Development and Evaluation of Pantoprazole Sodium Gastro Retentive Floating Tablet

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Abstract

Drugs can stay in the stomach for several hours, extending the gastric residence period. It can be used to deliver local drugs to the stomach and proximal small intestine. Prolonged stomach retention improves bioavailability, decreases drug waste, and increases solubility. Gastroesophageal reflux disease, also known as acid reflux or GERD is a chronic ailment. 10mg of medication has been dissolved in 20ml of methanol. The wavelength from maximum absorption was 276.5nm when a standard solution of pantoprazole (10mg/ml) was scanned. The polymers HPMCK15M and PVP prolonged medication release from floating tablets. Pantoprazole was chosen for this study as it has a shorter biological half-life and better bioavailability. This issue can be remedied by developing a gastro-retentive drug delivery device. Finally, it was determined that among all formulations (F1-F12), formulation F4 demonstrated better buoyancy and dissolution profile prepared with HPMCK4M, HPMCK15M, and PVP slowed high regression values of 0.992 for zero order on the basis of observed and predicted value (Box bhenken design) with drug release in 6 hr, making it (F4) to be selected as optimised formulation when compared to other formulations. based on observed and anticipated value The polymers HPMCK15M and PVP aided in the prolonged release of the medication (pantoprazole) from the floating tablet.

Keyword: GERD, HPMCK, PANTOPRAZOLE SODIUM, Bioavailability

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INTRODUCTION

Drug administration systems are designed to overcome physiological challenges such as short stomach residence periods and erratic gastric emptying times. Prolonged stomach retention improves bioavailability, decreases drug waste, and increases solubility for medicines that are less soluble in high-pH environments. It can be used to deliver local drugs to the stomach and proximal small intestine. [1] [2] Floating systems, also known as dynamically regulated systems, are low density systems with enough buoyancy to float above gastric contents and remain buoyant in the stomach. Many buoyant systems based on grains, powders, capsules, tablets, and laminated films have been created. [3] [4] Gastroesophageal reflux disease (GERD) is a condition in which stomach liquids regurgitate (back up or reflux) into the oesophagus. Although apparent signs of inflammation occur in a minority of people, liquid can inflame and damage the lining (esophagitis). The cause of GERD is complicated and may involve several factors. Swallowing is essential for removing acid from the oesophagus. [5][6] A small percentage of GERD patients create excessively large amounts of acid, but this is uncommon. Some patients' stomachs empty excessively slowly after eating. Heartburn is characterised by a burning discomfort in the centre of the chest that may originate high in the abdomen or extend into the neck. [7] Nerve fibres in the oesophagus are stimulated in people with gastroesophageal reflux disease (GERD). Patients with GERD frequently experience nausea. Fasting and fed states both have gastric emptying. Every 2-3 hours, a sequence of electrical impulses occurs that cycle through the stomach and intestine. All undigested material is carried out of the stomach and into the small intestine by this wave. [8] [9] The gastric retention time (GRT) is a function of dosage form buoyancy, which is density dependant. When comparing consecutive meals to a single meal, GRT might increase by almost 400 minutes. Elderly persons, particularly those above the age of 70, have much longer GRT. [10] [11]

MATERIAL AND METHODS

Material

There are variety of material has been used for the formulation of floating tablet including active ingredients. [12] The excipient and therapeutic agent are mentioned in table 1

Table 1: - Excipients involved in floating tablet formulation

Ingredient	Application
Pantoprazole sodium	Anti-ulcer drug
HPMC	Rate controller, film former
PVP	Binder
Sodium bicarbonate	Gas forming agent
Citric acid	Sequestering agent and antioxidant
Talc	Lubricant& diluents
Mg. Stearate	Lubricant

Mathod:-

Standerd calibration curve

Preparation of stock solution

10mg of drug has been dissolved in 20 ml of methanol and make up the volume up to 100ml by using 0.1 N HCl to form 100µg/ml and label it as stock solution A. From stock solution a pipette out 10ml and make up the volume to form 10µg/ml, label it as stock solution B. From stock solution B pipette out 2ml,4ml, 6ml,8ml,10ml and dilute with 0.1 N HCl up to 10 ml form 2µg/ml. 4µg/ml 6µg/ml, 8µg/ml and 10µg/ml. [13] [14]

