EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 8
300-308
Year: 2022

FORMULATION AND EVALUATION OF DELAYED RELEASE PANTAPRAZOLE SPHERES BY USINGFLUIDISED BED PROCESSOR

Shivaraj Bhaskar Pagare*, Dr. Avish D. Maru and Rajendra K. Surawase

Loknete Dr. J D Pawar College of Pharmacy, Manur Kalwan, Nashik, Maharashtra.

***Corresponding Author: Shivaraj Bhaskar Pagare**
Loknete Dr. J D Pawar College of Pharmacy, Manur Kalwan, Nashik, Maharashtra.

Article Received on 29/05/2022 **Article Revised on 19/06/2022** **Article Accepted on 09/07/2022**

ABSTRACT
The present study was an attempt to formulate and of Delayed Release Pantaprazole Spheres by Using Fluidised Bed Processor". Different tablets were prepared and formulation in different batch, the suspension layering approach was utilised to produce pellets. Friability tests, assays, and in-vitro release studies were conducted for 1 hour in acidic media containing 0.1N HCL, followed by 1 hour in a 6.8 pH Phosphate buffer to evaluate the finished products. From the evaluation, it was determined that the percentages of friability and assay for all formulations from F1 to F9 fell within the acceptable range. Formulation F9 exhibited superior resistance to 0.1 N HCL and excellent solubility in phosphate buffer with a pH of 6.8 as determined by in vitro dissolution testing. Based on the aforementioned results and discussion, it is possible to conclude that formulation F9 of enteric coated pellets of Pantaprazole is stable in acidic medium and exhibits superior drug release in basic medium. Therefore, this formulation of enteric-coated pellets was perfect and optimised. The stability study was conducted for formulation F9 at 1 month for the invitro dissolution investigation, and it was observed that no changes occurred, indicating that the improved formulation F9 was stable.

KEYWORD: peptic ulcer, pantaprazole, enteric coated tablet, density.

INTRODUCTION
An ulcer in the lining of the stomach or duodenum is referred to as a peptic ulcer. Peptic ulcers that are located in the stomach are referred to as gastric ulcers, and those that are located in the duodenum are referred to as duodenal ulcers.[1] Peptic ulcers are brought on by the production of pepsin and acid in the stomach, both of which are enzymes. Patients who acquire ulcers typically create a greater quantity of acid than people who do not have ulcers. Additionally, the patient's stomach or intestinal wall may not have natural defences that are robust enough to withstand the effects of acid and pepsin. This might make the ulcer worse.[2] Taking nonsteroidal anti-inflammatory medicines (NSAIDs) like aspirin or ibuprofen, for example, is another potential cause of this condition. Pantoprazole is a proton pump inhibitor that is widely used. It is an important drug in the treatment of acid-related disorders[3], and it is also useful in the treatment of Helicobacter biliary infections, either on its own or in combination with other medications like metronidazole, clarithromycin, or amoxicillin.[4] Pantoprazole (PAN) has various advantages over its counterparts, such as omeprazole, including a specific location of binding, higher stability in an environment with a neutral pH, and a longer duration of action.[5] These benefits can be found in pantoprazole. Aside from that, there is no evidence that it can either stimulate or suppress the CYP450 enzyme.[6] It is an inhibitor of acid secretion that is more selective than those of the proton pump that are currently available. At low pH values, pantoprazole changes into cationic sulfenamide, which is its active form.[7] This drug gathers in the acidic environment of the parietal-cell canalicular lumen, where it is then activated. This is one part of the mechanism of action of pantoprazole. Another part of the mechanism is that pantoprazole turns into cationic sulfenamide at low pH values. Tetracyclic cationic sulfonamide, which is the active form, combines with the thiol group of cysteines 813 and 822 in transmembrane H+/K+ ATPase.[8] This transformation needs to take place close to the gastric parietal cells for pantoprazole to be absorbed unaltered from the gastrointestinal tract. Pantoprazole is degraded in the stomach since it is an acid-labile drug. As a result, the medication needs to be directed at the site of its absorption in order to circumvent the influence of the stomach's acidic medium. Due to the requirement that acid-labile pharmaceuticals must make it through the stomach in one piece in order to be absorbed in the duodenum, the gastro resistant drug delivery system was designed for these types of medications.[9] Either a solution for intravenous injection (lyophilized powder for reconstitution) or a gastric-resistant (oral delayed-release) dosage form can be used to construct the

dosage form so that it can be administered without passing through the stomach.[10] When the medicine is taken orally, the enteric coating protects the acid-sensitive active ingredient from being broken down by the stomach's digestive juices. The "Formulation and Evaluation of Delayed Release Pantaprazole Spheres Using Fluidized Bed Processor" is the goal of this study.

