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DEVELOPMENT AND CHARACTERIZATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM OF PANTOPRAZOLE

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ABSTRACT

Objective: In the current research pantoprazole loaded osmotically controlled release tablets were prepared utilizing a two-step process. **Methods:** Firstly, compression of tablets and second is coating of tablet by a semi-permeable membrane. Precompression parameters were performed like, tapped and bulk density along with angle of repose. Six formulations were prepared out of which one optimized formulation was selected, according to evaluation parameters like hardness, Friability, Content uniformity of drug and *In vitro* studies. **Results:** The hardness was revealed be in the limit as mention in Pharmacopoeias. The release of drug was found to be up to 8 hours. The tablets were also optimized for their effect of pH and agitation speed. **Conclusion:** The results concluded that the tablets have no significant effect for pH and agitation speed. Stability studies as ICH guidelines were performed, the results concluded that for 90 days the tablet shows stability and hence suitable for effective use.

KEYWORDS: Pantoprazole, Osmotic Drug Delivery System, Peptic Ulcer, Dip Coating.

INTRODUCTION

Osmotically controlled drug delivery systems (OCDDS) utilizes osmotic pressure as a driving force for controlled delivery of dynamic agents. OCDDS has a significant difference from conventional diffusion based system by the means of its deliver.[1] OCDDS is driven through osmotic gradient whereas conventional delivery is accomplished through drug plasma concentration.[2] Side effects are less and drug plasma concentration within the therapeutic window is achieved, reducing the frequency of administration thereby increasing the patient compliance. The main process utilized in this delivery system depends on the process of osmosis.[3,4]

Osmosis is a process involving inward tendency of solvent molecules from lower to higher concentration permeating through semi-permeable membrane. Semipermeable only allows permeation of water molecules no other substance.[5,6]

Peptic ulcer is a disease which is characterized as mucosal disintegrations equal to or more prominent than 0.5 cm at a specific region of the gastrointestinal tract that's usually acidic and therefore greatly excruciating.[7]

These are lesions that develop inside the edge of the stomach, lower esophagus, or small digestive tract. The process of irritation caused by the microscopic organisms H. pylori, additionally from disintegration from stomach acids. The disease ends up with surgical treatment after failure of H2-blockers, proton-pump inhibitors.[8]

Pantoprazole is used for treating peptic ulcer, which is a new proton-pump inhibitor. It is chemically more stable than the other proton-pump inhibitors, particularly at near-neutral pH.[9,10] It is also used to treat inflammation of oesophagus or gullet and severe gastro-oesophageal reflux (leakage of acid from stomach to gullet). It is also used in treatment of H. pylori infection and one of the rare diseases Zollinger-Ellison syndrome. It is also used to heal gastric and duodenal ulcers caused during gastroesophageal reflux disease (GERD).[11]

The present investigation aimed at formulating osmotically controlled drug delivery system comprising pantoprazole.

MATERIALS AND METHODS

Materials-Pantoprazole was procured Aarti drugs Ltd. Haridwar. All the solvents used were of analytical grade.

Cellulose acetate phthalate, acetone and glycerol were purchased from central drug house, New Delhi, India.

METHODOLOGY

Preparation of Core Tablet

Core tablets of pantoprazole were formed by wet granulation method. Pantoprazole and other excipients in quantities (as shown in **Table 1**) were mixed in graded manner and passed through sieve number 65. Then the starch solution was added in above mixture to prepare dough. This dough was passed through sieve number 20 form granules.[12] These granules were dried at 50-60°C for complete removal of moisture. This process was repeated till the value of loss on drying reaches between 0.9% to 1.1%. Thereafter, these granules were passed through 25-mesh sieve and blended with lubricants (magnesium stearate, talc).[13] The dried granules were evaluated for various pre-compression parameters such as, angle of repose, bulk density, tapped density, Carr's index, and Hausner'sratio. Subsequently, these granules were then compressed to tablets, with the average weight of 330-345 mg using tablet punching machine.

Table 1: Composition of Core Tablet.

