Research Article

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

ISSN Print 2231 – 3648
Online 2231 – 3656

Formulation and evaluation of mucoadhesive microcapsules of pantoprazole sodium

Mudavath Hanumanaik, Ramavath Lakshmi Durga, Kokkilagadda Vinod Kumar, Tunuguntla Bhavani Ramesh, Balaji Maddiboyina

Department of Pharmacy, Vishwabharathi College of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India

ABSTRACT

The main objective of the study was to design site specific controlled release mucoadhesive micro beads containing pantoprazole sodium for the treatment of digestive ulcers. Novel Sodium alginate beads containing pantoprazole sodium were successfully prepared by ion tropic gelation technique with mucoadhesive polymers during formulation. Sodium alginate (SA), sodium carboxy methyl cellulose (SCMC), Methyl cellulose (MC) and Hydroxy propyl methyl cellulose (HPMC) were suitable biodegradable and biocompatible synthetic polymers for preparing intestinal mucoadhesive beads. These includes no risk of dose dumping, flexibility of blending units with different release patterns, relative merits of bioavailability more consistent blood levels, reproducible and all or none effects. Nine formulations were prepared and labelled as F1, F2, F3, F4, F5, F6, F7, F8, and F9. Overall, the mucoadhesive beads provided a prolonged and controlled release that would be beneficial for therapy of digestive ulcers. The % yield of all batches was found to be in the ranges of 97.14–99.33%. The mean particle size was obtained in the range of 927.54 – 1012.32µm and 955.36 – 1041.29µm for uncoated and coated beads respectively. Mucoadhesion test showed a significant effect on mucoadhesive property. The greater the polymer concentration associated with mucoadhesive alginate matrix, greater will be the adhesion. An increase in drug load has no effect on mucoadhesive property.

Keywords: Pantaprazole sodium, Sodium alginate, Mucoadhesion, methyl cellulose, Hydroxyl propyl methyl cellulose

INTRODUCTION

The improved controlled drug delivery system is designed to deliver drug to a patient over a specific time period (temporal control) and to a particular portion of the patient's gastro intestinal tract (spatial control). It avoids dose dumping and results in the most effective therapeutic

Author for Correspondence:
Mudavath Hanumanaik
Department of Pharmacy,
Vishwabharathi College of Pharmaceutical Sciences,
Guntur, Andhra Pradesh, India.

administration of the drug to a patient. A controlled drug delivery system is usually designed to deliver the drug at particular rate safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuation observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Considerable efforts have been made in the last few decades to develop new pharmaceutically viable and therapeutically effective controlled drug delivery system [1].

The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time [2]. The mucosa lines a number of regions of the body including the gastrointestinal tract, the urogenital tract, the airways, the ear, nose and eye. Microbeads are one of the most interesting modes of drug delivery systems. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Mucoadhesive microbeads can be tailored to adhere to any mucosal tissues, including those found in the eye, nasal cavity, urinary tract, colon, and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of the drug [3].

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H^+,K^+)- ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose- related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus [4].

MATERIALS AND METHODS

Pantoprazole sodium was obtained from Nice Chemicals, Sodium Alginate, Carboxy methyl cellulose Sodium (CMC Na), Methyl Cellulose (MC), Hydroxy methyl cellulose (HMC) are obtained from Finar Chemicals. Hyderabad.

Preformulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physicochemical properties of a drug substance alone and when combined with the excipients, to generate data useful to the formulator in developing safe, stable, potent, bioavailable and efficous dosage form, which can be mass produced.

Identification

Solubility

The solubility of Pantoprazole was tested in various solvents such as distilled water, methanol, ethanol (95%), dichloromethane, Chloroform, acetone, acetic acid, n-hexane, isopropyl alcohol, 0.1N hydrochloric acid and pH 7.4 phosphate buffer.

Identification of Drug

The Infra-Red (IR) spectra of Pantoprazole sodium were recorded using Fourier Transform Infra-Red (FTIR) spectrophotometer. Sample preparation involved mixing the sample with potassium bromide (KBr), triturating in glass mortar and finally placing in the sample holder. The spectrum was scanned over a frequency range 4000 – 500 cm^{-1}.