2. MATERIAL AND METHODS

2.1 Preparation of Delayed Release Pantaprazole Spheres

Took weighed 1/3rd of the total quantity of dematerialized water in stainless steel vessel and heat the water up to80-85ºC.Sodium lauryl sulphate, poly-ethylene glycol 6000, di-sodium hydrogen phosphate was weighed and added one by one in the water and dissolved. Hydroxylpropyl methyl cellulose was weighed and transferred in hot purified water under stirring and slurry of HPMC was prepared. Remaining quantity of dematerialized water was added in the hot slurry under stirring to dissolve HPMC Cooled the solution up to room temperature under stirring. Checked pH and adjusted pH to 9.0 (Acceptable Range 8.5 – 9.5) if necessary, by adding more buffer. Pantaprazole was weighed and added in above solution slowly under stirring; stirred until uniform slurry to be formed. Then purified talcum was added under stirring. Finally mixed properly for 10 minutes, and passed solution through 100 meshes. Stored the solution in a well closed container. Coated Pellets were collected in double polythene lined container. Unloaded & weighed the pellets in double lined polythene bags in clean, tared and labeled it & closed (air tight) the bags.

2.2 Preformulation Studies

To formulate an ideal formulation, the pre-formulation studies are usually the quantitativeassessment of chemical stability of drug as well as stability in presence of other excipients for a formulation. Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the Preformulation phase begins early in the discovery process such the appropriate physical, chemical data is available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form are also considered in the present study. The following Preformulation studies were performed. **Organoleptic properties.**

2.2.1 Solubility analysis

Solubility is important pre-formulation parameter because it affects the dissolution and bio availability of drug

METHOD

Appropriate quantity of drug was weighed and added to the suitable volume of solventlike hexane, ethanol, and water.

2.2.2 Melting point

The melting point of Pantaprazole was determined by capillary method, using small quantity of Pantaprazole was taken and placed in apparatus and determined the melting point and matched with standards.

2.2.1 Bulk density

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density will increase. In addition, as the granule size increases bulk density decreases.

Method

A given quantity of the powder was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume is obtained. This volume is bulk volume and it includes the true volume of the powder and the void space among the powder particles.

Bulk Density = Bulk Mass / Bulk Volume

2.2.2 Tapped density

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder. An accurately weighed 5gm sample of powder was carefully added tothe cylinder with the aid of a funnel. The initial volume was noted, and the sample was then tapped (500,750 or 1250 tapping) until no further reduction in volume is noted or thepercentage of difference was not more than 2% a sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density is calculated using following formula.[11]

Tapped density = Wt. of sample in gm / Tapped volume

2.2.3 Hausner's ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = v_i / v_t$$

Where v_t = Tapped volumev_i = untapped volume

2.2.4 Angle of repose

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by allowing the pellets to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height. The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured.

The angle of repose is given as,
$\theta=\tan^{-1}(h/r)$
Where, θ= angle of reposeh= height of the heap
r = radius of the base of the heap

2.2.5 Loss on drying

Determined on 1 g by drying in an oven at 100^0c to 105^0 c for 3 Hours accurately weighed the substance to be tested. If the sample is in the form of large crystals, reduced the particles size to about 2 mm by quickly crushing. Tarred a glass topper, shallow weighing bottle that has been dried for 30 minutes under the same condition to be employed in the determination. Put the sample in bottle, replaced the cover, and accurately weighed the bottle and the contents. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature from constant weighed. Upon opening the chamber, closed the bottle promptly, and allowed it to come to room temperature in desiccators before weighing. The difference between successive weights should not be more than0.5mg. The loss on drying is calculated by the formula.