S.No.	Ingredients	Formulations					
		F1	F2	F3	F4	F5	F6
1.	Pantoprazole	40	40	40	40	40	40
2.	HPMC	60	45	45	45	45	45
3.	Mannitol	30	45	55	40	45	40
4.	MCC	180	180	170	185	180	185
5.	Talc	3	3	3	3	3	3
6.	Magnesium stearate	2	2	2	2	2	2
7.	Starch Solution	10%	10%	10%	5%	5%	5%

Coating of Compressed tablets

Dip coating process was used for the coating of tablets which result into 'controlled porosity osmotic pump' type formulation. Here cellulose acetate phthalate (CAP) (2% w/v in methanol) was used to form a rigid, semipermeable membrane around the compressed tablet. Poly ethylene glycol (PEG-6000, 2–4.5% w/v of CAP solution) was used as *in-situ* pore former. PEG-6000 also act as plasticizer, hence its dose not require plasticizer separately. The coating solution was prepared as per the scheme given in **Table 2**. The tablets were dipped into this solution and air dried for five seconds, then again dipped and dried till it gained optimum weight of coating solution. Thereafter, the coated tablets were air dried for 12 hours. After obtaining completely dried tablets, these were weighed and kept for further evaluation.[14]

Table 2: Composition of coating solution for compressed tablets.

S.No.	Ingredients	Formulations					
		F1	F2	F3	F4	F5	F6
1.	Cellulose Acetate Phthalate (w/v)	2%	2%	2%	2%	2%	2%
2.	PEG-6000 (w/v of CAP solution)	2%	2.5%	3%	3.5%	4%	4.5%

Evaluation of tablets

Physico-chemical properties

The prepared tablets were evaluated for their physical parameters like, appearance, (cracks, color uniformity, machine impression), weight variability, hardness, thickness, and friability. It was also evaluated for drug content uniformity by UV-Visible method.

Thickness

The thickness of the prepared tablets was evaluated by utilizing Vernier caliper. The readings were taken in triplicate for calculating mean and standard deviation.[15]

Hardness test

Hardness test was performed using Pfizer hardness tester. For these six tablets were taken (randomly selected from each batch). The readings were taken thrice.

Friability test

Friability test was determined by using Roche friability test apparatus. For evaluation, six tablets from every batch were weighed and kept in a friabilator, and test was performed at the rate of twenty five r.p.m for four minutes. The tablets were re-dusted and weighed again.[16] The loss of weighed was calculated in terms of percentage friability by applying the following formula:

$$Friability(\%) = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} \times 100$$

Weight variation test

For evaluating weight variation, initially average weight of 20 unit tablets were calculated by weighing using an electronic weighing balance. Then individual weight of each tablet was taken and deviation from average weight wad calculated in term of standard deviation (SD) of each formulation. The obtained results were analyzed according to official limits given in US pharmacopoeia.[17]

Content uniformity of drug

5 tablets were casually taken from each batch and crushed to a fine powder. The fine powder (10mg) was

transferred to 100ml volumetric flask filled with phosphate buffer (pH 7.4), the volume was made up to 100 ml. The volumetric flask was shaken occasionally. After 30 minutes, 10 ml of the solution from volumetric flask was taken and this solution was centrifuged. The supernatant solution obtained from centrifugation process was filtered and absorbance was taken at 290 nm using UV spectrophotometer. The final estimation of drug content was calculated using the absorbance obtained and the linearity equation obtained from calibration curve.[18]

In vitro drug release

In vitro drug release studies for formulated tablets were evaluated using USP II (paddle) dissolution apparatus. Phosphate buffer (pH7.4) was used as dissolution media, which was kept at 37± 0.5°C with the volume of 900ml. The paddle was revolved at the speed of 50 rpm. At regular time interval, aliquots were withdrawn and filtered through Whatman filter paper. The aliquots were replaced with the equal amount of fresh dissolution media to maintain the dissolution volume. The withdrawn samples were analyzed at 290nm using UV spectrophotometer. The readings were taken in triplicate to obtain mean average and standard deviation.[19]

Drug-excipients compatibility by FT-IR

FT-IR spectroscopy was done to explore the possible chemical interaction between drugs and polymer(s). SHIMADZU 8400S spectrophotometer was utilized for scanning the samples. The FTIR spectra of individual drug and excipients were obtained by scanning the KBr pellet in the range of 400 to 4000 cm^{-1} with a resolution of 2 cm^{-1}.

Stability studies

Stability study was performed to check thecapability of any formulation in any specific container to remain within its physical, chemical, therapeutic efficiency. It was done as per ICH guidelines. The tablets were kept in aluminum strips and stored in stability chamber at 40±2°C and 75±5% RH for 3 months. The samples were evaluated for hardness, appearance and drug content.

RESULTS AND DISCUSSION

The tablets were successfully formulatedandshown in **Figure 1**. The results obtained from evaluation parameters have been detailed below.