Compatibility Studies [5]

Fourier Transform Infrared (FT-IR) analysis measurements of pure drug, carrier and drug-loaded microbead formulations were obtained using a Bruker alpha system spectrophotometer with spectrum opus 6.5 software. The pellets were prepared on KBr-press under a hydraulic pressure of 150 kg/cm^2, the spectra were scanned over the wave number range of 4000–500 cm–1 at the ambient temperature.

Formulation Development

Nine formulations were prepared by varying polymer concentration keeping the concentration of drug and mucoadhesive polymer in different ratios.

Preparation of Pantoprazole Mucoadhesive Microbeads [6]

Pantoprazole mucoadhesive microbeads were prepared by using blends of sodium alginate as the coat material with three mucoadhesive polymers such as Sod. CMC, MC and HPMC by micro-orifice ionic gelation method. The sodium alginate and mucoadhesive polymers were mixed in 0.25:0.25, 0.5:0.5, and 1:1 ratios. The drug, Pantoprazole sodium (1g), was added to this mixture and homogenized thoroughly with a magnetic stirrer to form a homogeneous dispersion. The resulting bubble free dispersion was added drop wise manually with a 10 ml syringe fitted with an 18 gauge needle, into 100 ml of (10%w/v) calcium chloride (CaCl2) solution kept under stirring in a 250 ml beaker. The gelation time of 15 min was allowed to complete the curing reaction and produce spherical rigid microbeads. The beads so prepared were collected by decantation, washed with n-hexane and dried at < 40oC for 2h. The microbeads prepared along with their coat composition are listed in Table 1.

Table 1: Experimental design of various formulations

Formulation Code	Pantoprazole sodium (%)	Sodium Alginate(SA) (%)	Mucoadhesive polymer (MAP) (%)	Drug – Polymer (SA+MAP) ratio	Cross linking agent – $CaCl_2$ (% W/V)	Curing Time	Coating concentration (% W/V)
F1	1	0.25	0.25	1:0.5	10	15	12.5
F2	1	0.50	0.50	1:1	10	15	12.5
F3	1	1	1	1:2	10	15	12.5
F4	1	0.25	0.25	1:0.5	10	15	12.5
F5	1	0.50	0.50	1:1	10	15	12.5
F6	1	1	1	1:2	10	15	12.5
F7	1	0.25	0.25	1:0.5	10	15	12.5
F8	1	0.50	0.50	1:1	10	15	12.5
F9	1	1	1	1:2	10	15	12.5

Preparation of enteric-coated beads

The prepared beads were transferred into acetone solutions of Eudragit S-100 at a concentration of 12.5% w/v, and coated for 15 min under stirring. The resulting coated beads were filtered and air dried. This coating process was repeated thrice [7].

EVALUATION OF PREPARED MICROBEADS

Particle size analysis [8]

All the batches prepared were analyzed for particle size where the microbeads were placed on a set of standard sieves ranging from sieve No. 16# to 60#. The sieves were arranged in such a way that they were in a descending order with the mesh size 16# on the top and 60# mesh in the bottom. The microbeads passed through the set of sieves and the amount retained on each sieve was weighed and the average mean diameter was determined and considered as mean particle size:

$$\text{Mean particle size} = \frac{\sum (\text{Mean particle size of the fraction} \times \text{Weight fraction})}{\sum (\text{Weight fraction})}$$

Flow Properties [9]

Bulk Density (BD)

Bulk density = Weight of powder / Bulk volume

Tapped density (TD)

Tapped Density = Weight of powder / Tapped volume

Carr's Index

It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100]/TD

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material and their standard values are given in table 2.

Hausner's Ratio = TD / BD

Table 2: Effect of Carr's Index and Hausner's Ratio and Angle of repose on flow property

Flow Character	Carr's Index (%)	Hausner's Ratio	Angle of repose
Excellent	≤10	1.00-1.11	<20
Good	11-15	1.12-1.18	20-30
Fair	16-20	1.19-1.25	-----
Passable	21-25	1.26-1.34	30-34
Poor	26-31	1.35-1.45	-------
Very poor	32-27	1.46-1.59	>35
Very very poor	>38	>1.6	-------

Angle of repose

tan θ = h/r

Where, h and r are the height and radius of the powder cone respectively.