$$\% \text{ LOD} = \frac{(W2-W3)}{(W2-W1)} \times 100$$

Where,
W1 = Weight of empty weighing bottle
W2 = Weight of weighing bottle + sample
W3 = Weight of weighing bottle + dried sample

2.2.6 Drug- excipients compatibility studies

Infrared spectrophotometer is a useful analytical technique utilized to check the chemical interaction between the drug and the other excipients used in the formulation. The sample (1 mg) was powdered and mixed with the (10 mg) of dry powdered potassium bromide. The powdered mixture was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000-400 cm^{-1} using FTIR spectrophotometer.

2.2.7 Ultraviolet visible (UV) spectroscopy

Pantaprazole (100 mg) was accurately weighed and dissolved in 100 ml purified water to form a stock solution (1000 µg/ml). The stock solution was further diluted suitably to get a working standard solution of concentration 100 µg/ml. This working standard solution was suitably diluted to give a concentration of 20 µg/ml and this was then scanned in UV range. This showed an absorption maximum at 281 nm. Aliquots (0.5,1.0,1.5,2.0 and 2.5) ml of working standard solution (100 µg/ml) corresponding to 5-25 µg were taken in a series of 10 ml volumetric flask and volume made up with water. The absorbance measurements of these solutions were carried out against purified water as blank at 281 nm. A calibration curve of Pantaprazole was plotted. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

3.1 EVALUATION OF FORMULATED PANTAPRAZOLEPELLETS

3.1.1 Friability

There was no standard method established for evaluating friability of pellets. Thefriability of pellets was determined by using Roche friabilator. But the mechanical stress applied is less due to the low weight of the pellets. This can be corrected by increase stress by adding glass or steal balls into pellets. The friability was calculated as percentage weight loss according to the following equation.[12]

$$\%\text{friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} *100$$

3.1.6 Particle size determination

In order to determine the particle size distributions of the prepared pellets containing Pantaprazole, standard sieve method was used. Mechanical sifter with sieves between apertures 355-2000 µm were used by using all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

3.1.7 Gastric acid resistant test

Acid resistance test is a significant index of drug dissolution performance of enteric coated formulations. Model fraction of coated pellets was subjected for acid resistance test in USP dissolution test apparatus –II (SR-8, Hanson Research, and Chatsworth, USA). Weighed amount of pellets were placed in the vessel and test was carried out in 0.1N HCl for 1hr at 75 rpm. Pantaprazole released at 1hr in 0.1 N HCl was estimated as per method specified in USP. Minimal amount of drug release in this test is indicative of gastric acid resistance.

3.1.8 In vitro dissolutionstudy[13]

3.1.9 Method

Dissolution studies were carried out for all the formulations, employing USP-II paddle Method 500 ml of 0.1 N HCL for first 1 hr. and 900 ml of phosphate buffer pH-6.8 for next 1 hr. were used as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Pellets were placed in the vessel and the vessel was covered and operated for 1 hr. in 0.1 N HCL at 75 rpm and next 1 hr. pH-6.8 phosphate buffer at 100 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 281 nm using UV-spectrophotometer.

3.1.9 Scanning electron microscopy

Photo micro graphs were taken with a scanning electron microscope for visualization of spherocity of the pellets. Pellets were coated with platinum by means of a sputter coaterto assure conductivity.

3.1.10 Accelerated stability study[14]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retesting for the drug substance or a shelf-life for the drug product and recommended storage conditions.

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use.

The ICH Guidelines have established that accelerated stability testing should be done at 40^0C/75%RH for 3 months.

Stability study was carried out for the optimized formulation. Tablets of optimized formulation were packed in strip and kept in stability chamber for 3 months on above mention temperature. Samples were analyzed at 1, 2, 3 months for invitro dissolution study.

4. RESULT

4.1 Preformulation study

Identification and characterization of drug

A. Organoleptic properties

Pantaprazole received was studying for Organoleptic characters such as color, odor andappearance.

Table 1: Organoleptic properties of Pantoprazole.