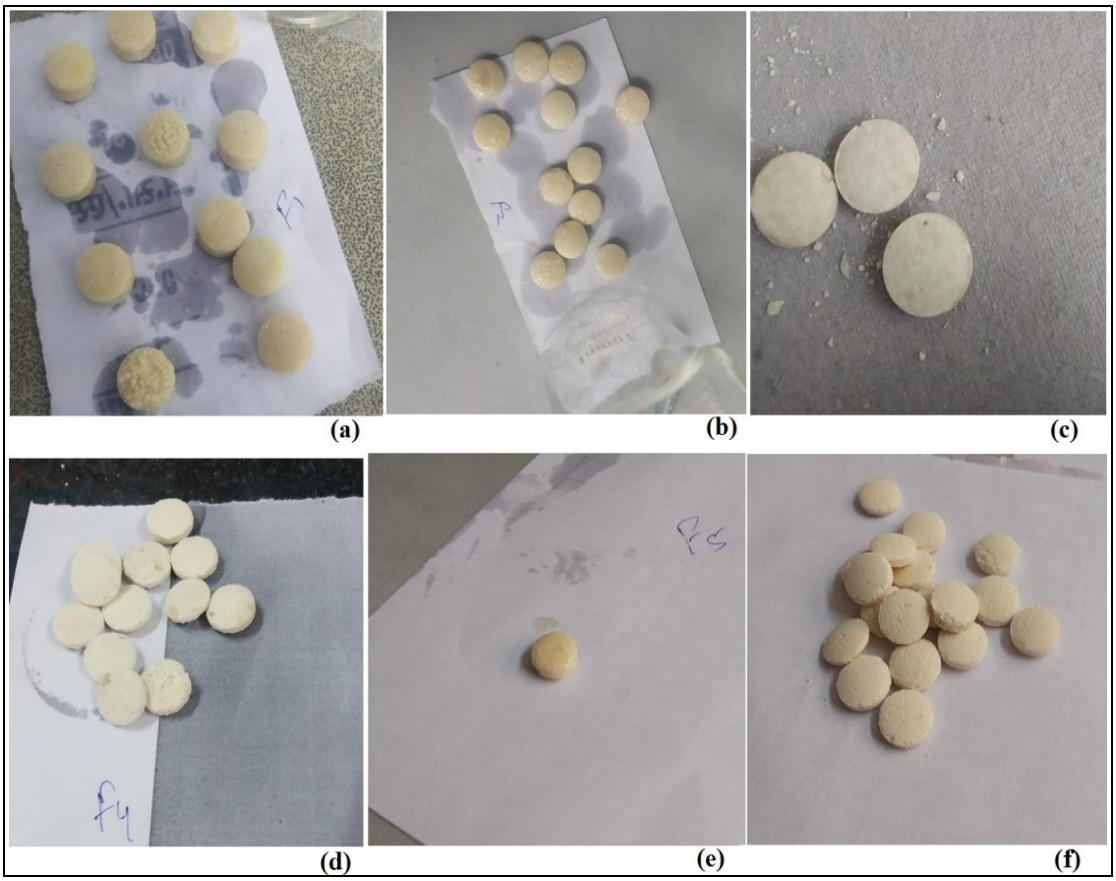

Figure 1: Formulated tablets of different batches viz. (a)F1, (b)F2, (c)F3, (d) F4, (e)F5, (f)F6.

Pre-compression properties

Bulk and tapped density of powder was calculated. The angle of repose was found to be in the range of 23.0°±0.05° to 33.0° ±0.09°, and thus found to be possessing good flow properties (according to USP limits, the angle of repose should be ≤ 30°)**.** The value of angle of repose, bulk density and tapped density have been tabulated in **Table 3.**

Table 3: Results for Pre-compression properties.

Formulation	Angle of repose (θ)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's Ratio
F1	23.0±0.05	0.49±0.07	0.5±0.03	5.5±0.02	1.05±0.01
F2	27.9±1.8	0.3±0.02	0.4±0.08	28.8±0.8	1.4±0.06
F3	25.6±0.01	0.5±0.1	0.7±0.02	16.9±0.1	1.5±0.02
F4	28.7±1.5	0.35±0.08	0.47±0.1	26.7±0.9	1.4±0.1
F5	25.0±0.05	0.5±0.07	0.5±0.03	5.8±0.01	1.0±0.01
F6	30.0±0.01	0.4±0.01	0.59±0.02	28.8±0.02	0.1±0.01

Mean ± SD, n=3

Physico-chemical properties

The results obtained from evaluation parameters like, appearance, (cracks, color uniformity, machine impression), weight variability, hardness, thickness and friability have been mentioned below.