% Drug content evaluation

Drug content in the microbeads was estimated by UV-Spectrophotometric method at a wavelength of 289 nm in phosphate buffer of pH 7.4. The method obeyed Beer's law in the concentration range 0-12µg/ml. Microbeads equivalent to 100 mg of Pantoprazole were crushed into fine powder and made up to 100 ml with pH 7.4 buffer. 1ml of the sample solution was made up to 100ml with phosphate buffer pH.7.4 and the absorbance was measured at a wavelength of 289 nm. The procedure was repeated with pure pantoprazole. The absorbance values from the pure drug pantoprazole and microbeads were measured and the % drug content was calculated. The method was validated for linearity, accuracy and precision.

Microencapsulation efficiency [10]

Microencapsulation efficiency was calculated using the following formula:

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated percent drug content}}{\text{Theoretical percent drug content}} \times 100$$

Swelling index [11]

Pre-weighed pantoprazole sodium microbeads (W_0) formulated with mucoadhesive polymers by employing different coat, core ratios were placed in pH 7.4 phosphate buffer maintained at 37°C. After 3h, the microbeads were collected and blotted to remove excess water and weighed (W_t). The swelling index was calculated with the following formula.

$$\text{Swelling Index} = \frac{W_t - W_0}{W_0} \times 100$$

Where W_t = weight of microbeads observed at the end of 3h and W_0 = the initial weight of microbeads.

Mucoadhesion testing [12]

The mucoadhesive property of the microbeads was evaluated using *in vitro* adhesion testing method known as wash-off method. A piece of goat intestinal mucus (2 × 2 cm) was mounted onto glass slides of 3×1 inch with elastic bands. Glass slide was connected with a suitable support. About 50 microbeads were spread onto each wet tissue specimen, and thereafter the support was hung onto the arm of a USP tablet disintegrating test machine. The disintegration machine containing tissue specimen was adjusted for a slow, regular up and down movement in pH 7.4 phosphate buffer maintained at 37°C taken in a beaker. At the end of 1h and later at hourly intervals up to 12 h, the machine was stopped and the number of microbead still adhering onto the tissue was counted.

Morphological and Surface characteristics [13]

The surface morphology was determined using Scanning Electron Microscopy (SEM-LEICA, S430, UK). Dry microbeads were placed on an electron microscope brass stub that was coated with gold (thickness 200 nm) in an ion sputter. Pictures of microparticles were taken by random scanning of the stub under reduced pressure (0.001 torr).

FTIR Studies of Optimized Formulation

The FTIR spectroscopy was used to identify any of the possible interactions between the formulation components.

In vitro release studies of microbeads

In vitro drug release studies of pantoprazole microbeads was carried out using USP type I dissolution rate test apparatus (LABINDIA DS 8000) with a basket stirrer at 50 rpm in 900 ml in phosphate buffer of pH 7.4 and temperature 37 ± 0.5°C. Microbeads equivalent to 40mg of pantoprazole sodium were taken in the basket. 5ml samples of the dissolution fluid was withdrawn at regular intervals and replaced with fresh dissolution medium. The samples were filtered, diluted and analyzed using UV-Visible Spectrophotometer (Elico Ltd. SL 159) at a wavelength of 289nm. The dissolution was carried out for every batch in triplicate. %Drug release, order and mechanism of the release were determined by the absorbance values obtained.

Determination of the Gastric-Resistance of enteric coated beads [14]

The gastric resistance of prepared coated beads was determined by the method described as follows. The samples were placed in dissolution bath containing 0.1N HCl at 37± 0.2^0 C for 2h. During this acid step, no sample was collected for quantification, as any amount of Pantoprazole released at this pH was quickly degraded. After the acid step, the HCl solution was replaced by the phosphate buffer pH 7.4. Sampling was done at predetermined time intervals and the samples were analyzed using UV spectrophotometry at 289nm.