Determination of absorption maximum

The standard solution of pantoprazole (10µg/ml) was scanned in the wavelength from maximum absorption was found to be 276.5 nm. [15]

Preformulation Studies

Assay

Materials:

Shimadzu 1800 spectronic UV spectrophotometer with 1 cm matched quartz cells was used for data collection and analysis. Methanol was used as a solvent and reagent for drug substance. [16] [17]

Methodology:

Preparation of standard stock solution:

Standard stock solution of pantoprazole sodium was prepared by dissolving accurately weighed quantity of pantoprazole sodium 50mg in few ml of methanol and transferred it to 50 ml of volumetric flask the flask was swirled dissolve solid volume made up to the mark with methanol, which gave 1000 g/ml of the drug. Aliquot from the stock solution was appropriately diluted with methanol to obtain working standard solution of 100ug/ml of drug. [18] [19]

Determination of absorption maximum:

The standard solution of pantoprazole sodium (10µg/ml) was scanned in the wavelength at 400 and absorption maximum was found to be 276.5 nm. [20] Also determine the angle of repose, bulk density, tapped density, Carrs index and Hausner's ratio. [21]

Tablet manufacturing methods

Tablets are the unit solid dosage forms meant for oral use and are manufactured by using tablet compression machines. The tableting mixture that is going to be compressed can be prepared by either of the three techniques- wet granulation, dry granulation or direct compression. Each of the individual technique mentioned above has its own advantages and disadvantages respectively. [22] [23]

Formulation of pantoprazole floating tablets:

Pantoprazole tablets were developed by direct compression method. Ingredients are weight accurately and mix all the ingredient except talc and magnesium stearate in the mortar and pestle. [24] The resulting powder was punched by using a rotary compression machine (16 stations) by cad match CMD. [25]

Unit operations for tablet preparation by direct compression method: -

1. Weighing: the required amount of pantoprazole sodium and the other excipients for a batch of tablet formulation were weighed accurately by using the electronic weighing balance.

2. Mixing: all the ingredients were mixed manually in a mortal and pestle, except lubricants.

3. Screening: after mixing powered mixture was passing through #44 meshes sieve to break agglomerates if any present in the raw materials for uniform distribution or for proper granulation.

4. Blend lubrication: the prepared blend was lubricated using magnesium stearate and talc in a mortar and pastel for 15 minutes.

5. Compression: the prepared blend was compressed. [26] [27]

Table 2: Composition of different formulations of floating tablets

For 1 tablet												
Batch no.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Pantoprazole	10	10	10	10	10	10	10	10	10	10	10	10
HPMC k15M	5	10	15	20	25	_	_	_	_	_	35	_
HPMC k4M	_	_	_	_	_	5	10	15	20	25	_	35
PVP	30	25	20	15	10	30	25	20	15	10	_	_
Sodium bi carbonate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium sterate	2	2	2	2	2	2	2	2	2	2	2	2
Totle	50	50	50	50	50	50	50	50	50	50	50	50

Advantages of direct compression

Direct compression tablets are more suitable for moisture and heat sensitive API's since it eliminates wetting and drying steps and increases the stability of active ingredients. [28] The tablets prepared by direct compression disintegrate into API's particles instead of granules that directly come into contact with a dissolution fluid. [29]

Evaluation of floating tablets:

Evaluation of pre-compression parameters of drug and polymeric blend Excipients, polymers, and drug were characterized for their physical properties such as the angle of repose, bulk density, tapped density, compressibility, hausner‟s ratio, **Hardness, Friability, Weight variation test, Floating behaviour**, **Buoyancy time, Uniformity of drug content and, Thickness:** [30] [31]

RESULT AND DISCUSSION

Standard calibration curve of Pantoprazole

The standard calibration curve of Pantoprazole is prepared by using 0.1 N HCl as a solvent and the absorbance was taken by the help of ultraviolet spectroscopy using different concentrations at 276.5 nm. The concentration and absorbance are mentioned in table 3 and Fig. 1.