Thickness

The values obtained from thickness parameter have been shown in **Table4.** The tablet thickness was found to be 4.0±0.1 to 4.26±0.11 mm, indicating insignificant variations and uniformity of thickness among tablets.

Hardness test

The tablets formulated were found to be easily compressible. As reported, the acceptable limit for hardness ranges in between 5-10 kg/cm^2. The result concluded that all the tablets formulated passes the hardness test. Higher value of hardness implies a long-lasting coating, whereas lesser hardness implies an eroded coating of tablets, hence tablets will be able to remain in its coating, no erosion will occur. The results have been shown in **Figure 2.**

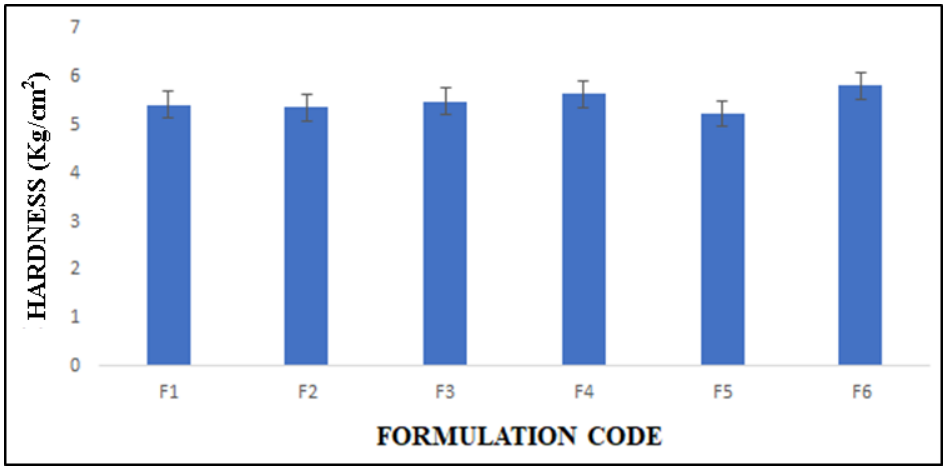

Figure 2: Hardness of different formulations. mean±SD, n=3.

Friability test

The results obtained from friability test have been depicted in **Figure 3.** The friability was found to be in permissible limit as mentioned in pharmacopoeia (weight loss should not be more than 1%). Tablet with good friability will be able to exempt from several complications that occur during coating process and the tablet will be having a good adhesion property between active pharmaceutical ingredient and excipients.

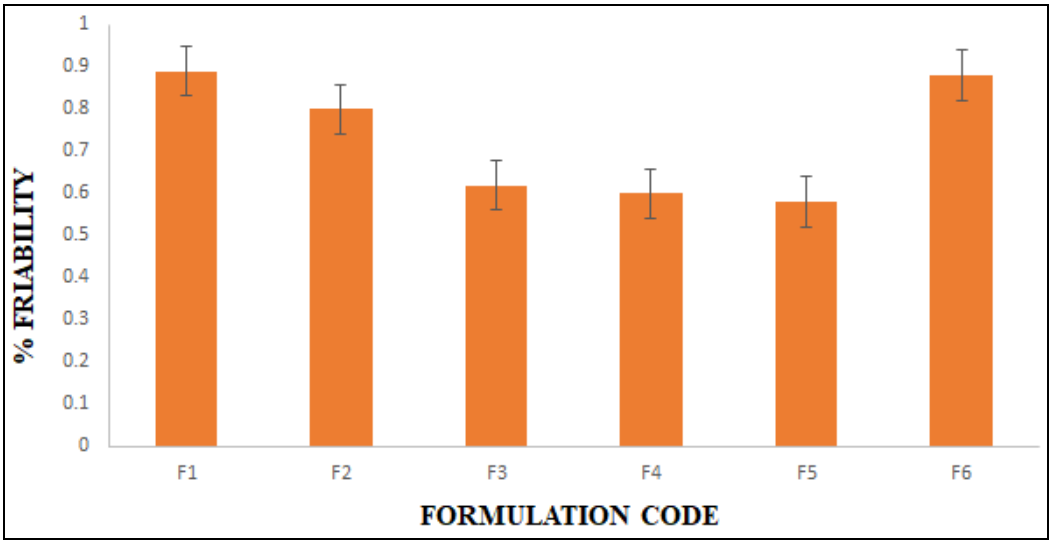

Figure 3: Figure Depicting Percentage Friability. The values are expressed as mean±SD, n=3.