Release kinetics [11]

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic equations namely zero order (% release vs time), first order (log% unreleased vs time), and Higuchi matrix (% release vs square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analyzed by Peppas equation, $Mt/M\infty=ktn$, Where $Mt/M\infty$ is the fraction of drug released, "KKP" the release constant, "t" the release time and "n" is the

diffusion exponent for the drug released that is dependent on the shape of the matrix dosage form. When 'n' approximates 0.43, a Fickian/diffusion control release is implied; where $0.43<n<0.85$, it implies non-Fickian transport; and $n \geq 0.85$ for zero-order release. Baker Lonsdale release model: This model represents the controlled drug release from the spherical matrix and is represented by the formula:

$$3/2[1-(1-F)^{2/3}] - F = K_{BL}\, t$$

Where F is the fraction of the drug released, t is the time of release and K_{BL} is the Baker-Lonsdale release constant. The release constant can be calculated by finding the slope of $3/2[1-(1-F)^{2/3}] - F$ v_s. time plot.

Stability Studies [15]

The stability studies were carried out as per ICH guidelines at refrigerator & work bench for the following selected formulation for 3 months. Optimized formulation of the microparticles was selected for stability studies Formulations were packed in a screw capped bottle and studies were carried out for 90 days by keeping at 40 + 2oC and 75 + 5% RH. Samples were withdrawn on 30th, 60th & 90th day and were analyzed for physical appearance, entrapment efficiency, and In-vitro drug release.

RESULTS AND DISCUSSION

Preformulation

Solubility Analysis

The Pantoprazole sodium sample was found to be freely soluble in water, methanol and ethanol (95%). It was also soluble in 0.1N HCl (pH 1.2) and slightly soluble in pH 7.4 phosphate buffer and insoluble in isopropyl alcohol and in n-hexane. Solubility analysis is important because the drug has to dissolve in the solvents and also in the dissolution medium used.

Identification of Drug

The Fourier Transform Infra-Red (FTIR) spectroscopy of Pantoprazole sodium were recorded and displayed in Fig.

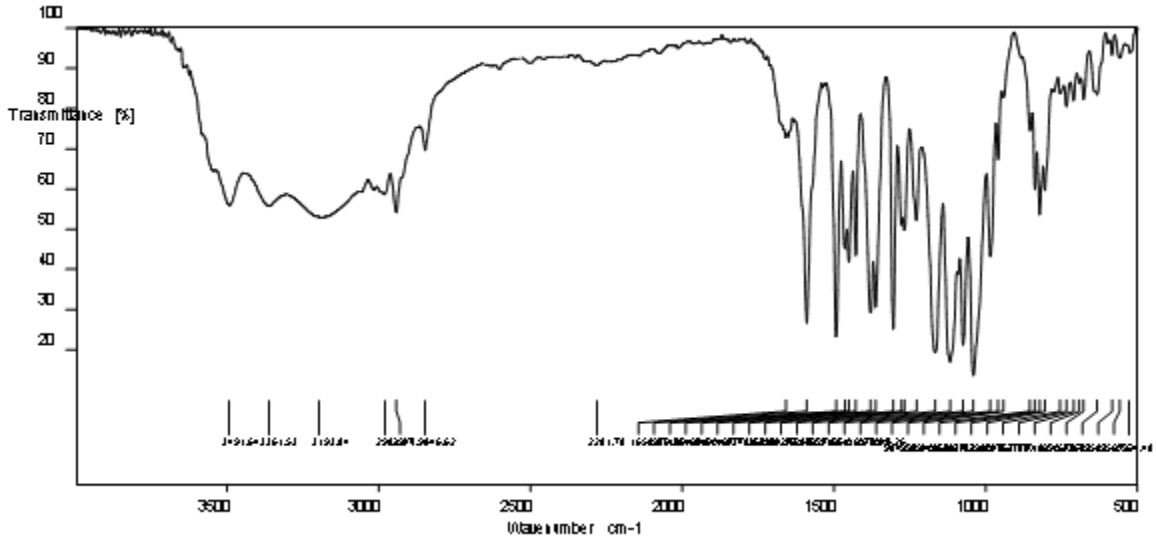

Figure 1: IR Spectra of pure drug Pantoprazole sodium

Compatibility Studies

FTIR studies of pantoprazole sodium, sodium alginate, sodium carboxy methyl cellulose, methyl cellulose, hydroxyl propyl methyl cellulose and their physical mixture confirmed that there was no significant interaction between them.