Sr. No.	Parameters	Observed result	Reported standard	Inference
1.	White to off white	White to off white	White to off white	Complies IP
2.	Odor	Aromatic	Aromatic	Complies IP
3.	Taste	Bitter	Bitter	Complies IP
4	Appearance	Crystalline powder	Crystalline powder	Complies IP

The all test of Pantaprazle complies as per IP 2014 therefore it is confirmed that modeldrug has good properties.

B. Melting point

The melting point was determined by capillary method and was found to be.

Table 2: Melting point of Pantoprazole.

Parameter	Observed result	Reported standard	Inference
Melting point	138-140^{0}c	132-134^{0}c	Complies IP.

The melting point of Pantaprazole was complies as per I.P

C. Solubility

Table 3: Solubility of drug in different solvent.

Sr. No.	Solvent	Descriptive term
1	Water	Freely soluble
2	Phosphate buffer	Very slightly soluble
3	0.1 N HCL	Completely soluble

D. Calibration curve of Pantoprazole in water

Calibration curve of Pantoprazole was determined by plotting absorbance vs concentrationat 292 nm, the results were obtained given in following table

Table 4: Standard Graph Readings (visible spectra)

Concentration (µg/ml)	Absorbance (nm)
0	0.0
5	0.158
10	0.282
15	0.422
20	0.567
25	0.653
30	0.832

The linear regression analysis was done on absorbance data points. A straight linegenerated to facilitate the calculation of amount of drug, the equation is as follows.

Y= mx+c

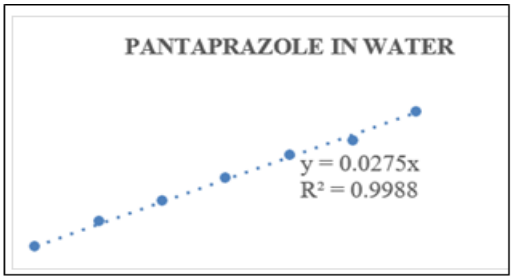

Figure 1: Calibration curve of Pantoprazole in Water.

D. Bulk and Tapped density

Table 5: Bulk and tapped density of formulations of F1 to F9.

Formulation code	Bulk density	Tapped density	Hausner ratio	Carr's index
	g/ml			
F1	0.923±0.02	0.989±0.03	1.07±0.01	5.47±0.03
F2	0.937±0.03	1.0048±0.06	1.07±0.05	5.71±0.06
F3	0.921±0.02	0.988±0.02	1.07±0.04	4.38±0.07
F4	0.934±0.02	0.991±0.04	1.06v0.02	4.96±0.08
F5	0.915±0.3	0.959±0.05	1.04±0.02	5.21±0.04
F6	0.952±0.04	0.999±0.02	1.04±0.06	5.47±0.04
F7	0.947±0.01	1.028±0.04	1.08±0.07	5.39±0.06
F8	0.928±0.02	0.972±0.06	1.04±0.01	5.11±0.03
F9	0.938±0.04	0.987±0.4	1.05±0.04	4.96±008

All values represent mean ± standard deviation (SD) n=3.

The result showed in table no. 8.8 given the bulk and tapped density, Hausner ratio and Carr's Index for all formulation and all values were found within limit; therefore, it revealed that the pellets of all formulations has good flow property.

E. Angle of repose.

Results for angle of repose given in table no:6.

Table 6: Angle of repose of formulations.

Formulation code	Angle of repose
F1	27.30
F2	26.50
F3	28.02
F4	28.44
F5	28.21
F6	26.76
F7	25.23
F8	24.45
F9	29.88

All values represent mean (n) =3.

The angle of repose of formulations from F1 to F9 found between 24.45 to 29.88, so angle of repose of all formulation were below 30, therefore it was indicating that pellets were having good flow property.

F. Particle size determination

Results for particle size determination were given in the table no.7.

Table 7: Particle size determination.

Formulation code	Particle size(µm)
1	1075.47
2	1208.56
3	1194.34
4	1064.23
5	1134.51
6	1198.57
7	1057.25
8	1187.78
9	1163.45

All values represent mean (n) =3.