Table 3: Standard calibration of Pantoprazole

S. No.	Concentration(µg/ml)	Absorbance*
1	0	0
2	2	0.075
3	4	0.109
4	6	0.159
5	8	0.206
6	10	0.257

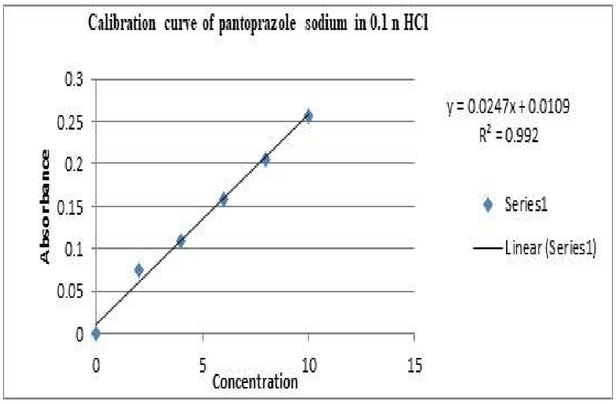

Fig 1: Standard calibration curve of Pantoprazole in 0.1 N HCl (276.5 λ max)

Pre-compression results

The pre-compression results that comprises flow property of granules by determining the angle of repose, other include bulk density, tapped density, Hausner's ratio are mentioned in table 4.

Table 4: Pre-compression parameters

S. No.	Angle of repose (º)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's compressiblity Index (%)	Husrner's ratio (%)
F1	30.96 ±1.68	0.3021±0.007	0.3280±0.003	7.98±0.53	1.08±0.07
F2	33.02±1.41	0.3358±0.004	0.3086±0.005	11.77±0.56	1.13±0.04
F3	29.24±1.92	0.3228±0.006	0.3749±0.002	13.89±0.47	1.16±0.03
F4	31.79±2.28	0.3017±0.005	0.3583±0.007	4.75±0.28	1.18±0.05
F5	34.21±1.73	0.2741±0.007	0.2878±0.006	15.79±0.64	1.05±0.08
F6	33.42±2.15	0.3229±0.007	0.3767±0.004	14.28±0.31	1.16±0.03
F7	27.92±1.56	0.2901±0.003	0.3053±0.008	4.97±0.72	1.05±0.06
F8	29.68 ± 1.83	0.2925±0.008	0.3250±0.005	10±0.38	1.11±0.05
F9	23.32±1.45	0.3351±0.004	0.4137±0.009	16.35±0.24	1.09±0.04
F10	23.55±1.33	0.3726±0.006	0.3619±0.003	14.33±0.43	1.05±0.02
F11	26.18±1.24	0.3132±0.002	0.3274±0.004	11.85±0.38	1.32±0.07
F12	29.27±1.85	0.3614±0.003	0.3385±0.002	10.24±0.81	1.21±0.08

Table 5: - Evaluation parameter of Pantoprazole floating tablets

S. No.	Average weight (mg)	Hardness (kg/cm^2)	Friability (%)	Floating lag time (sec)	Floating time (hr)	Drug release (%)
F1	48.91	4.4±0.15	0.29±0.07	28±2.97	6±2.93	48.91±1.12
F2	50.01	4.3±0.21	0.12±0.03	33±1.86	8±3.77	57.42±2.48
F3	46.08	4.5±0.18	0.064±0.03	32±3.53	12±2.46	53.36±3.26
F4	48.27	4.2±0.25	0.25±0.07	31±3.64	8±2.76	46.3±0.42
F5	47.07	3.4±0.24	0.24±0.08	32±3.72	9±1.30	44.22±0.60
F6	49.49	3.9±0.15	0.70±0.04	32±2.42	10±2.32	51.33±0.90
F7	49.08	3.8±0.16	0.24±0.05	30±1.33	7±2.64	63.89±1.97
F8	48.97	4.2±0.17	0.14±0.06	28±1.27	8±1.94	51±1.82
F9	49.47	4±0.22	0.68±0.05	29±3.16	10±1.48	49.38±2.34
F10	52.36	4.3±0.25	0.32±0.04	28±2.21	9±3.64	48.13±2.87
F11	51.14	4.3±0.19	0.43±0.05	30±1.58	11±3.33	53.42±2.47
F12	45.96	4.2±0.13	0.38±0.052	35±2.81	10±2.53	65.98±1.82

