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Formulation and Evaluation of Floating Matrix Tablet of Pantoprazole Sodium Sesquihydrate

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ABSTRACT

The objective of this research work was to formulate and evaluate the floating drug delivery system containing Pantoprazole sodium sesquihydrate as a model drug and to optimize its drug release profile. Pantoprazole sodium tablets were prepared by direct compression technique. Formulations contained Xanthan gum, PVP K_{30} and gas generating agent such as sodium bicarbonate and citric acid were taken as independent variables. The physical parameters of the tablets were characterized and were found within the limits. By comparing dissolution profiles of different formulations, the formulation F5 was considered as a better formulation. The drug release from all the formulations was found to follow zero order kinetics and Peppas modeling. The diffusion exponent of formulations was found ($n<0.89$) to have non-fickian (anomalous) diffusion mechanism. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former

Keywords : Floating tablet, Pantoprazole sodium sesquihydrate, PVP K_{30}, Xanthan gum

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INTRODUCTION

Oral route of drug delivery has been the most versatile, expedient and commonly employed route for systemic action, due to its ease of administration, patient compliance and flexibility in formulation. Oral controlled release drug delivery system (OCRDDS) facilitates the continuous oral delivery of drugs at predictable and reproducible rates throughout the course of their GI transit[1]. The major goal of OCRDDS is to achieve more predictable and better bioavailability of drugs.

Over the last three decades, a variety of approaches have been used to enhance the retention of an oral dosage form in the stomach, including floating systems[2,3,4], swelling and expanding[5,6], bioadhesive[7,8,9,10], modified shape systems[11,12,13,14], high density systems[15], concomitant administration of pharmacological agents that delay gastric emptying[16,17], raft forming systems[18,19,20] and other delayed gastric emptying devices[17,21,22]. From the formulation point of view, FDDS appears to be the most suitable and logical approach to prolong gastric residence time of drugs.[23]

Gastro retentive dosage forms are the systems that can stay in the gastric region for several hours and thus, prolong the gastric residence time of the drugs. After oral administration, such a dosage form is retained in the stomach and releases the drug there in a controlled and sustained manner so that the drug can be supplied continuously to its absorption sites in the upper GIT.[24]

Floating drug delivery systems (FDDSs) are the systems having a bulk density less than gastric fluids. They remain buoyant in the stomach for a prolonged period of time and defy the gastric emptying rate[25]. The floating of dosage form on the gastric contents allows the drug to be released slowly at the desired rate from the system. Once the drug is released, the residual system is emptied from the stomach. It causes an increased gastric residence time (GRT) and a better control of fluctuations in plasma drug concentration.[26]

Pantoprazole is protein pump inhibitor (PPI) used for the treatment of acute duodenal ulcer, acute benign gastric ulcer, gastroesophageal reflux disease (GERD) and prophylactic use in duodenal ulcer. It acts by competitive inhibition of H^+/K^+ ATPase enzyme of the gastric parietal cells resulting in reduced gastric acid secretion i.e. having local action in the stomach. The recommended oral dosage is generally 45 mg for acute duodenal ulcer, acute benign gastric ulcer and gastro esophageal reflux (GERD) and is prescribed for the duration of 8-12 weeks. The drug has a short biological half life (1-2 h) and local action in stomach which makes it suitable candidate for FDDS.

Therefore, the objective of the study was to develop stomach-specific FDDS of Pantoprazole to achieve local action of drug in the stomach by increasing its gastric residence time and also releasing it at a controlled rate to ensure 'once a day' administration and optimum bioavailability, thereby, minimizing its side effects and hence enhanced patient compliance.

MATERIAL AND METHODS

Materials

Pantoprazole sodium sesquihydrate was provided as a gift sample by Oiester Pharma Pvt. Ltd., Ambala, India. Xanthan gum and PVP K_{30} were purchased from Yarrow Chem. Ambala. All the other chemicals are of analytical grade and used as received.

Formulation of floating matrix tablets

The floating matrix tablets of Pantoprazole sodium Sesquihydrate with different polymers like xanthan gum and PVP K_{30} were prepared by direct compression method. Drug, polymer and other excipients (except talc and magnesium stearate) were mixed thoroughly, passed through sieve number 40 and compressed using multi-punch tablet compression machine after adding talc and magnesium stearate. 8 different formulations were prepared (Table 1) in which amount of all the ingredients (except polymers) were kept constant including drug.