From above results it was observed that the average particle sizes of the pellets were nearly 1200µm for all 9 formulations

G. Loss on drying

Loss on drying of Pantoprazole was found to be 0.40 w/w (not more than 2% of w/w)

H. FTIR Study

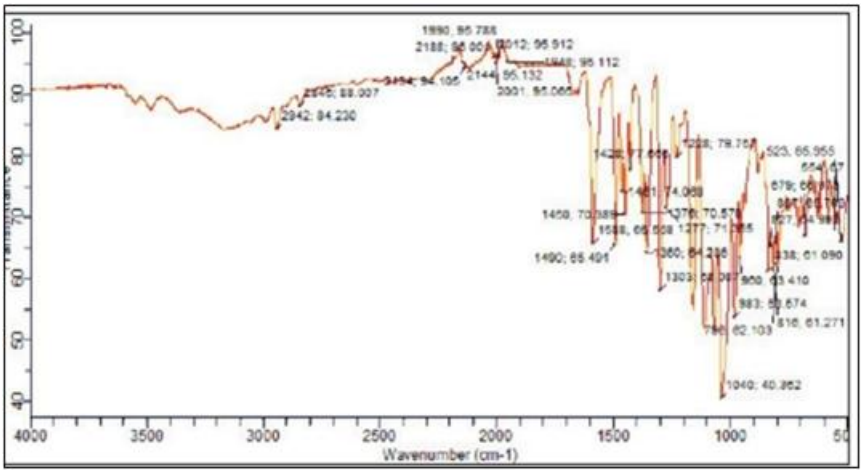

Figure 2: FTIR spectrum of pure drug of Pantoprazole.

I. DSC study

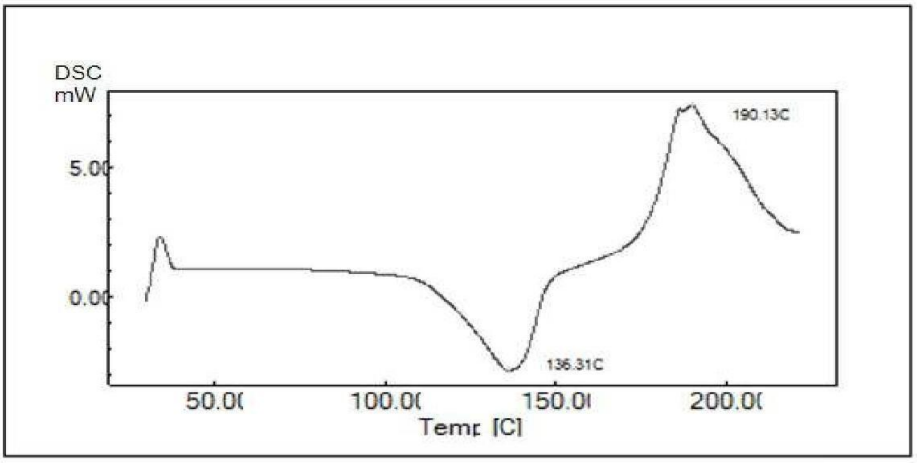

Figure 3: DSC spectrum of pure drug of Pantoprazole.

J. Solid state compatibility studies of drug with Excipients

There is always possibility of drug-excipients interaction in any formulation due to their intimate contact. The Drug-excipient interaction studies were carried out by employing IR spectroscopic technique, which is one of most powerful analytical technique.

Table 8: Compatibility study of drug with different excipients.

Sr. No.	Ingredients	Observation (After 30Days)
1	Pantoprazole	No change
2	Pantoprazole + Sugar spheres	No change
3	Pantoprazole + Ethyl cellulose	No change
4	Pantoprazole + HPMC E5	No change
5	Pantoprazole + Polyethylene glycol	No change
6	Pantoprazole + Talc	No change
7	Pantoprazole + Disodium hydrogen phosphate	No change
8	Pantoprazole + Polysorbate 80	No change
9	Pantoprazole + Triethyl citrate	No change
10	Pantoprazole + Eudragit L30 D55	No change

4.2 Evaluations of formulated Pantoprazole pellets

Evaluation of formulated Pantoprazole pellets was carried out according to procedure givensection.

