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Formulation and Evaluation of Pantoprazole Sodium Microspheres

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ABSTRACT: Microspheres are typically free flow powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. An attempt was made to prepare floating microspheres of pantoprazole using polymers of PVP and HPMC by coacervaton technique. It was concluded that the drug release from the floating microspheres was controlled by the polymer. The nature of the polymers and their concentration influenced the physical and floating behaviour of the prepared microspheres. In vitro release data obtained from buoyant microspheres showed good buoyancy and prolonged drug release for formulations.

KEYWORDS Microspheres, Controlled released, HPMC, PVP , Pantoprazole.

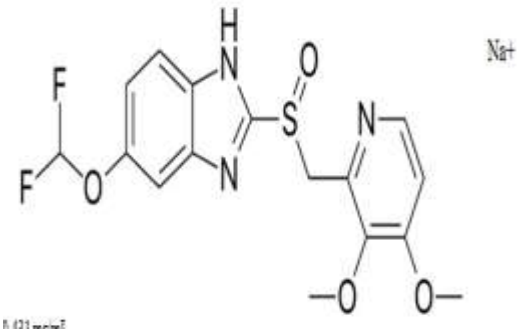
I. INTRODUCTION

Drug delivery systems (DDS) that can precisely control the release rates or target drug to a specific body site have had an enormous impact on the health care system. The last two decades there has been a remarkable improvement in the field of novel drug delivery systems. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc. which modulates the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics.

Ion gelation technique is one of the several methods that is used for production of microspheres. Although this way may not be the main method, but it is the simplest one that several variables can affect the outcome, as well.[1]

Sustained release microspheres may be produced by several methods utilizing emulsion system (oil-in-water, oil-in-oil, water-in-oil-in-water), as well as by spray drying. The common emulsion system used oil-in-water (o/w), with microspheres being produced by the emulsion solvent evaporation method. This relatively simple method enables the entrapment of a wide range of hydrophobic drugs.[2]

Pantoprazole is used to treat certain stomach and esophagus problems (such as acid reflux). It works by decreasing the amount of acid your stomach makes. This medication relieves symptoms such as heartburn, difficulty swallowing, and persistent cough. It helps heal acid damage to the stomach and esophagus, helps prevent ulcers, and may help prevent cancer of the esophagus. Pantoprazole belongs to a class of drugs known as proton pump inhibitors (PPIs).



Appearance: White to off white ampholytic crystalline powder.
Solubility: freely soluble in water and Slightly soluble in phosphate buffer at PH 7.4. Water Solubility : 0.431 mg/mL
Molecular Formula : $C_{16}H_{14}F_2N_3NaO_4S$
Molecular Weight : 423.367 g/mol
Iupac Name : Sodium;5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2 yl)methylsulfinyl]benzimidazole-1-ide;hydrate
Storage: Store Pantoprazole at 20^0- 25^0C (68^0 - 77^0 F); excursions permitted to 15^0 - 30^0C (59^0 – 86^0 F)
Category: Proton Pump Inhibitor (PPI)
Melting point: 139-140°C
Log P: 2.18
Bioavailability: 77%
Half life: 1-2 hr

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Preformulation Study: Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms. It involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance which are characterized with the goal of designing optimum drug delivery system.
Organoleptic evaluation: These are preliminary characteristics of any substance, which is useful in identification of specific material. Following physical properties of API were studied.

For Pantoprazole Sodium
Appearance: This was done by visually inspection of drug.
Odor: This was done by sensory organ.
Solubility :in various solvents like water, methanol

UV spectroscopy: Stock solution of Pantoprazole sodium was prepared by dissolving 10 mg of drug in 100 ml of water. After dilution of above stock solution, the sample solution was scanned in the range of of 200 to 400 nm by using UV-visible spectrophotometer (Systronics India limited, Ahmedabad).
Formulation and Development[3]

Preparation of Microspheres of Pantoprazole sodium
Microspheres were prepared by ionotropic gelation method.

Microspheres were prepared by ionotropic gelation method.

Initially, required quantity of sodium alginate was accurately weighed and dissolved in distilled water using mechanical stirrer.

↓

After some time, to this solution drug and polymer were added. The above solution was mixed thoroughly by means of mechanical stirrer.

↓

Then the solution was sonicated for about 30 min so as to remove air bubbles. After sonication, the solution was kept aside for 30 min.

↓

The resultant solution was dropped via a 23-gauge syringe needle (0.65 mm internal diameter) into 80 ml of 2% w/v calcium chloride (CaCl2) solution containing 10% v/v acetic acid.