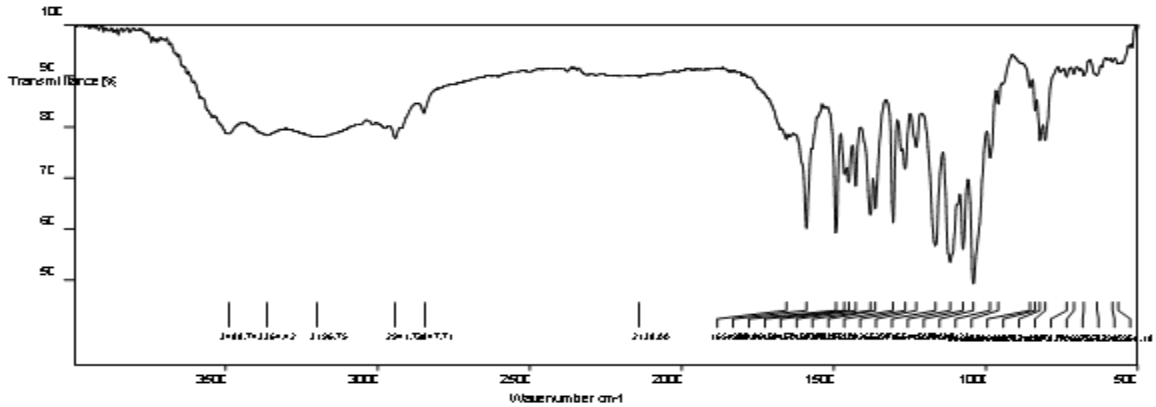

Figure 2: IR Spectra of drug with sodium alginate

Table 3: FTIR spectroscopy

S.No	Characteristic peak	FTIR SPECTRA VALUES (cm^{-1})						
		Range	Pure drug	Drug + sodium alginate	Drug + Sod.CMC	Drug + methyl cellulose	Drug + HPMC	Formulation F6
1	C-H aliphatic stretching	< 3000	2941.95	2941.71	2941.80	2941.00	2941.59	2940.56
2	C=N stretching in aromatic ring	1600-1430	1589.28	1589.45	1589.41	1589.50	1589.45	1589.28
3	C=C stretching in aromatic ring	1600-1430	1492.46, 1463.84, 1450.48, 1427.71	1492.38, 1464.37, 1450.38, 1427.80	1492.56, 1463.85, 1450.69, 1427.79	1492.39, 1464.04, 1450.69, 1427.78	1492.18, 1464.20, 1450.49, 1427.60	1492.47, 1464.39, 1450.84, 1427.86
4	C-H bending of CH_2,CH_3	1485-1340	1378.62, 1362.08	1378.97, 1362.36	1378.88, 1362.30	1362.68, 1378.52	1378.20, 1362.57	1379.27, 1362.54
5	C-F stretching	1400-1000	1304.32	1304.43	1304.36	1304.69	1304.77	1304.38
6	S = O stretching	~1050	1073.95	1074.23	1074.28	1074.12	1073.91	1074.28
7	CO stretching of $–OCH_3$	1350-1000	1040.26	1040.23	1040.28	1040.60	1040.64	1040.21

Formulation Development

Pantoprazole sodium mucoadhesive microbeads were prepared by orifice-ionic gelation method. Nine formulations were prepared with sodium alginate and three mucoadhesive polymers in three different drug to polymer ratios. The experimental design and various independent variables like polymer type and drug to polymer ratio. Each of the variables significantly influenced the various physico-chemical parameters of microbeads.

EVALUATION OF DEVELOPED FORMULATION

Particles Size analysis

Effect of different parameters on the particle size of microbeads were summarized in table 2 (formulations F1-F3/F4-F6/F7-F9) indicated that with increase in the polymer concentration the mean particle size of the microbeads is increased, which is attributed to the increase in viscosity, which in turn increases in the droplet size during

the addition of polymer solution to the cross-linking agent solution. The obtained beads were evaluated for mean particle size (µm). The mean particle size was obtained in the range of 927.54–1012.32µm and 955.36–1041.29µm for uncoated and coated beads respectively. The size of the beads increased with increasing polymer ratio.