Weight variation test

The results of weight variation are shown in **Table 4**. Weight of individual tablet range from -330 to 340 mg and it was found within the limit of ±5% variation from average weight as per USP. Acceptable range indicated that the granules was formed properly and it flow from hopper to fill the punching die uniformly, and hence result into uniform weight of tablets.

Content uniformity of drug

Values obtained from drug content have been depicted in Table 4. The drug content was found to be in the range of 95.53±0.4% to 99.66±0.1%. The reported limit given for drug content ranges from 90% to 110% (according to pharmacopoeia), therefore the drug content of formulated tablets was in the acceptable limit, indicating the standard quality of tablets.

Table 4: Results for Physicochemical Properties.

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Thickness (mm)	4.0±0.1	4.13±0.11	4.13±0.15	4.2±0.1	4.06±0.15	4.26±0.11
Weight Variation Test(mg)	310±0.42	309±1.02	310±0.12	295±0.55	306±0.70	310±1.22
Drug Content Uniformity (%)	96.33±0.2	98.46±0.4	99.66±0.1	97.60±0.3	96.56±0.41	95.53±0.4

The values are expressed as mean±SD, n=3

1. Effect of pH of dissolution media on in vitro release profile

The formulation (F4) were evaluated for effect of pH on in vitro drug release **(Figure4).** From the results obtained it can be concluded that no significant changes were obtained in the release profile, indicating that the drug release is independent of pH.

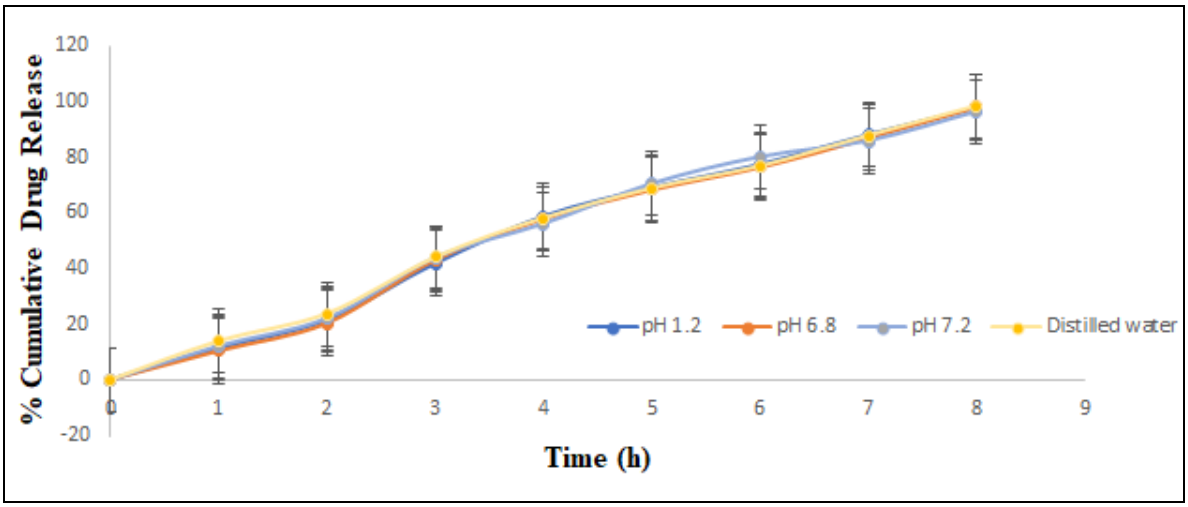

Figure 4: Figure depicting enact of pH media on *in- vitro* release profile. The values are expressed as mean±SD, n=3

2. Effect of agitation speed on release of drug

No significant difference in the drug release was obtained by varying agitation the speed. The resulted graph obtained from *in vitro* release have been depicted in Figure 5.