4.2.1 Friability test: Result of friability test were given in table No.9

Table 9: Results of % friability of F1 to F9 formulation.

SR.NO.	FORMULATION	FRIABILITY%
1	F1	0.65±0.01
2	F2	0.72±0.03
3	F3	0.55±0.02
4	F4	0.62±0.07
5	F5	0.73±0.03
6	F6	0.58±0.01
7	F7	0.46±0.02
8	F8	0.62±0.03
9	F9	0.77±0.05

Above table showed the percent friability of all formulations and it was observed that all the prepared pellets showed that percent friability value less than 1%, therefore the results were within the range.

4.2.2 Gastric acid resistance test

Results for the acid resistant test were given as follows

Table 10: Percent gastric resistant of formulations F1 to F9.

FORMULATION CODE	% ACID RESISTANCE
F1	89.68±0.05
F2	91.06±0.03
F3	95.87±0.07
F4	87.97±0.01
F5	92.33±0.04
F6	89.49±0.03
F7	90.56±0.02
F8	96.87±0.06
F9	95.78±0.02

All values represent mean ± standard deviation (SD) n=3. The above table showed the percent acid resistant of all formulations and it was observed that theall formulations have better acid resistant.

5 INVITRO DISSOLUTION STUDIES

All values represent mean (n) =3

Table 11: Cumulative percentage of Pantoprazole release in 0.1N HCL and Phosphate Buffer pH 6.8

	Cumulative percent drug release in 0.1N HCL								
TIME(MIN)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	0.55	0.61	0.59	0.67	0.58	0.66	0.59	0.54	0.49
30	0.68	0.72	0.65	0.72	0.65	0.73	0.62	0.58	0.56
45	0.82	0.84	0.78	0.79	0.73	0.77	0.74	0.68	0.64
60	0.89	0.91	0.85	0.83	0.84	0.81	0.79	0.72	0.71
	Cumulative percent drug release in Phosphate Buffer pH 6.8								
75	58.18	60.32	58.18	65.72	67.33	69.23	71.67	68.51	72.82
90	62.1	65.49	63.16	68.12	67.64	73.52	77.44	74.12	81.49
105	75.45	67.65	74.67	74.96	78.34	80.05	88.63	81.22	86.64
120	72.59	75.24	78.54	81.09	84.82	88.74	92.64	89.66	94.48

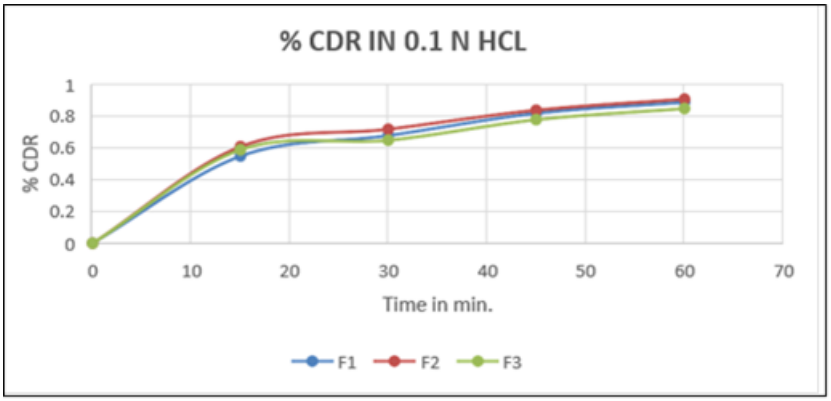

Figure 4: Cumulative percent drug release of Pantaprazole in 0.1N HCL.