Flow characteristics of Microbeads

Results indicate all the flow characteristics of nine formulations as shown in table 4. The values of angle of repose, compressibility indexes (I) and Hausner's ratios were obtained between 19.44 to 29.89, 1.7 to 2.7 and 1.018 to 1.028 respectively. The values obtained for the nine formulations were within the normal acceptable range, indicating the good flow property.

Table 4: Flow characteristics of various formulations

Formulation code	Bulk density	Tapped density	Porosity	Angle of Repose	Carr's Index	Hausner's ratio
F1	0.651	0.669	0.027	19.44	2.7	1.027
F2	0.663	0.682	0.027	20.55	2.7	1.028
F3	0.745	0.761	0.021	22.83	2.1	1.021
F4	0.544	0.554	0.018	25.34	1.8	1.018
F5	0.535	0.545	0.017	24.56	1.7	1.024
F6	0.621	0.635	0.021	20.72	2.1	1.027
F7	0.598	0.612	0.023	30.14	2.3	1.023
F8	0.602	0.617	0.024	29.35	2.4	1.024
F9	0.533	0.543	0.017	27.75	1.7	1.018

% Drug content evaluation

The % yield of all batches was found to be in the ranges of 97.14– 99.33% as shown in table 5.

Microencapsulation efficiency

The Microencapsulation efficiency of batches was in the range of 50.67 – 69.74% as shown in table 5.

Table 5: % Yield, Particle Size, % Drug Entrapment Efficiency, Swelling and Mucoadhesion Studies of Various Formulations

Formulation code	% Yield	Mean particle size(µm) Mean ± SD		% Micro-encapsulation efficiency	Swelling index (%)	Mucoadhesion (%)
		uncoated	Coated			
F1	97.82	933.45±11.13	961.47±13.25	50.67	180	36
F2	98.20	961.32±13.49	988.15±11.20	52.48	320	52
F3	98.66	995.15±15.78	1023.26±14.25	56.89	510	71
F4	97.68	942.65±14.34	972.45±12.21	54.13	120	48
F5	98.50	973.24±12.33	1001.33±11.32	58.90	270	66
F6	99.33	1012.32±13.41	1041.29±12.22	62.74	410	78
F7	97.14	927.54±10.68	955.36±14.61	53.64	130	28
F8	97.80	948.76±09.51	975.27±12.64	62.65	180	40
F9	98.10	972.85±11.23	1001.20±13.31	69.35	240	54

Swelling studies

The swelling behaviour of uncoated microbeads was determined gravimetrically. The result indicated that as the amount of polymer (formulations F1-F3/F4-F6/F7-F9) in microspheres was increased the swelling ratio also proportionately increased. The higher percentage of polymer in microbeads renders high swelling and gel formation. The obtained beads were evaluated for swelling index. It was found to be the higher percentage of polymer in micro beads renders high swelling and gel formulations as shown in table 5.

Mucoadhesion testing

The adhesion of microbeads to the intestinal mucosa of goat was evaluated as the mean percent of microbeads remain adhered after a defined period of washing. Mucoadhesion test results indicated that the polymer to drug ratio showed a significant effect on mucoadhesive property. The greater the polymer concentration associated with mucoadhesive–alginate matrix, greater will be the adhesion. An increase in drug load has no such effect on mucoadhesive property Table 5. Mucoadhesion test showed a significant effect on mucoadhesive property. The greater the polymer concentration associated with mucoadhesive alginate matrix, greater will be the adhesion. An increase in drug load has no effect on mucoadhesive property.

Morphological and Surface characteristics

Scanning electron microscopy (SEM) was carried out to study the morphological and surface characteristics. The SEM microphotographs (Fig.11) of the prepared microbeads (F6 formulation) showed the particles' spherical shape and rough texture with shrinkage which is due to removal of water from microbeads during drying. Thus the rate of removal of water from microbeads exerts an influence on the morphology of final product. The enteric coated microbeads (Fig. 3) revealed smooth and almost discontinuous film on to the spherical surface of the microbeads. The uncoated and coated beads of batch F6 observed under SEM, uncoated beads were spherical and rough texture and enteric coated beads revealed smooth and almost discontinuous film on spherical surface of beads.

