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Formulation and Evaluation of Floating Microspheres of Pantoprazole Sodium

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ABSTRACT

The aim of this study was to develop and evaluate floating microspheres of Pantoprazole Sodium. Floating microspheres of Pantoprazole Sodium were prepared by solvent evaporation method using HPMC K15M and ethyl cellulose as polymer. Seven different formulations were developed. The developed floating microspheres were evaluated for, percentage yield, particle size, entrapment efficiency, *in vitro* buoyancy, scanning electron microscopy and drug release. Results show that as the concentration of polymer ethyl Cellulose increases it affects the particle size, percentage yield, *in vitro* buoyancy and drug release of microsphere.. Results of our present study suggest that floating microsphere of Pantoprazole sodium can be successfully designed for controlled drug delivery which can reduce dosing frequency making the formulation an effective alternative to conventional dosage forms.

INTRODUCTION

Oral route is the most preferable route of drug administration due to better patient compliance. However there arises a problem by oral route with the use of certain types of dosage form, i.e. fluctuation in plasma drug level. By the use of controlled drug delivery system we can prolong the action of drugs in our body. Gastric emptying is a complex process in our body variable in different individuals. The aim of designing oral controlled drug delivery system is to increase the bioavailability of drugs. A major problem associated with the oral controlled drug delivery system is limited gastric residence time. To improve the retention of an oral dosage form in the stomach various approaches have been developed, e.g. floating systems, swelling and expanding systems, bioadhesive systems, altered density systems and other delayed gastric emptying devices. Gastro retentive dosage form prolongs the gastric residence time of drug by remaining in the gastric region for several hours. Floating microspheres are one of the gastro retentive dosage form that float over gastric contents due to their buoyancy and remain in the stomach for prolonged period. Suitable drugs that can be used in gastro retentive system include ;

1) Drugs with narrow absorption window in the stomach.
2) Drugs locally acting in the stomach
3) Drugs which are unstable in intestinal and colonic environment

Floating drug delivery system is a type of gastro retentive drug delivery system. This system remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period time as they have a bulk density less than gastric fluids. These systems release the drug slowly at a desired rate, and increases the gastro retention time. Further it helps to reduce the fluctuations of plasma drug concentration. The aim of using floating drug delivery system is to retain the drug in the stomach. The floating system is very useful for drugs that are poorly soluble and unstable in the stomach. The principle of floating drug delivery system is to make the dosage form less dense than gastric fluids. Floating systems are hydro dynamically balanced low density system. Gastric retention of floating drug delivery system increases the bioavailability and therapeutic benefit of the dosage form .

Microspheres are spherical particles ranging in size from 1 to 1000 micrometer. Microspheres are biodegradable in nature. They are characterized as free flowing powders consisting of

proteins or synthetic polymers and which have large surface area due to their smaller size. The use of microspheres in pharmaceutical products have a number of advantagesviz., Taste and odor masking, achievement of sustained release, controlled release in targeted medications, conversion of oils and other liquids to solids for ease of handling, separation of incompatible materials, to improve flow of powders, protection of drugs against environment (moisture, heat, light and oxidation).

MATERIALS AND METHODS

Pantoprazole Sodium was obtained from Southern Chemicals, Trissur. Ethyl Cellulose and HPMC were purchased from Chemdyes Corporation, Gujarat. Ethanol was purchased from Merck Limited Mumbai. Dichloromethane was purchased from Nice Chemicals Pvt. Ltd, Cochin. All other chemicals used in study belong to analytical grade.

Pre-Formulation Study

Pre-Formulation studies such as solubility determination, infrared spectroscopy, DSC Thermal Analysis were performed to determine the solubility paramters of drug and to assure the compatibility between the drug and polymers. Calibration curve of Pantoprazole sodium was obtained by using methanol as solvent.

Formulation of Microspheres

The microspheres were prepared by solvent evaporation technique using ethyl cellulose and HPMC as polymers. Five formulations were prepared using different ratios of these two polymers. To the mixture of ethanol and dichloromethane (1:1), the polymers in various ratio were added. The drug was dispersed in above solution of polymers. This dispersion was added slowly with stirring into the distilled water containing 0.01% Tween 80 maintained at the temperature between 30-40^{0}C. Stirring was continued for 20 minutes, which allowed the evaporation of dichloromethane and ethanol completely. After evaporation of solvents, the microspheres formed were collected by filtration, washed 3 to 4 times with distilled water and dried at room temperature for 24 hrs. The prepared microspheres were stored in a desiccators.