II. MATERIALS AND METHODS

Materials: Pantoprazole Sodium was obtained as gift sample from S.S Medical agencies, Hyderabad. All other polymers and chemicals were of either pharmaceutical or analytical grade.
Methods
Analytical method development for pantaprazole sodium sesquihydrate UV-Visible spectrophotometer.
Preparation of phosphate buffer Ph 1.4: 250ml of 0.2 M potassium chloride with 425 ml of 0.2M hydrochloric acid solution, add 0.02% tween 80 to this solution and dilute with required amount of water (1000ml)
Preparation of phosphate buffer pH 6.8: Weigh required quantities of disodium hydrogen orthophosphate and potassium dihydrogen orthophosphate, add 0.5% tween 80 to this solution and dilute with required amount of water (1000ml).

Calibration curve of pantoprazole sodium sesquihydrate:
From the stock solution prepared (100 mg in 100 ml phosphate buffer of pH 1.2) 0.2,0.4,0.6,0.8 and 1.0 ml was diluted to 10 ml in a volumetric flask with phosphate buffer pH 1.23 to give test solutions of concentrations 2,4,6,8 and10 ug/ml respectively**.**
The absorbance of each test solution was measured at 260 nm by using UV-Visible spectrophotometer against Ph 1.2 phosphate buffer as a blank.

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Table1: Data for standard plot of pantaprazole at pH 1.2

Concentration (ug/ml)	Absorbance(nm)
0	0.000
2	0.182
4	0.381
6	0.572
8	0.766
10	0.961

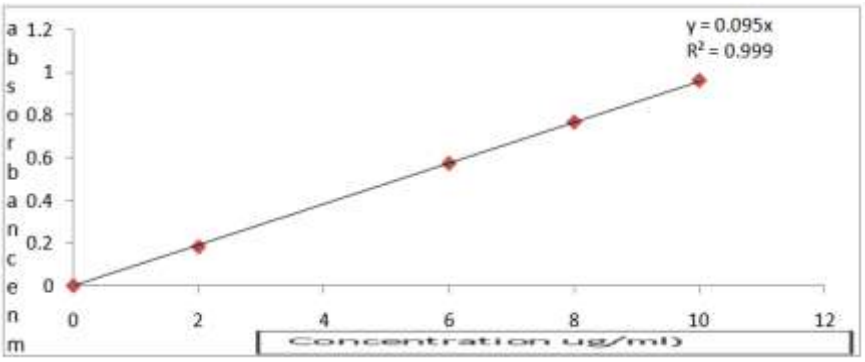

Fig1: Standard plot of pantaprazole at Ph 1.2

Table :2 Data for standard plot of pantaprazole at pH 6.8

Concentration (ug/ml)	Absorbance(nm)
0	0.000
2	0.162
4	0.321
6	0.472
8	0.640
10	0.808

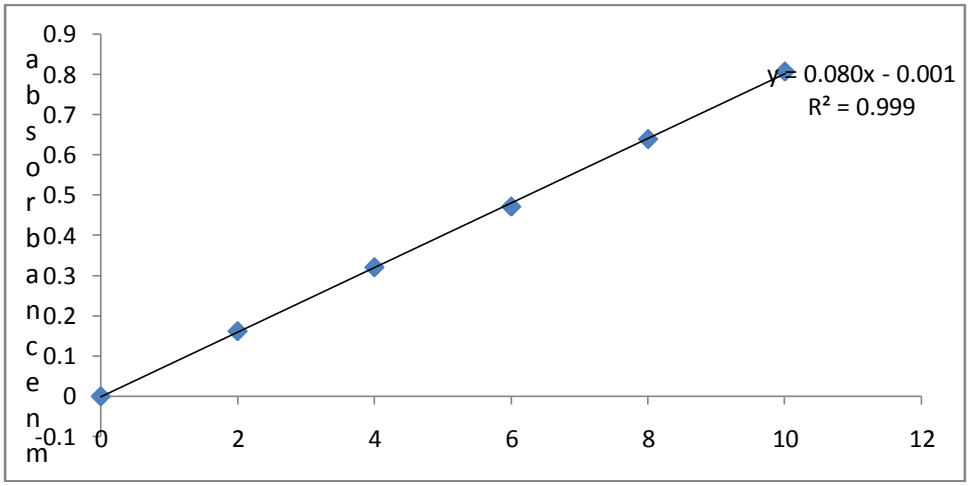

Fig 2: Standard plot of pantaprazole at pH 6.8

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Table 3 : Preparation methods of current study