(0min) **(30 min)** **(6 hr)** **(12 hr)**

Fig 2:- photographic image showing in vitro bioumcy of celecoxib floating tablet

Table 6: Optimum desirability with observed values of the responses for the optimized

Factor	Optimize value	Response	Predicted value	Observed value	Residual
HPMC K4m	20	Floating lag time sec	30.5	31	0.5
HPMC K15m	10	Floating time hr	8.94444	9	0.05556
PVP	15	% drug release 3hr	22.04	22.73	0.69
		% drug release 6hr	45.38	46.32	0.84

Dissolution kinetics of pantoprazole floating tablet

For the analysis of release studies of pantoprazole floating tablets, these models were evaluated

A. Zero-order model
B. First order model
C. Higuchi model
D. Hixon-crowell model [32]

A. Zero-order models:

Zero-order process 1s defined as the one whose dosage form is represented as independent of the concentration of drug undergoing reaction. Release of drug from [33]

Doses form is represented as: -

$$Q_1=Q_0-K_0t$$

Where,

Q1 amount of drug dissolved in time

Q_0 initial amount of drug in solution [33]

The zero order model data and plot are shown in table 7 and fig 3

Table 7: Zero order model data

S. No.	Time (min)	% cumulative drug release
1	0	0
2	15	1.44
3	30	2.47
4	60	9.62
5	120	16.62
6	180	21.73
7	240	27.31
8	300	35.13
9	360	39.44
10	420	46.3

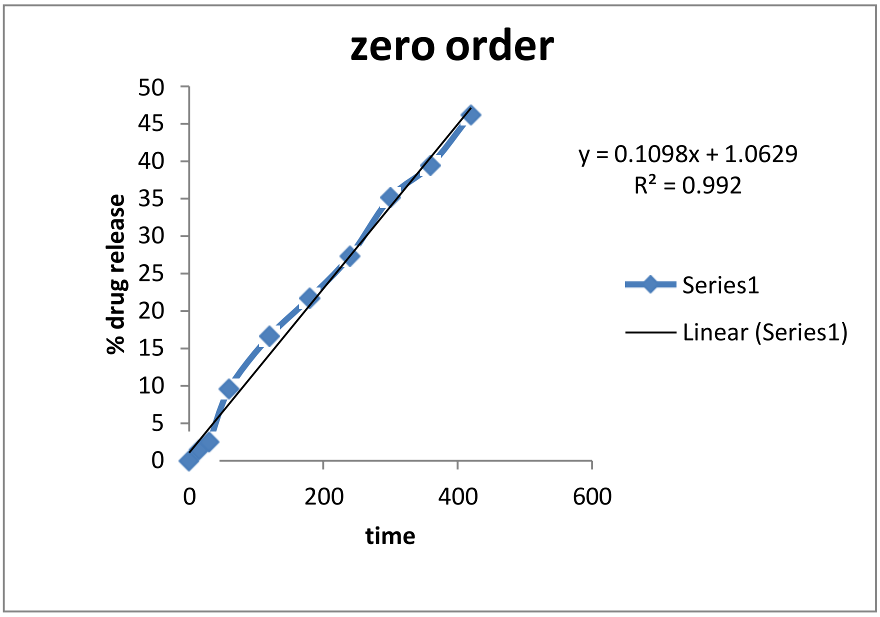

Fig 3: zero order plot

B. First order model:

This model is the one in which rate of reaction is directly proportional to the concentration of drug undergoing reaction first order release kinetics can be expressed as: [34]

Log C =log C_0 – kt/2.303

Where, K first-order rate constant

Co=initial concentration of drug

T=time

The graph of the first order is plotted between 'log cumulative % drug remaining vs time, this evs & negative slope of- k/2. 303. [35] First order model data and their plot are shown in given Table: 8 and fig 4

Table 8: - First order model data

S. No.	Time (min)	% cumulative drug remaining	Log % cumulative drug remaining
1	0	100	2
2	15	98.56	1.99
3	30	97.53	1.99
4	60	90.38	1.96
5	120	83.38	1.92
6	180	78.27	1.89
7	240	72.69	1.86
8	300	64.87	1.81
9	360	60.56	1.78
10	420	53.80	1.73