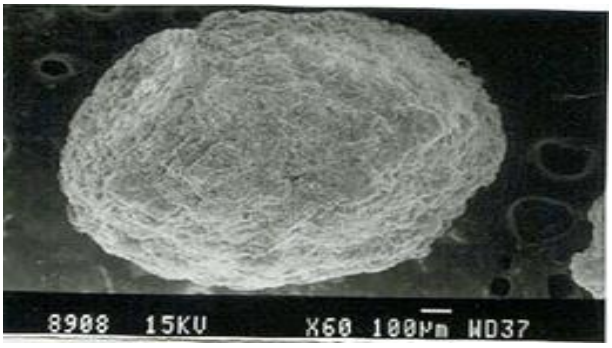

Figure 3a: SEM microphotograph formulation F6 (uncoated)

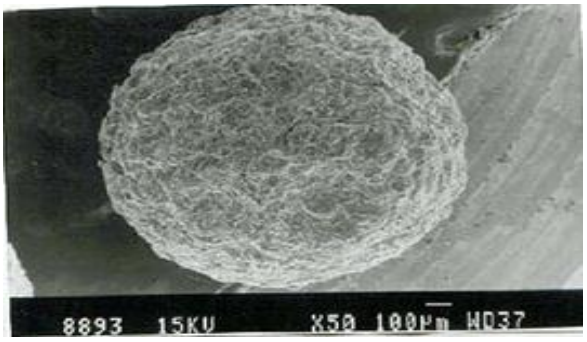

Figure 3b: SEM microphotograph of formulation F6 (coated)

FTIR Studies of Optimized Formulation

The FTIR spectroscopy was used to identify any of the possible interactions between the formulation components and is done by comparing the IR spectra of the formulation with that of the pure drug. As shown in Fig.4 & table 3, there was no significant difference in the FTIR spectra of drug-polymer.

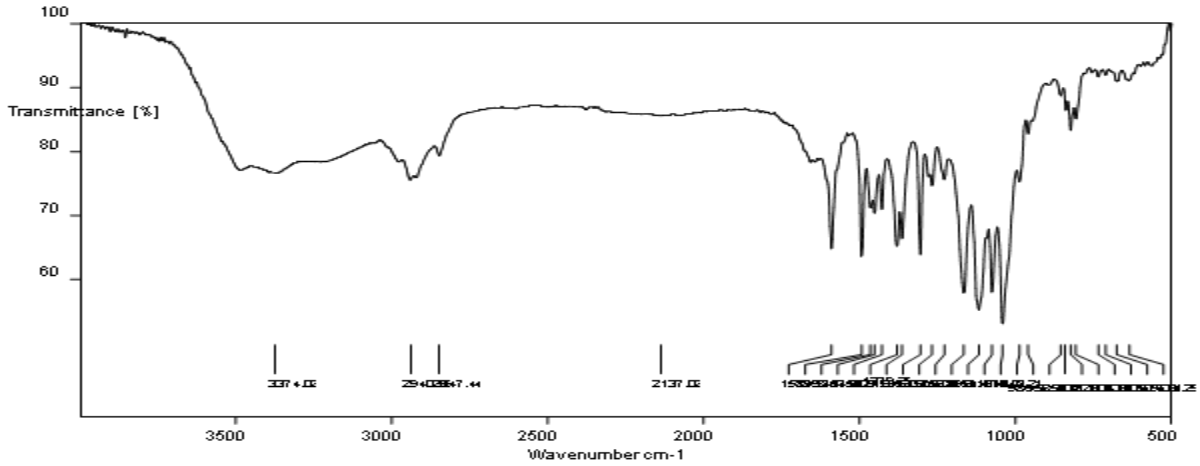

Figure 4: IR Spectra of drug with sodium alginate and methylcellulose (Formulation F6)