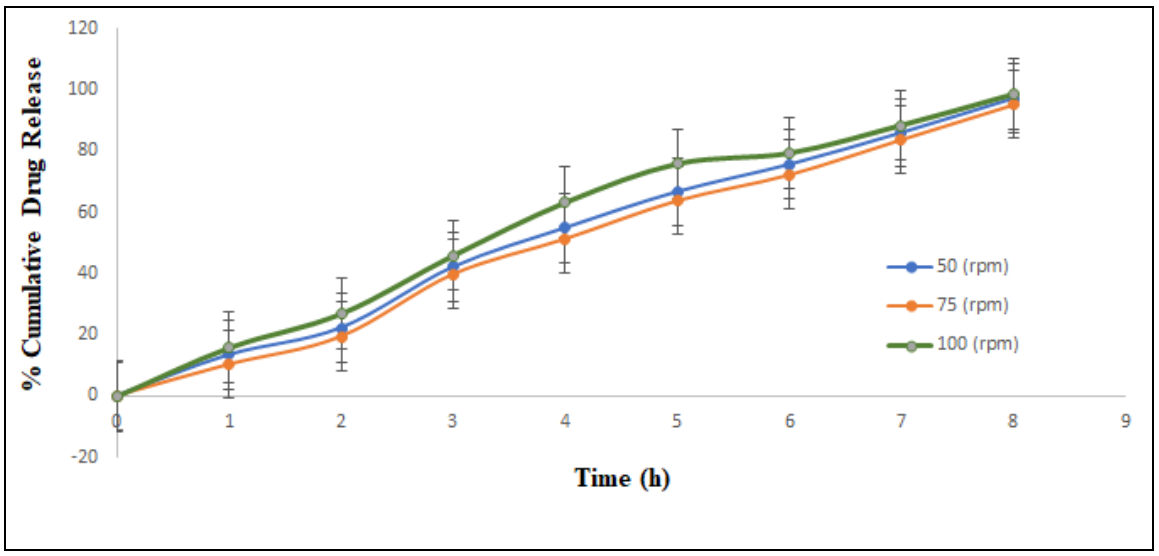

Figure 5: Figure depicting effect of agitation speed on release of drug from (F4) the values are expressed as mean±SD, n=3

3. *In vitro* drug release

Drug release through zero order kinetics signifies that the release rate was not dependent on time and the process of constant drug release will occur. The level of drug in blood will remain constant throughout the delivery.

In vitro drug release was observed for the period of 8 hours Figure 6. Formulation batch F4 shows highest percentage of drug release. The results concluded that the presence of mannitol contributed to increased release, this may be due to increased water uptake due to the process of osmosis leading to higher driving force for drug release.

Release kinetics was applied to the optimized formulation, to identify the best fit model. This was evaluated by the value of correlation coefficient (r) and the value of n particularly for Korsmeyer Peppas's Equation.[20] Drug release from the optimized formulation was best described through zero order kinetics, with R^2 value of 0.9882 followed by Higuchi's equation (R^2 = 0.9376) Figure 7. Drug release through zero order kinetics signifies that the release rate was not dependent on time and the process of constant drug release will occur. The level of drug in blood will remain constant throughout the delivery.

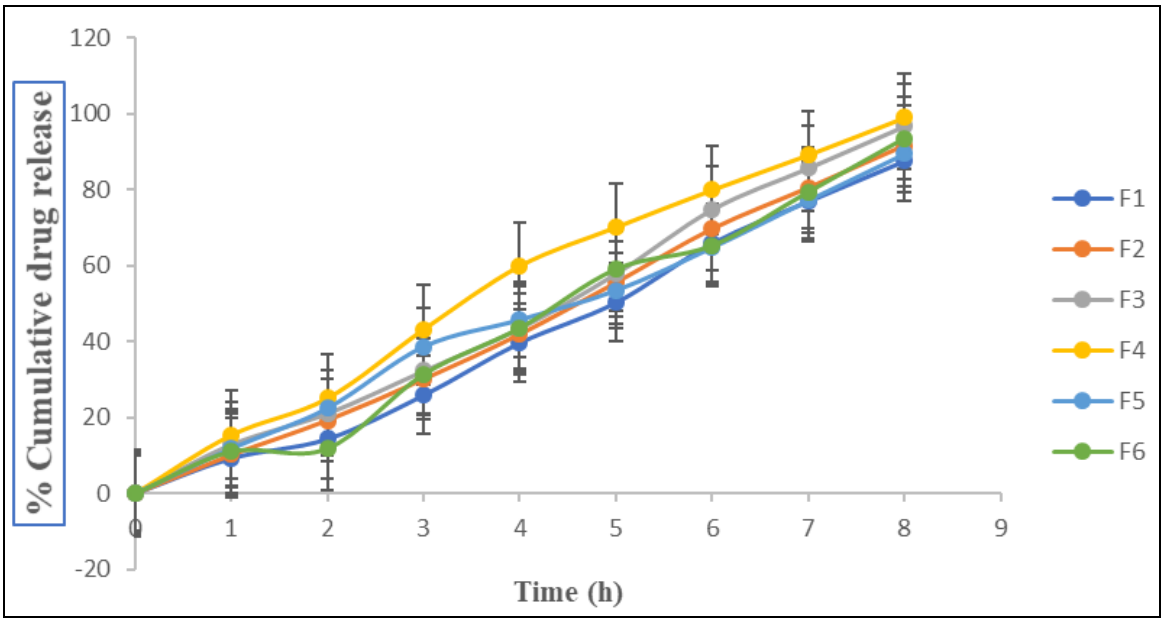

Figure 6: Percentage drug release of prepared formulation. The values are expressed as mean±SD, n=3.