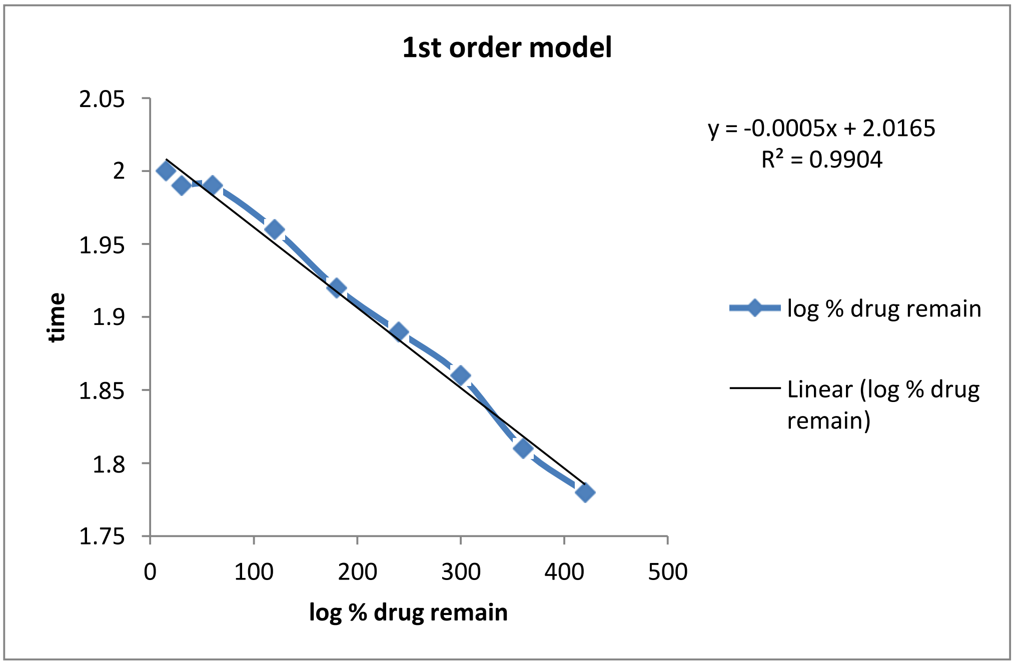

Fig 4: - First order model plot

C. Higuchi model:

Drug release from a matrix is expressed by higuchi model expression which is given by-l

F1=Q=AD(2C-Cs) Cst

Where

Q= amount of drug release at time t per unit area a

C= initial drug concentration

Cs= drug solubility in matrix medium

D=diffusivity of drug molecule in the matrix substance

The dissolution rate is examined by plotting the cumulative percentage drug release vs square root of time. [36] The higuchi model data and plot are shown in table 9 and Fig 5

Table 9: - Higuchi model data

S. No	Time (min)	Square root of time	Cumulative % drug release
1	0	0	0
2	15	3.87	1.44
3	30	5.48	2.47
4	60	7.75	9.62
5	120	10.95	16.62
6	180	13.42	21.73
7	240	15.49	27.31
8	300	17.32	35.13
9	360	18.97	39.44
10	420	20.49	46.3