Formulation code	Polymer ratio (PVP/HPMC)	Temperature	Outer aqueous phase 1% calcium chloride in glacial acetic acid (10%v/v)
P1	1:0.5	$30\text{-}40^0$	100 ml
P2	1:1	$30\text{-}40^0$	100 ml
P3	1:1.5	$30\text{-}40^0$	100 ml
H1	1:0.5	$30\text{-}40^0$	100 ml
H2	1:1	$30\text{-}40^0$	100 ml
H3	1:1.5	$30\text{-}40^0$	100 ml

Characterization Of Pantaprazole Floating Microspheres

Particle size analysis

Particle size analysis was carried out by using the optical microscopy method with the help of a calibrated eye piece micrometer. The size of around 200 particles were measured and an average diameter was calculated.

Particle size analysis of the prepared microspheres

Table 4: Data for particle size analysis of the prepared microspheres

S No	Formulations	Particle size range (um)
1	P1	20-30
2	P2	25-40
3	P3	40-60
4	H1	15-30
5	H2	20-40
6	H3	30-60

It was observed that the formulations P3, H3 showed relatively higher percentage of particle size and formulations P1 and H1 showed relatively small size floating microspheres

In vitro dissolution studies

Dissolution studies are carried out for the determination of rate of drug release and solubility.

A USP dissolution test apparatus Type-1 was used to determine the dissolution profiles of the prepared pantoprazole microspheres (100 mg of sample was used).The dissolution medium used was 900 ml phosphate buffer of pH 1.2 for the first 2 hours. After 2 hours filter the microspheres and continue the dissolution process by placing these filtered microspheres in a freshly prepared 900 ml phosphate buffer of pH 6.8 upto 12 hours equilibrated to 37^0 C. The basket was rotated at a speed of 100 rpm. From the dissolution flask 5 ml samples were withdrawn at various time intervals such as 0,1,2,3,4,5,6,7,8,9,10,1 and 12 hours. Concentration of the pantoprazole in the samples were determined by UV-Visible spectrophotometer at 260 nm. The amount of pantaprazole dissolved was calculated from the concentration after correcting for the change in the volume of distribution.

The following are the results of dissolution studies of various microspheres prepared. The results of dissolution of pantoprazole microspheres of PVP with different concentrations are shown in the following table

Table 5: Dissolution data of pantoprazole microspheres obtained from different concentrations of PVP (0.5,1,1.5% w/v)

Time (hours)	Cummulative % drug release		
	P1	P2	P3
0	0	0	0
1	1.6	2.8	0.96
2	6.7	8.2	3.4

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3	12.8	15.4	8.9
4	19.4	20.1	14.4
5	21.6	25.6	20.4
6	29.8	33.8	26.8
7	37.2	46.2	39.9
8	48.3	58.3	48.2
9	59.2	64.6	54.9
10	67.9	76.2	66.2
11	76.6	83.4	74.3
12	84.6	92.8	80.2

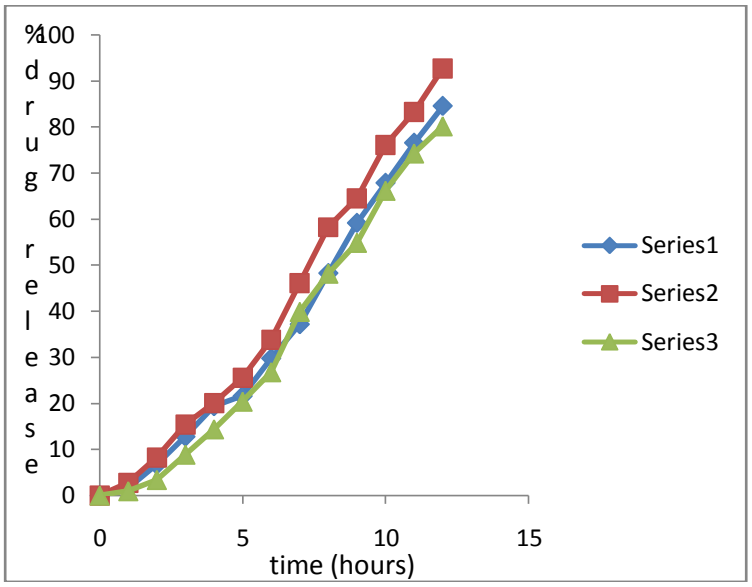

Fig 3: Comparitive drug release profiles of pantoprazole microspheres of different concentrations of PVP

Table 6: Dissolution data of pantoprazole microspheres obtained from different concentrations of HPMC