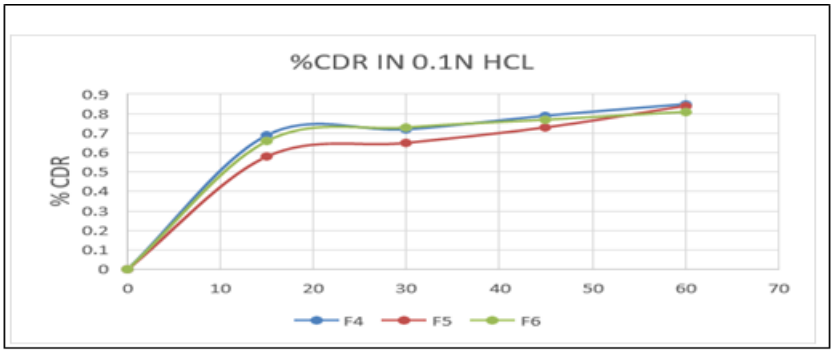

Figure 1: Cumulative percent drug release of Pantaprazole in 0.1N HCL.

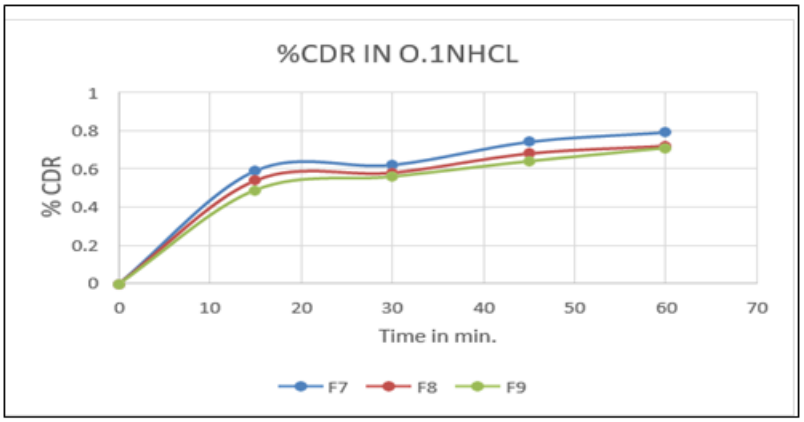

Figure 5: Cumulative percent drug release of Pantaprazole in 0.1N HCL.

6. Scanning electron microscopy

The scanning electron microscopy of formulation F9 showed that prepared pellets have Good coating and film former and it are helpful in controlling. SEM photomicrographs that The drug layered pellets were discrete, spherical or oval with a slightly rough surface. The SEM photomicrographs of Eudragit L30 D55 coated pellets it shows that the applied film Was smooth, continuous and showed good adhesion to the drug layered pellets.

DISCUSSION

From the results it was observed that the formulation F9 has better cumulative percent drugrelease as compared to other formulations. Because it may be in formulation F9 Eudragit L-30 D55 was used in low concentration, therefore the drug release from pellets occurs fastly in phosphate buffer pH 6.8. While keeping in 6.8 pH buffer, 72.82 cumulative percent drug releases occur at 75 minutes, after 120 minutes 94.48 cumulative percent drugreleases was attained, when compared to other formulation F9 showed better release, so F9was selected as optimized formulation.

SUMMARY AND CONCLUSION

The study was undertaken with an aim to develop an optimized formulation and evaluation of delayed release Pantaprazole sphere by using Fluidised bed processor this Eudragit L30 D55, HPMC E5 as retarding agent. Pantaprazole was selected and formulated as Enteric Coated Pellets comparable to the innovators product. In the present work, reformulation studies were conducted to know the drug excipients compatibility by using FTIR spectroscopy. Based on the results, suitable excipients were selected for formulation development. FTIR spectra revealed that there was no significant interaction between drug and polymer.

Pellets were prepared by using Suspension layered method. Finished products were evaluated for friability test, assay, and In-vitro release studies performed for 1 hr in acidicmedia at 0.1N HCL, after that 1 hr in 6.8 pH Phosphate buffer.

From the evaluation it was concluded that percent friability and percent assay for all formulations from F1 to F9 were found within the limit. Invitro dissolution study showed that Formulation F9 having the better resistance in 0.1 N HCL and good release in phosphate buffer pH 6.8.

From the above results and discussion it might be concluded that the formulation F9 of enteric coated pellets of Pantaprazole was found to be stable in acidic medium and shows better drug release in basic medium. Therefore it was an ideal and optimized formulation of enteric coated pellets. The stability study was carried out for formulation F9 at 1 month for invitro dissolution study and from this it was observed that there were no changes and clearly showing that the optimized formulation F9 was stable. In future, this work extends for in-vivo study.