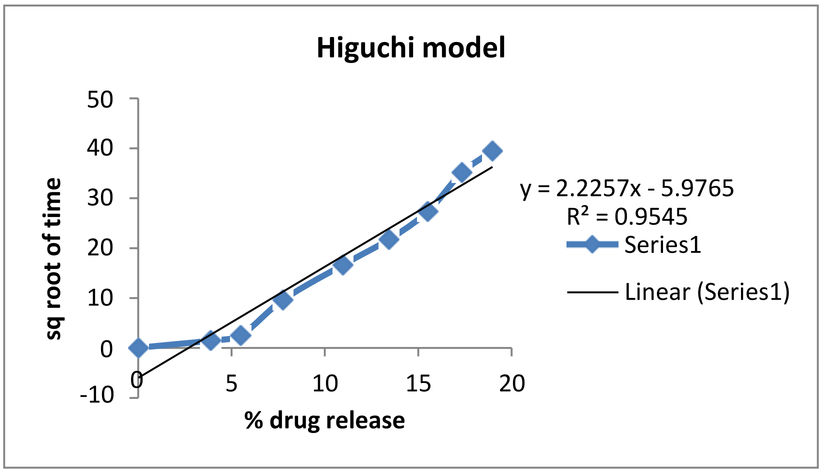

Fig 5: - Higuchi model plot

D. Hixon-crowell model:

The model given by hixon-crowell, they observed that the regular area of the particle is proportional to the cube root of its volume. To determine the release kinetics, cube root of dig remaining in the matrix is to be plotted against time. [37] The hixon-crowell model data and plot are shown in table 10 and Fig.6

Table 10: - Hixon-Crowell model data

S. N.	Time (min)	Cumulative % drug release	Log % cumulative drug remaining	Cube root of % drug remaining
1	0	0	0	4.64
2	15	1.44	97.47	4.62
3	30	2.47	94.80	4.6
4	60	9.62	94.15	4.49
5	120	16.62	82.40	4.37
6	180	21.73	73.80	4.28
7	240	27.31	64.60	4.17
8	300	35.13	53.38	4.02
9	360	39.44	46.89	3.93
10	420	46.3	40.36	3.78

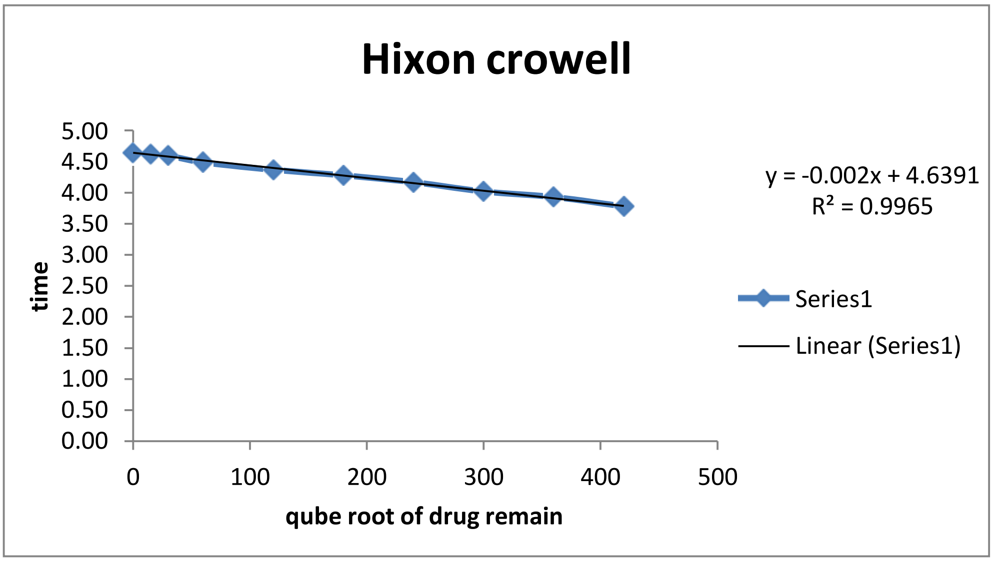

Fig 6: - Hixon crowell model plot

CONCLUSION

The current study established a floating gastro retentive system for pantoprazole. Pantoprazole was chosen for this study because it has a shorter biological half-life, improves bioavailability by keeping the medicine in an acidic environment, and reduces waste. For some medications, an extended retention duration of the dose form in the stomach is required. This issue can be remedied by developing a gastro-retentive drug delivery device.

Finally, it was determined that among all formulations (F1-F12), formulation F4 demonstrated better buoyancy and dissolution profile prepared with HPMCK4M, HPMCK15M, and PVP slowed high regression values of 0.992 for zero order on the basis of observed and predicted value (Box bhenken design) with drug release in 6 hr, making it (F4) to be selected as optimised formulation when compared to other formulations. based on observed and anticipated value The polymers HPMCK15M and PVP aided in the prolonged release of the medication (pantoprazole) from the floating tablet.

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