.03
B2	25.45± 0.32	0.56± 0.012	0.60± 0.014	1.02± 0.01	2.82± 0.07	83.40± 0.971	0.12± 0.25
B3	25.33± 0.71	0.56± 0.012	0.64± 0.015	1.03± 0.02	2.97± 0.07	87.72± 0.337	0.12± 0.028
B4	25.74± 0.27	0.56± 0.012	0.58± 0.013	1.03± 0.02	3.75± 0.08	96.49± 0.73	0.13± 0.054
B5	25.63± 0.65	0.58± 0.013	0.60± 0.014	1.04± 0.03	3.89± 0.08	95.87± 0.65	0.12± 0.03
B6	25.59± 0.87	0.60± 0.014	0.64± 0.015	1.05± 0.02	5.38± 2.26	95.80± 0.29	0.12± 0.026

Table 3: Model fitting data for coated pellets

Sr.no	Formulation	Models	R	n	K
1	B1	Zero Order	0.6410	0.3085	22.123
		First Order	0.8891		
		Matrix	0.9732		
		Korsmeyer Peppas	0.9456		
		Hixon Crowell	0.9100		
2	B2	Zero Order	0.7121	0.3000	21.112
		First Order	0.9124		
		Matrix	0.9192		
		Korsmeyer Peppas	0.9652		
		Hixon Crowell	0.9123		
3	B3	Zero Order	0.7112	0.3124	20.211
		First Order	0.9125		
		Matrix	0.9457		
		Korsmeyer Peppas	0.9321		
		Hixon Crowell	0.8120		
4	B4	Zero Order	0.7410	0.3189	22.7404
		First Order	0.9891		
		Matrix	0.9754		
		Korsmeyer Peppas	0.9879		
		Hixon Crowell	0.9455		
5	B5	Zero Order	0.7558	0.3249	21.6664
		First Order	0.9604		
		Matrix	0.9780		
		Korsmeyer Peppas	0.9910		
		Hixon Crowell	0.9480		
6	B6	Zero Order	0.7303	0.3376	20.1023
		First Order	0.9799		
		Matrix	0.9785		
		Korsmeyer Peppas	0.9956		
		Hixon Crowell	0.9603		