INGREDIENTS	FORMULATIONS						
	F1	F2	F3	F4	F5	F6	F7
PANTOPRAZOLE SODIUM	50mg	50mg	50mg	50mg	50mg	50mg	50mg
HPMC	300mg	250mg	200mg	150mg	100mg	50mg	0
ETHYL CELLULOSE	300mg	350mg	400mg	450mg	500mg	550mg	600mg
ETHANOL	10ml	10ml	10ml	10ml	10ml	0ml	10ml
DICHLOROMETHANE	10ml	10ml	10ml	10ml	10ml	10ml	10ml
TWEEN 80	0.25µl	0.25µl	0.25µl	0.25µl	0.25µl	0.25µl	0.25µl
DISTILLED WATER	250ml	250ml	250ml	250ml	250ml	250ml	250ml

EVALUATION OF FLOATING MICROSPHERES

Percentage Yield of microspheres

The prepared microspheres were collected and weighed. Percentage yield was obtained by dividing measured weight of microspheres by the total weight of drug and polymers.

Particle Size Analysis

The particle sizes of the microspheres were obtained by optical microscopy method. By using stage micrometer eye piece micrometer was calibrated. The microspheres were mounted onto the slide and mean particle size was determined by the measuring the sizes of hundred particles.

Micromeritic Properties

Micromeritic Properties such as angle of repose, bulk density, tapped density, hausner's ratio, Carr’s compressibility index were determined.

Percentage Entrapment Efficiency

To determine entrapment efficiency, 50 mg accurately weighed microspheres were dissolved in 0.1 N HCl and added 50ml of standard flask . The microspheres were stirred for 24 hours using a magnetic stirrer. After that the solution was filtered through a filter paper. From this 1ml was pipetted and made upto 10 ml with 0.1N HCl. The drug content was determined spectrophotometrically at 292nm.

***In-vitro* Buoyancy studies**

Microspheres (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N HCl containing 0.02% tween 80. The medium was agitated with a paddle rotating at 50rpm for 8 hrs. After agitation for a predetermined time interval, the microspheres that floated over the surface of the medium and those settled at the bottom of the flask were recovered separately. The microspheres were dried and weighed.

Scanning Electron Microscopy

The surface morphology and particle size of microspheres were determined by Scanning Electron Microscopy using a JEOL JSM-6390 scanning microscope. Dry microspheres were placed on an electron microscope brass stub and coated with platinum in an ion sputter. Picture of microspheres were taken by random scanning of the stub.

***In-vitro* drug release profile**

A USP basket apparatus was used to study *in-vitro* drug release from floating microspheres. *In-vitro* drug release studies were carried out in USP type I dissolution test apparatus using 900 mL of 0.1 N HCl solution at 100 rpm and temperature was adjusted to 37±0.50C. Microspheres containing 50mg of drug was introduced into dissolution medium . One mL of the aliquot was withdrawn at predetermined intervals. Required dilutions were made with 0.1 N HCl solution and filtered the solution and analyzed for the drug content spetrophotometrically (UV 1800, Shimadzu, Japan) at 292 nm against suitable blank.

Kinetic modeling of dissolution profiles[66]

The drug release kinetics was studied by various kinetic models such as Korsmeyer-peppas, Higuchi plot, First order plot and Zero order plot. To study the release kinetics, data obtained from *In-vitro* drug release studies were plotted in various kinetic models. Zero order as cumulative amount of drug released Vs time, First order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released Vs square root of time. The best fit model was confirmed by the value of correlation coefficient near to 1

- **Zero-order model**

Zero order model can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms such as transdermal patches as well as matrix tablets with low soluble drugs in coated forms. This model describes dissolution from dosage forms which release the drug slowly and can be represented by the equation

$$Q_0 - Qt = K_0 t$$

Qt = Amount of drug dissolved in time't'

K_0 = zero order release constant

Q_0 = initial amount of drug in solution.

- **First order model**

First order model can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices. This model has also been used to describe absorption and/or elimination of some drugs. The following relation could be used to express this model.

$$\text{Log } Qt = \log Q_0 + Kt \cdot t / 2.303$$

Qt = Amount of drug dissolved in time't'

Q0 = Initial amount of drug in the solution

Kt = First order release constant.

- **Higuchi model**

Higuchi model can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs. The system aimed to describe drug release from a matrix system where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix. The mathematical expression for drug release is as given below.

$$Q = [D (2C-CS) CS.t] 1/2$$

Q = Cumulative % of drug released in time‘t’ per unit area.
C = Initial drug concentration
CS = Drug solubility in the matrix media
D = Diffusion coefficient.