Table 1. Compositions of various formulations

Formulations	Drug*	Xanthan Gum*	PVP K_{30}*	Sodium bicarbonate*	Citric Acid*	Talc*	Mg Stearate*
F1	45	75	45	50	20	5	5
F2	45	80	40	50	20	5	5
F3	45	85	35	50	20	5	5
F4	45	90	30	50	20	5	5
F5	45	95	25	50	20	5	5
F6	45	100	20	50	20	5	5
F7	45	105	15	50	20	5	5
F8	45	110	10	50	20	5	5

* All quantities are in (mg)

Physical Evaluation of floating matrix tablets

Weight Variation

20 tablets of each formulation were weighed individually using digital weighing balance and their average weight was calculated. Then individual tablet weight was compared with average weight.

Hardness

The tablet hardness was measured using Monsanto tablet hardness tester. The force required to crush the tablet was recorded as hardness in Kg/cm^2.

Friability

10 tablets were weighed accurately and then placed in Roche-type friabilator which was rotated at 25 rpm for 4 min (i.e. 100 revolutions). Then tablets were taken out of the friabilator and again weighed after dusting. The percent friability was calculated as follows:

$$\% \text{ Friability} = (W_i - W_f / W_i) \text{ X } 100$$

Where,

W_i – initial weight of tablets

W_f – final weight of tablets

Assay

From each formulation, ten tablets were weighed and powdered. A quantity of powder equivalent to 45 mg of Pantoprazole sodium Sesquihydrate was accurately weighed and dissolved in 100 ml of 0.1 N HCl and stirred for 30 minutes. The solution was filtered, diluted appropriately and analyzed spectrophotmetrically at 288 nm using 0.1 N HCl as blank. The drug content was determined from absorbance values using calibration curve.[27]

Floating Lag Time (FLT) and Total Floating Time (TFT)

The floating behavior of the tablets was evaluated by placing them in beaker containing 200 ml of 0.1N HCl (pH 1.2). The beaker was kept over a magnetic stirrer. The time taken by the tablets to emerge on the surface of medium was noted as floating lag time and the total time duration for which tablets remained buoyant was noted as total floating time.[28]

Dissolution study

In vitro drug release study of the tablet Pantoprazole sodium sesquihydrate 45 mg was performed in USP XXIII dissolution apparatus type II (paddle type) containing 900 ml of 0.1 N HCl (pH 1.2) kept at 37^0C with paddle speed of 75 rpm. Samples of 5 ml were withdrawn at predetermined time intervals of 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16 and 24 h and replaced with fresh medium each time.[29] The samples were filtered and analyzed spectrophotmetrically at 288 nm. The effect of different polymers in different concentrations on the release profile of Pantoprazole sodium sesquihydrate from FDDS was determined.

Analysis of drug release mechanism

In order to examine the release of Pantoprazole sodium Sesquihydrate from prepared floating matrix tablets, the results of dissolution study of all the formulations were examined using different kinetic models i.e. zero order, first order, Higuchi model and Korsmeyer-Peppas model. The r^2 (regression coefficient) value closer to 1 indicated the model fitting to release mechanism.[30] The major advantage of fitting the data to such an expression is that the dissolution properties can be treated and analyzed by statistical and mathematical methods.[31]

Water Uptake Study

The swelling of the tablets takes place due to the ability of polymers to hydrate and swell. The swelling property of the tablet was determined by immersing the tablet in a beaker containing 200 ml of 0.1 N HCl (pH 1.2) and stirred at 37^0C. After the predetermined time intervals, tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed. Swelling index (SI), expressed as percentage, was calculated using following equation.[29,32]

$$SI = \frac{\text{Weight of swollen tablet-initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

RESULTS AND DISCUSSION

Evaluation tests for floating matrix tablets

All the batches of prepared tablets were evaluated for various physical parameters like weight variation, hardness, friability and drug content uniformity. The hardness of all the formulations was kept between 4-6 Kg/cm^2. The tablets must have an optimum hardness in order to have less floating lag time and longer total floating time. The reason is that a high degree of hardness may reduce the porosity of tablets and the compacted polymer particles on the surface of tablets cannot hydrate rapidly on contact with gastric fluid. Consequently, the ability of tablet to float can be significantly reduced. On the other hand, very low hardness results in tablets which are friable and therefore not acceptable. Hence, there must be an optimum hardness for tablets to remain buoyant and to meet Pharmacopoeial requirements of stability.