Funding: None.

Conflicts of interest: None.

Disclaimer statements

Contributors Dr Avish D Maru contributed to the conception and supervision of the study, checking, editing and all revisions of the manuscript. Shivaraj Bhaskar Pagare and Rajendra k. Surawasecontributed in carrying out all the experiments, statistical analysis of the data and preparing the first draft of the manuscript including table and figures.

REFERENCES

1. L. Kuna, J. Jakab, R. Smolic, N. Raguz-Lucic, A. Vcev, and M. Smolic, “Peptic ulcer disease: A brief review of conventional therapy and herbal treatment options,” J. Clin. Med, 2019; 8(2). doi: 10.3390/jcm8020179.
2. F. Jaiswal, A. K. Rai, P. Wal, A. Wal, and S. P. Singh, “Peptic Ulcer: a Review on Etiology, Pathogenesis and Treatment,” Asian J. Pharm. Educ. Res, 2021; 10(4): 1, doi: 10.38164/ajper/10.4.2021.1-17.
3. D. L. Avner, “Clinical experience with pantoprazole in gastroesophageal reflux disease,” Clin. Ther, 2000; 22(10): 1169–1185, doi: 10.1016/S0149-

2918(00)83061-1.
4. S. M. Cheer, A. Prakash, D. Faulds, and H. M. Lamb, "Pantoprazole: An update of its pharmacological properties and therapeutic use in the management of acid-related disorders," Drugs, 2003; 63(1): 101–132, doi: 10.2165/00003495-200363010-00006.
5. W. Beil, U. Staar, and K. F. Sewing, "Pantoprazole: a novel H+/K+-ATPase inhibitor with an improved pH stability," Eur. J. Pharmacol, 1992; 218: 2–3, 265–271, doi: 10.1016/0014-2999(92)90178-7.
6. A. Fitton and L. Wiseman, "Pantoprazole: A Review of its Pharmacological Properties and Therapeutic Use in Acid-Related Disorders," Drugs, 1996; 51(3): 460–482, doi: 10.2165/00003495-199651030-00012.
7. K. Nishioka, T. Nagao, and T. Urushidani, "Correlation between acid secretion and proton pump activity during inhibition by the proton pump inhibitors omeprazole and pantoprazole," Biochem. Pharmacol, 1999; 58(8): 1349–1359, doi: 10.1016/S0006-2952(99)00211-7.
8. M. Besancon, A. Simon, G. Sachs, and J. M. Shin, "Sites of reaction of the gastric H, K-ATPase with extracytoplasmic thiol reagents," J. Biol. Chem, 1997; 272(36): 22438–22446, doi: 10.1074/jbc.272.36.22438.
9. P. W. Jungnickel, "Pantoprazole: a new proton pump inhibitor.," Clin. Ther, 2000; 22(11): 1268–1293, doi: 10.1016/S0149-2918(00)83025-8.
10. R. Kamal, "development and characterization of gastroresistant microspheres of pantoprazole International Journal of Pharmacy and Pharmaceutical Sciences DEVELOPMENT AND EVALUATION OF GASTRORESISTANT MICROSPHERES OF," no. August 2010, 2016.
11. G. Goldstein, S. L. Mueller, A. Park, M. A. F. Kirkpatrick, and H. L. Smith, "The aim of the book,"1987; 90–91.
12. A. B. Nair, R. Gupta, R. Kumria, S. Jacob, and M. Attimarad, "Formulation and evaluation of enteric coated tablets of proton pump inhibitor.," J. basic Clin. Pharm, 2010; 1(4): 215–21, [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/24825991%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3979213.
13. B. U. Janugade, S. S. Patil, S. V. Patil, and P. D. Lade, "Formulation and evaluation of press-coated montelukast sodium tablets for pulsatile drug delivery system," Int. J. ChemTech Res, 2009; 1(3): 690–691.
14. S. C. Porter, M. K. Mukel, and J. N. Srinivas, "Preparation of Pantoprazole 40 mg Delayed-release Tablets Exhibiting Good Stability and Drug-release Characteristics," 2012; 1–3.