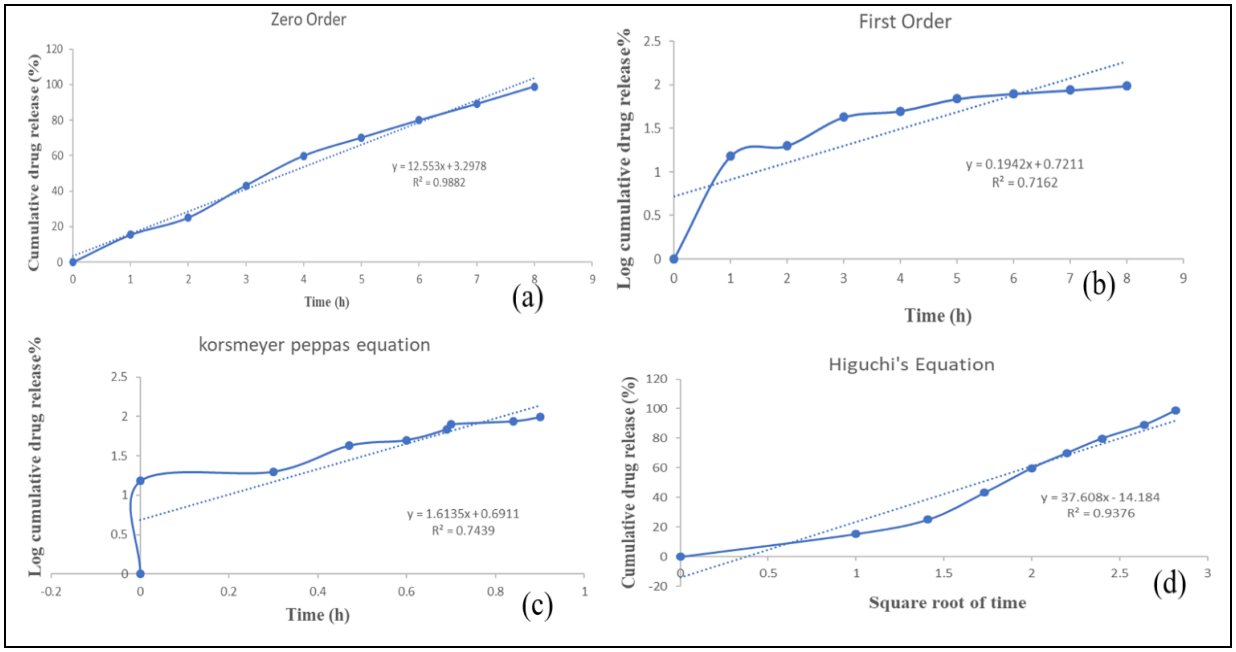

Figure 7: Release kinetics for optimized formulation.

Fourier transform infrared (FTIR) study

FTIR spectrum was obtained to standardize and to examine compatibility. Spectra of pantoprazole was obtained in the range of 4000-400 cm^{-1}. The results have been depicted in **Table 5 and Figure 8. Figure 6** also depicts that there is no interaction between drug and excipients used.

Table 1: Reported and Observed Characteristic IR Peak.

Observations	Reported Peaks(cm^{-1})	Observed Peaks(cm^{-1})
Complex strong multiple CF bond stretching	1169; 1231	1167; 1235
Asymmetrical C-H bending peak	1378	1380
Symmetrical C-H bending	1450	1454
C=C aromatic stretching bands	1654;1590	1655;1592
Aryl fluoride CF stretching	1120	1119
Strong –S=O stretching bands	1042	1045
-C-O-C- asymmetrical stretching of aryl alkyl ether	1073	1074