The friability values for all the prepared batches were less than 1. Weight variation and drug content were within the USP limits.

Table 2. Values of various physical parameters of Pantoprazole floating tablets

Formulation	Weight (mg) Mean ±S.D. (n=20)	Hardness (Kg/cm^2) Mean ± S.D.(n=3)	%age Friability (n=3)	Assay (n=5)
F1	243.8±1.12	5±.15	0.78±.48	98.65±1.2
F2	245.8±1.02	5±.15	0.62±.56	99.35±2.4
F3	244.4±2.03	5±.15	0.46±.68	97.3±2.8
F4	245.6±3.07	5±.15	0.64±.78	99.15±4.8
F5	244.6±1.14	5±.15	0.39±.12	102.64±1.2
F6	243.4±4.05	5±.15	0.42±.26	98.54±1.8
F7	244.3±3.94	5±.15	0.53±.24	99.25±2.6
F8	245.6±0.96	5±.15	0.65±.62	100.34±4.2

Floating Lag time and Total Floating Time

On placing the tablets in the beaker containing 0.1 N HCl, all the tablets first sank to the bottom and then they came up to the surface. The beakers were kept over magnetic stirrer to simulate the peristaltic movements of the GIT and FLT and TFT were recorded by visual inspection. All the tablets remained buoyant for more than 20 h (except F1, F2 & F3) on the medium without disintegration.

Table 3. Floating Lag time (FLT) and Total Floating Time (TFT) of different formulations.

Formulation	FLT	TFT
F1	200	<12
F2	180	<12
F3	190	<12
F4	210	>20
F5	160	>20
F6	240	>20
F7	220	>20
F8	245	>20

All the formulations had FLT between 2-5 minutes. F1-F3 had total floating time of 2 h, 2 h and 8 h respectively whereas F4 had 24 h. It was found that the formulation (F1,F2) having high quantity of PVP K_{30} floated for small duration of time (2 h) as compared to formulations (F4, F5, F6, F7 & F8) containing less concentrations of PVP K_{30} and high concentration of high viscosity xanthan gum. This may be due to the ability of higher viscosity grade and concentration of xanthan gum to hold the generated carbon dioxide for longer period of time.

In vitro dissolution studies

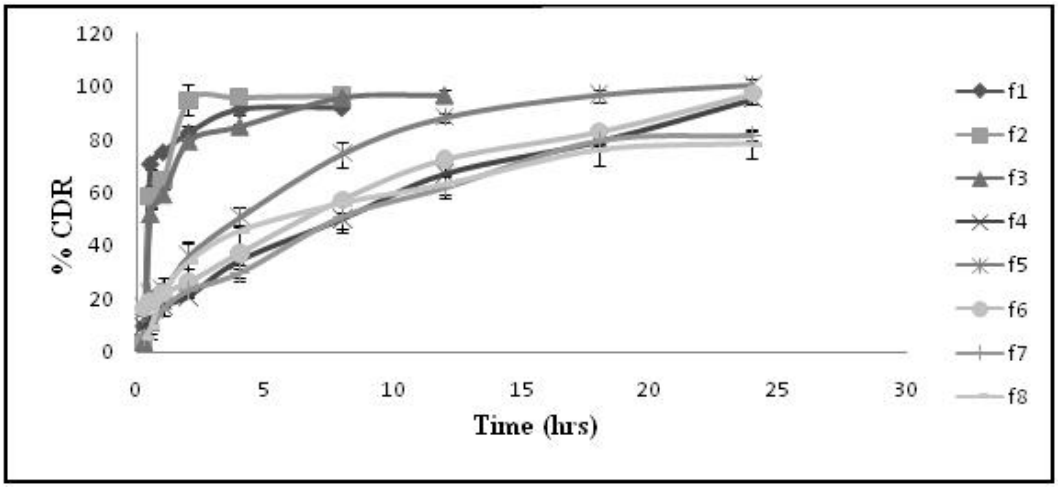

Figure 1: In-vitro release profile of formulation F1-F8

In vitro dissolution studies were carried out as per USP procedure using 0.1 N HCl (pH 1.2) as dissolution medium at 75 rpm. The *in-vitro* release profiles of Pantoprazole from various