Assuming that diffusion co efficient and other parameters remain constant during release, the above equation reduces to

$$Q = k.t ½$$

- **Korsmeyer-Peppas model**

Korsmeyer-Peppas model is often used to describe the drug release behavior from polymeric systems and the exponent n was calculated through the slope of the straight line. The rate of drug release could be expressed as;

$$Q = Ktn$$

Where Q is the % cumulative release of drug released, t is the time and n is the slope of linear plot of log Q Vs. log t. If the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n < 0.89, then it is non-Fickian or anomalous diffusion.

6.6 STABILITY STUDY

Stability studies of various dosage form must be conducted to determine the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. These studies are required to be

conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies.

The main aim of stability testing was to provide the evidence of how the quality of a dosage form varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability testing also includes the study of product related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials.

Procedure

To find out the effect of floating characteristic, percentage entrapment efficiency and *in-vitro* drug release, the selected formulation, F6 was exposed up to 30 and 45 days of stability studies at 40^0C and 75% RH

RESULTS AND DISCUSSION

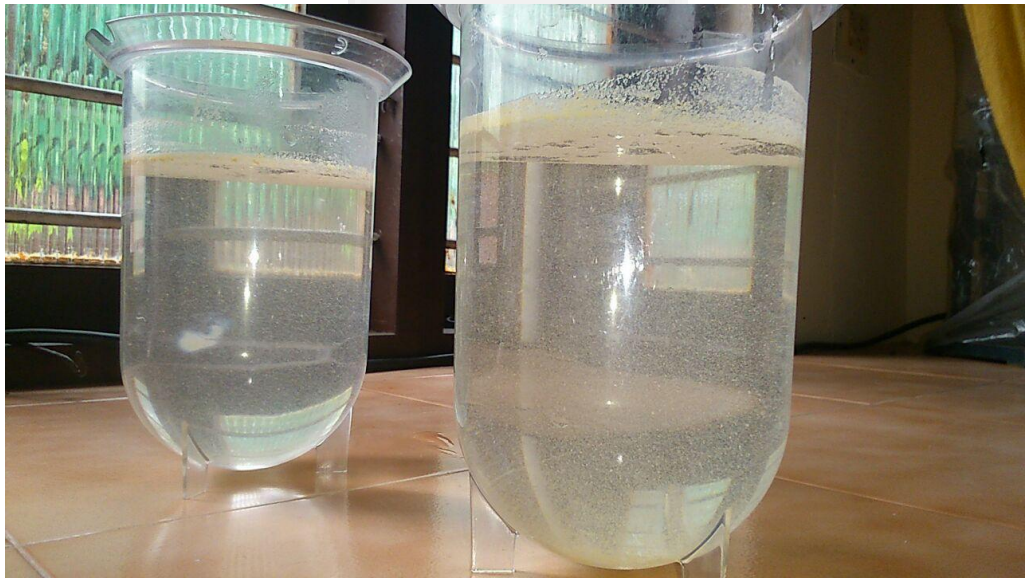
Pre-Formulation Study

Solubility studies showed that results were within the pharmacopoeial specifications. Compatibility studies showed that there was no incompatibility between drug and polymers.

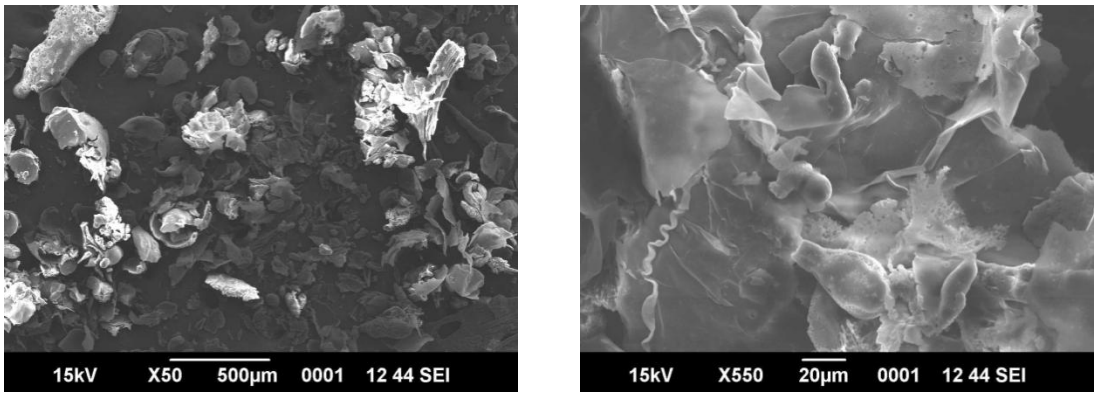
Prepared Floating Microspheres of Pantoprazole Sodium