Time (hours)	Cummulative % drug release		
	H1	H2	H3
0	0	0	0
1	0.8	1.9	0.6
2	4.5	6.6	2.1
3	12.6	13.4	10.3
4	20.1	22.6	16.4
5	28.4	30.6	24.6
6	32.6	41.4	32.8
7	41.4	50.3	40.3
8	46.2	55.2	48.4
9	50.1	63.9	53.2
10	56.4	72.8	61.9
11	60.2	80.7	66.4
12	68.9	88.8	72.8

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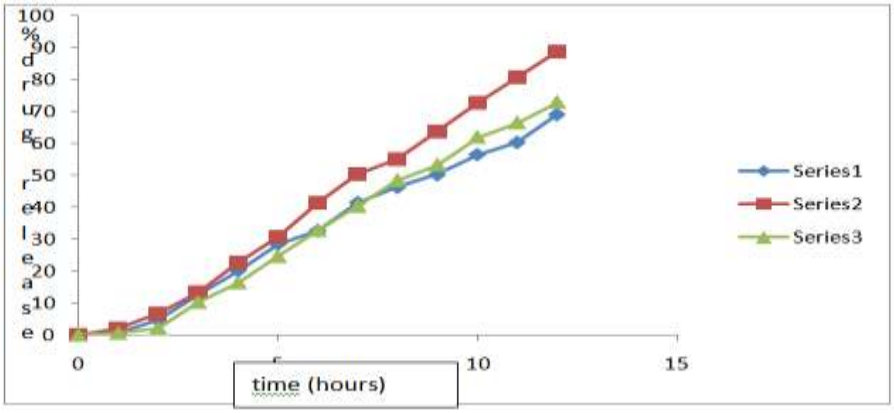

Fig 4 : Comparative drug release profiles of pantoprazole microspheres of different concentrations of HPMC

III. RESULTS AND DISCUSSION:

The particle size of floating microspheres varied among the formulations due to variations in thecomposition of formulations. The mean particle size of floating microspheres formulation which shows the high percentage of entrapment was in the range of 25-40 um. The formulations P3, H3 showed relatively small size floating microspheres.

Smaller the microspheres , more will be the buoyancy percentage and more sustained release of the drug was achieved. While larger the size, less will be the buoyancy percentage and there was no sustained release of the drug.

1. In vitro dissolution studies:

Microspheres were subjected to in vitro release using USP dissolution apparatus type I in the 900 ml phosphate buffer solution of pH 1.2 for about 2 hours and 900 ml of phosphate buffer solution of pH 6.8 upto 12 hours. Among the formulations P1,P2,P3, the P2 formulation showed sustained release of the drug and the drug release was found to be approximately linear. Furthermore, the drug release from the floating microspheres matrix was controlled by the polymer. As the polymer content was increased and the drug loading was decreased, the release of the drug was decreased significantly. While among the formulations H1, H2, H3, the H2 formulation showed the better release.

2. Incorporation efficiency and buoyancy percentage

The floating test was performed to investigate the floatability of the prepared microspheres. Good in vitro percentage buoyancy was observed for formulations P2 and H2. This may be attributed to the low tapped density of the microspheres. Microspheres of formulations P2 and H2 showed best floating ability (72% and 69%) as compared with other formulations.

Incorporation efficient tests were carried out for prepared formulations. Among them, P2 and H2 showed higher percentage of incorporation efficiency.Hence it was found that P2 and H2 formulations showed a desirable high drug content, buoyancy and adequate release characteristics. Hence the formulations of P2 and H2 are suitable for the development of gastric retention dosage forms.

For better absorption and enhanced bioavailability of some drugs, prolonged retention time of the dosage form in the stomach is essential. This problem can be solved by the preparation of gastro-retensive drug delivery systems. An attempt was made to prepare floating microspheres of pantoprazole using polymers of PVP and HPMC by coacervation technique.

From the obtained results, it can be concluded that the drug release from the floating microspheres matrix was controlled by the polymer. When the polymer proportion in the formulation was increased with decrease in drug loading, drug release was decreased significantly.

The nature of polymers and their concentration influenced the physical and floating behaviour of prepared microspheres. In vitro release data obtained from buoyant microspheres showed good buoyancy and prolonged drug release for formulations P2 and H2. The prepared microspheres had a different size and incorporation efficiency. Hence the formulatins P2 and H2 showed appropriate balance between buoyancy and drug release rate. Diffusion was found to be the main release mechanism. Thus the prepared microspheres may prove to be potential for multiple-unit delivery devices acceptable to any intra gastric conditions.

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