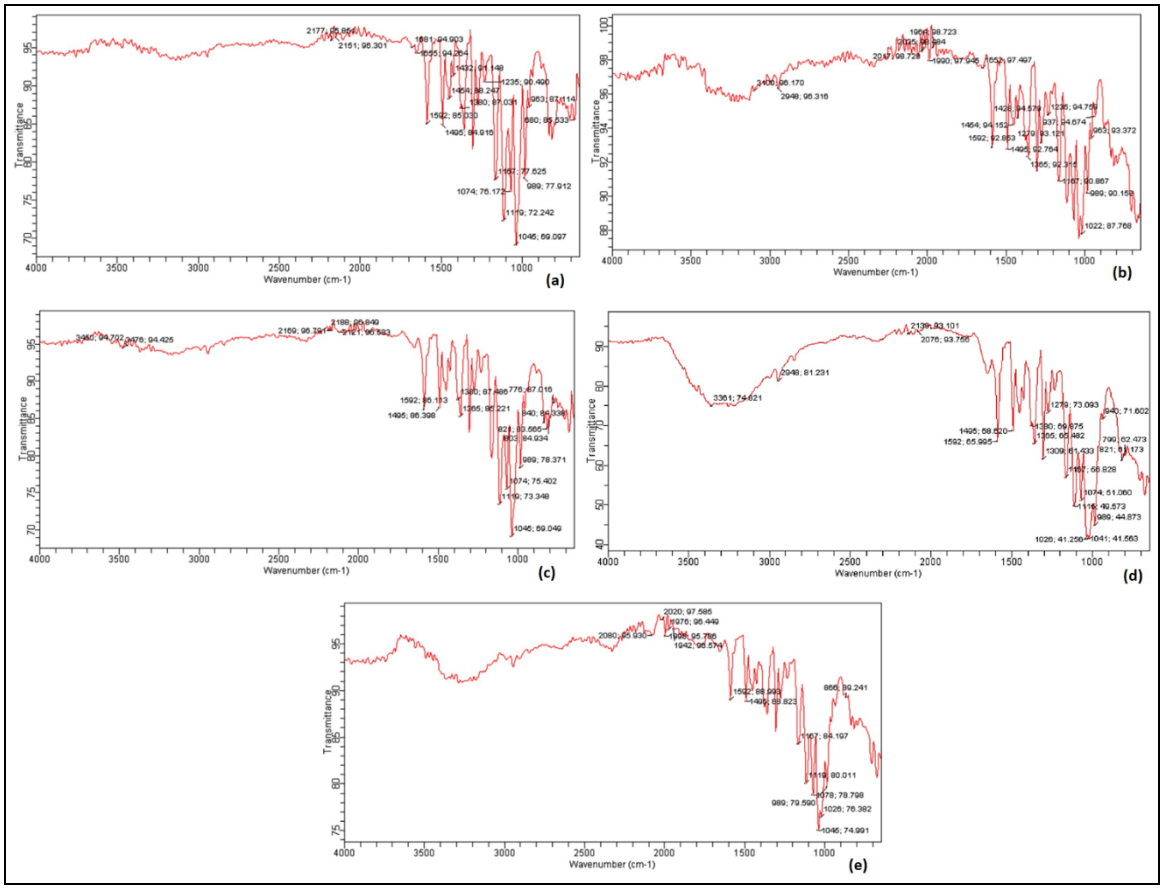

Figure 8: Figure Depicting FTIR of (a) DRUG (b) DRUG + MANNITOL (c) DRUG + HPMC (d) Drug+ MCC (e) Drug + HPMC + MCC + Mannitol.

Stability studies

The results obtained from stability studies revealed that the formulation F4 was able to be in its original form for 3 months. The result showed that the tablets were stabilized in matter of hardness, friability, percent drug content and in vitro release percent. The results have been shown in **Table 6.**

Table 2: Results of Accelerated Stability Studies of F4.

Evaluation parameters	Obtained values of designed parameters at specified time			
	0 Day	30 Day	60 Day	90 Day
Hardness (Kg/cm^2)	5.5	5.5	5.5	5.5
Friability (%)	0.6	0.6	0.6	0.6
Drug content (%)	99.66±0.1	99.0±0.1	98.9±0.2	97.8±0.05
In vitro drug release (%)	98.9±0.5	97.6±0.5	96.9±0.6	96.0±0.4

The values are expressed as mean±SD, n=3.

CONCLUSION

Osmotically controlled release tablets of pantoprazole were successfully prepared and coated with a semi permeable membrane. The precompression studies were performed and angle of repose, flowability, and carr's index were evaluated. Results concluded that the powder was having a good flow and limitable carr's index. Compatibility studies were performed using infra-red spectral analysis, and the results concluded that no chemical interaction was present between pantoprazole and excipients. The tablets were evaluated for hardness, weight variation and friability, the results concluded that the prepared tablets were in the limit given in various pharmacopoeias. The formulation shows the in vitro drug release for up to 8 hours. The release kinetics revealed the formulation to be in zero order, i.e. in zero order (ideal for osmotic controlled drug delivery). Accelerated stability study concluded that the prepared tablets are stable for 90 days.

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