EVALUATION OF FLOATING MICROSPHERES

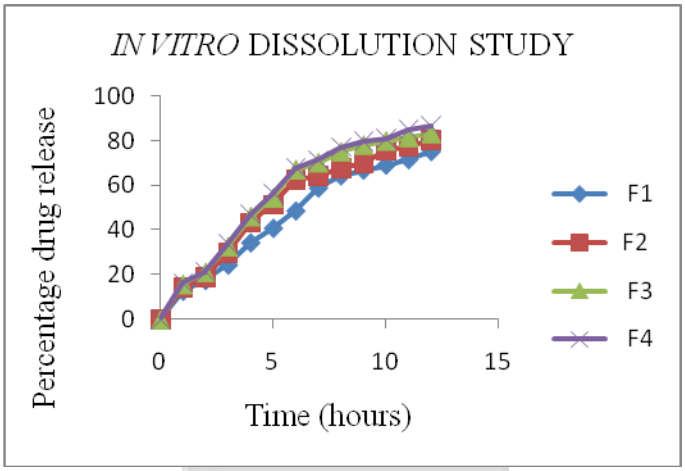
Formulations code	Percentage Yield	Mean particle size (µm)	% Drug Entrapment	% Buoyancy
F1	36.92	182	65.34	55.46
F2	52.61	185	67.77	60.33
F3	66.15	189	72.95	62.52
F4	71.84	198	81.09	71.52
F5	80.76	210	85.40	77.96
F6	87.69	224	89.02	82.03
F7	95.12	232	92.25	85.76



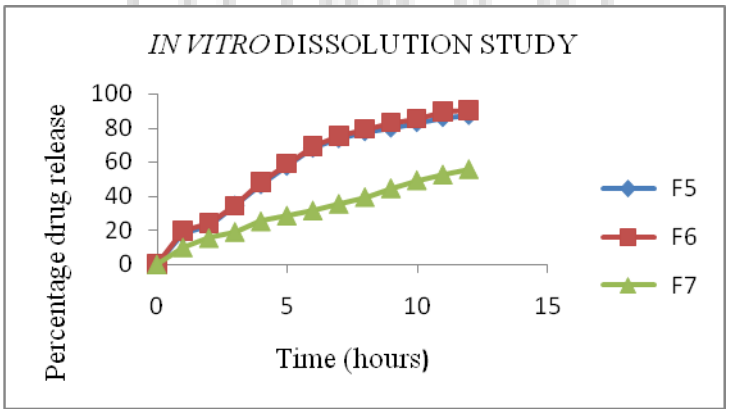
Pantoprazole microspheres floating in stimulated gastric fluid



SEM of Pantoprazole Sodium Floating Microspheres



***In-vitro* drug release study of Formulations F1-F4**



***In-vitro* drug release data of Formulations. F5-F7**

In the present study seven different formulation were prepared. The main polymers used were HPMC and Ethyl Cellulose. The dichloromethane and ethanol were used as solvent. Surfactant used was Tween 80. Preformulation studies were conducted. FTIR study results showed that there were no incompatibility between drug and polymers. Solubility study was performed and recorded the results. A calibration data was obtained by using UV spectrometer and calibration curve was plotted. Evaluation studies such as percentage yield, particle size analysis, percentage buoyancy, drug entrapment efficiency and *in vitro* release were conducted. All the seven formulation gave good results within the limits.

Percentage yield was calculated and it was in the range of 36.92%-95.12%. Particle size of these microspheres ranges from 182µm-232µm. The entrapment efficiency was in the range of 65.34 to 92.25. Percentage buoyancy was in the range of 60.33%-85.76%. Scanning electron microscopy showed that microspheres were spherical in shape and porous in nature. *In vitro* dissolution studies showed that formulation F6 has the release of 90.49%at the end of 12 hours. Kinetic study was conducted for the optimized formulation by using various models and it showed that this formulation follows zero order diffusion kinetics. Stability studies were conducted. There was no significant change in drug entrapment, buoyancy and drug release after 45 days.

CONCLUSION

The aim of present study was to formulate floating microspheres of Pantoprazole Sodium with different proportions of polymers such as Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose for oral drug delivery. From the results obtained by preformulation studies, it can be concluded that there was no incompatibility between drug and polymers. The evaluation studies such as particle size analysis, percentage drug entrapment, floating behavior, *in vitro* drug release and stability studies showed that formulation F6 is the optimized formulation. In vitro release kinetics study of formulation F6 showed that it follows Zero order diffusion kinetics. Stability studies showed that there was no change in the formulation after 45 days .Thus the aim of the study to formulate floating microspheres of Pantoprazole Sodium was achieved. In future this system can be developed by using various polymers in various proportions for more better results

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