formulations are shown in figure 1. Under fasting conditions, housekeeper waves clear the undigested material from the stomach every 1.5-2 h.[28] So when the tablet is taken orally, it remains in the stomach for 2 h and then expelled in the intestine. It can be seen from the table that marketed tablet releases 100 % of the drug within 2 h. But in case of floating matrix tablets, release of the drug was controlled significantly over a broad period of time. These studies were carried out for 24 h. In all the formulations, the amount of drug was kept constant i.e. 45 mg which is the dose of the drug. In case of formulations F1-F2 (containing Xanthan gum & PVP K_{30} in varying concentrations), a complete drug release was achieved within 2 h for F1 and F2. However, the release data showed that as the level of polymer increases, release rate decreases. A higher viscosity grade polymer Xanthan gum was used for formulations F1-F8 in varying concentrations. In case of F6, 97% drug release was achieved in 24h whereas in F7 & F8 almost 81% & 71% drug release was achieved in 24h whereas in case of F5, a complete 100% drug was released after 24 h.

The above results clearly reveal that an increase in amount of polymer has a profound effect on drug release. The reason may be due to the activity of PVP K_{30} because it also acts as solubilizing agent. But when we added the both polymers in a specific ratio, Formulation starts floating for 24 hrs and its release rate also increased. It happens because, with the increased amount of polymer (Xanthan gum), the formation of denser hydrogel network took place which offers more hindrance to the drug release. The formulations F1-F4 showed complete drug release within 16 h. The reason for inability of these formulations to sustain the drug release for 24 h may be the presence of PVP K_{30} in high concentration and on increasing the quantity of polymer leading to the formation of less denser hydrogel network around the drug. But even in this case also, the release rate was found to decrease with increasing concentration of polymer i.e. formulations F6, F7, F8 and F4 showing less than 100 % release in 24 h. It is thus concluded that effervescent FDDS of Pantoprazole showed slow and almost complete drug release over 24 h.

Influence of concentrations of Xanthan gum and PVP K_{30} on pantoprazole release from floating tablets

Xanthan gum and PVP K_{30} were used in different concentrations to study their influence on the *in-vitro* release of Pantoprazole from FDDS. It was found that the release rate of Pantoprazole from tablet formulations (F1-F4) prepared using high quantity of PVP K_{30} was higher as compared to xanthan gum. In the current study, it was also found that overall rate of drug release tends to decrease with increase in concentration of xanthan gum. These observations are in agreement with the results reported in literature[33] i.e. with the increase in polymer concentration and viscosity grade, the viscosity of gel layer around the tablet also increases leading to enhanced diffusional

path length for the drug to follow and thus limits the release of active ingredient. The figures between mean percent drug release vs time in hours for all Pantoprazole formulations are shown in Figure.

Analysis of Release Mechanism

Table 4. Analysis of Release Mechanism for different formulations

Formulation	Zero Order		First order		Higuchi Model		Korsmeyer-Peppas	
	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2
F1	6.1758	0.3569	-0.1057	0.6527	24.819	0.5047	0.4887	0.5468
F2	8.054	0.4339	-0.1685	0.6479	32.176	0.6065	0.7633	0.5774
F3	8.316	0.5578	-0.1553	0.9245	31.984	0.7146	0.7549	0.606
F4	5.1976	0.9811	-0.0334	0.995	17.626	0.988	0.4786	0.9797
F5	7.214	0.9917	-0.0645	0.9846	24.168	0.9747	0.4133	0.9583
F6	5.1637	0.998	-0.0369	0.9937	17.171	0.9666	0.3465	0.9389
F7	5.5401	0.9677	-0.035	0.9846	18.892	0.9854	0.6364	0.9858
F8	6.6134	0.7198	-0.0467	0.7953	24.647	0.8755	0.8046	0.8692

All the formulations were subjected to zero order, first order, Higuchi kinetics and Korsemeyer-Peppas model to examine the mechanism of drug release. Dissolution parameters, slope and r^2 values of all the formulations are given in table 3. The r^2 value in case of zero order was found to be higher than Higuchi and first order kinetics in all the formulations suggesting that the drug released from the formulation by diffusion process. The n value in case of Korsmeyer-Peppas model suggested whether the diffusion was fickian or non-fickian. The results suggested that drug release from 2 formulations (i.e. F5, F6) followed fick's law (i.e. fickian diffusion) and rest followed non-fickian anomalous transport.