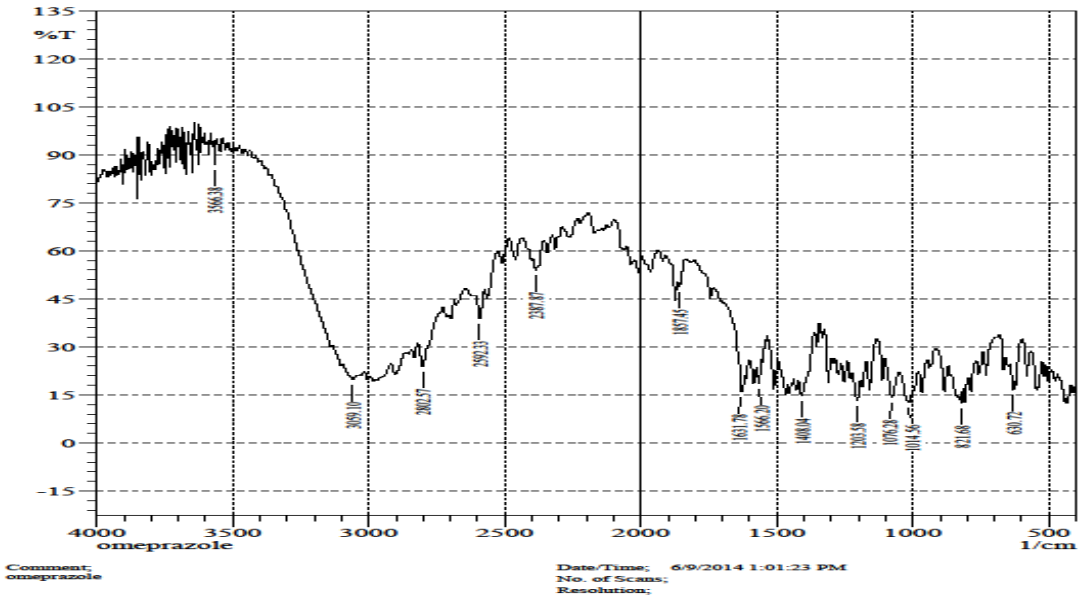

Figure 1: FT-IR of pure drug

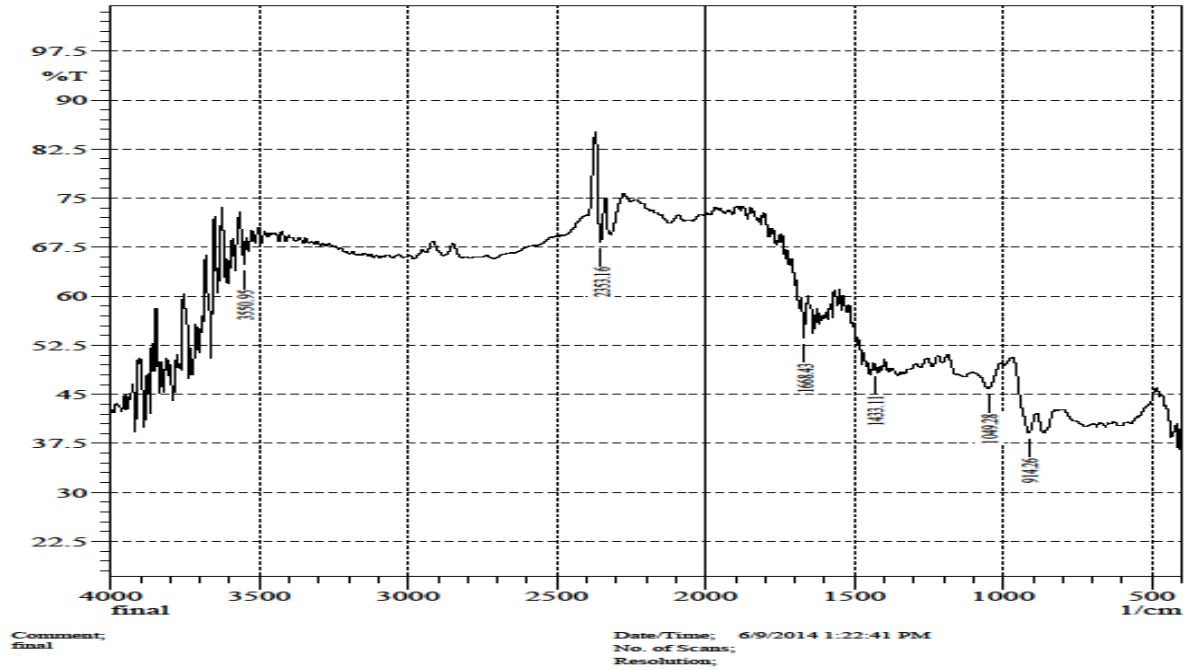

Figure 2: FT-IR of final optimized formulation, B6

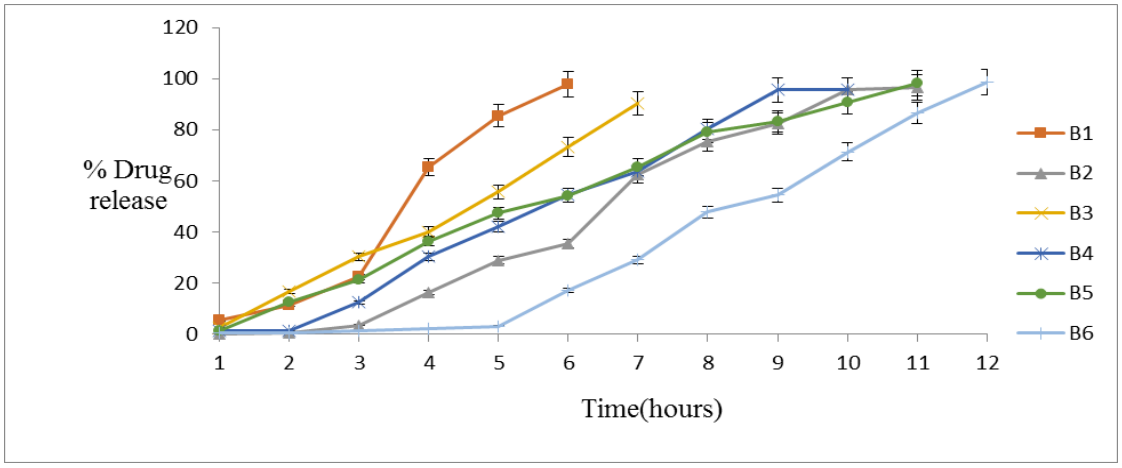

Figure 3: Dissolution profile for B1 to B6 batches for 12 hrs drug release

SUMMARY AND CONCLUSION

The delayed release pellets of Omeprazole thus prepared by this method was successfully employed. The micromeritic properties, friability of the pellets were within the limits which indicated good flow potential for the prepared pellets. From the FTIR studies, there was no chemical interaction, between the drug and polymers, used. From this study, it can be delayed the release for colon can be prepared successfully.

ACKNOWLEDGMENT

The authors are thankful to Wockhardt Pharmaceuticals Ltd, India, for providing standards sample of the drug.

REFERENCES

1. Charman SA, Charman WN, Rathbone MJ. Modified release drug delivery technology; 2nd ed. Marcel Dekker: NewYork, 2003.
2. Ghebre-Sellassie, I. Multiparticulate Oral drug delivery. Marcel Dekker: New York, 1994.
3. Muller RH, Bohm BH, Gran MJ. Handbook of pharmaceutical controlled release technology, 2nd ed.; Marcel Dekker: NewYork, 2008.
4. Bechgaard H, Nielson GH Controlled release multiple units and single unit doses. Drug Dev. Ind. Pharm., 1978; 4: 53-67.
5. Hellen L, Yliruusi J, Kristoffersson E. Process variables of instant granulator and spheronizer: I. physical properties of granules, extrudate, and pellets. Int. J. Pharm.,1993; 96: 197-204.
6. Harun AR. Hinamaki J, Antikanen O and Yiruusi J. Influence of centrifugal granulating process on the properties of layered pellets. Eur. J. Pharm. Biopharm., 2001; 51: 227-234.
7. Sadeghi F, Ford JL, "Comparative Study of Drug Release from Pellets Coated with HPMC or Surelease", Drug Development and Industrial Pharmacy,2000; 26:6,651 — 660.
8. Costa P, Manuel JS. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences 13 (2001) 123–133.