Swelling Studies

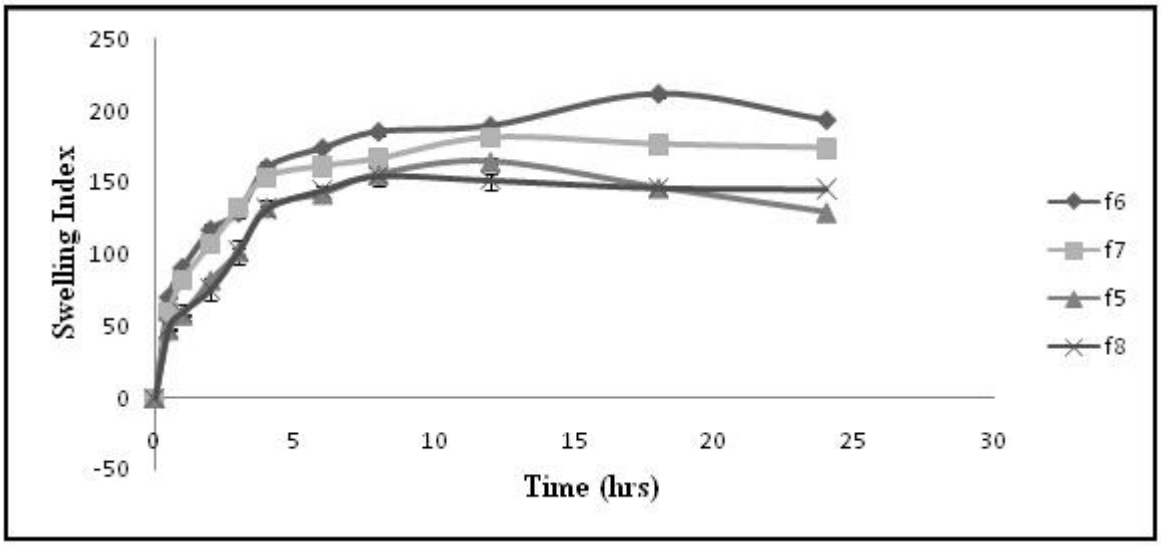

Figure 2: Plot of swelling index of optimized formulations versus time

Swelling studies of optimized formulations were carried out in 0.1 N HCl (pH 1.2) for 24 h at predetermined time intervals i.e. 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24 h respectively. Maximum swelling was achieved at the end of 8 h for formulation F5, 12 h for F6, F7 and 16 h for F8.

Swelling is generally essential to ensure floating. It was observed that quantity of xanthan gum also affected the swelling. A direct correlation between swelling and drug release was observed. It was found that with an increase in polymer concentration, swelling increased but the rate of drug release slowed down. It may be due to the reason that increase in polymer concentration resulted in formation of thicker gel network that retarded the drug release. The swelling of the tablet in release media ensured that it will have high gastric residence time and will not pass through the pyloric sphincter.

CONCLUSION

Floating matrix tablets of the drug were prepared using xanthan gum and PVP K_{30} in different ratio. All the formulations were evaluated for various parameters like floating lag time, floating duration, physical tests, *in-vitro* dissolution study, release mechanism and swelling characteristics. Weight variation, hardness, friability and drug content of all the formulations were within the pharmacopoeia limits. All the formulations had floating lag time b/w 2-4 minutes. Total floating time of formulations F1-F4 were > 18 h whereas all other formulations floated for more than 20 h. Complete drug release was achieved within 10 h in case of F1, F2, F3, F4. However, formulations F5, F6, F7and F8 sufficiently sustained the drug release for 24 h. The drug release mechanism from prepared formulations was confirmed to be mainly diffusion. Formulations F5 and F6 followed fickian diffusion (n = 0.456-0.498) whereas rest of the formulations followed non-fickian anomalous transport (n = 0.503-0.702). The overall rate of drug release was found to decrease with increase in concentration of the polymers. The formulations F1 & F2 dissolved within 4 h because in higher concentration, PVP K_{30} also acts as a disintegrating agent.

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