In vitro drug release study

The drug-polymer ratio was found to affect the drug release characteristics of the prepared microbeads. The increase in polymer concentration in microbeads showed a significant decrease in rate and extent of drug release. Table 5 and figure 9 showed the values of cumulative percentage drug release and plot of cumulative percentage drug released as a function of time for all the nine (F1–F9) formulations respectively. The drug release is prolonged over a period of 12h in case of formulation F6. Thus, F6 formulation appears to be more efficient in controlling the drug release till the 12th hour. It was also observed that the drug release is generally decreased as the polymer ratio increased. The *in vitro* drug release of formulated beads was in range of 7.59 to 21.66% and 90.72 to 98.55% in basic medium. Formulation F6 showed highest drug release in 12hrs. The order of prolongation of drug release duration from the microbeads observed as:

Alginate-HPMC(50cps)< Alginate-sodium CMC< Alginate-Methylcellulose

Determination of the Gastro-Resistance of enteric coated beads

The beads remained intact during the acid step because the degree of ionization of carboxylic acid groups in the Eudragit S-100 increased with pH. Eudragit S-100 is fully dissolved and released the drug rapidly from the core beads, whereas, at pH 1.2, the one is almost intact and retards the release of the drug. The dissolution profile shows that as the polymer concentration in coating solution increases, loss of drug during the acid step decreases. In alkaline medium initially the enteric coating retard the release to some extent but as such enteric coating has no effect on drug release due to rapid dissolution of the coating layer in pH 7.4 medium. The results demonstrated that the enteric coated beads provide a system of low permeability and a good barrier against drug diffusion under low pH conditions, at which protection is required.

Table 6: Cumulative percentage drug release profile of pantoprazole sodium from F1–F9

Time (hours)	Dissolution Profile (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	21.66279	7.587209	10.36047	17.73837	15.90698	11.14535	18.57558	18.4186	14.18023
2	33.92267	25.15843	25.64477	24.7439	25.46628	23.81773	31.3939	30.29419	25.92762
3	45.04651	46.38517	39.54855	36.02616	41.6189	35.19971	44.3875	49.87471	43.02471
4	66.48692	50.14767	42.59273	55.37616	51.42442	42.87674	61.74302	51.30145	51.37297
5	80.9811	58.27267	47.74564	60.91395	65.10291	51.38023	83.01337	76.69971	55.68488

6	96.60029	69.58081	58.99564	79.56221	77.49535	53.75523	96.02791	87.58634	71.16453
7	-	76.76395	61.41134	97.78895	91.52442	60.85116	-	96.43808	78.87965
8	-	84.50814	66.45494	-	96.21047	69.55465	-	98.53401	89.775
9	-	90.72326	73.61773	-	-	78.30465	-	-	97.0657
10	-	-	86.05087	-	-	87.62442	-	-	-
11	-	-	94.36483	-	-	94.90058	-	-	-
12	-	-	-	-	-	98.55174	-	-	-

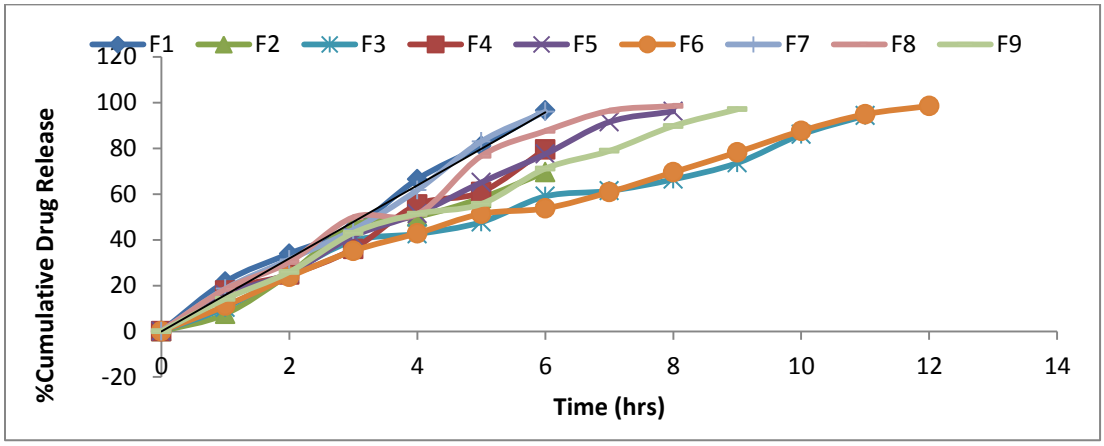

Fig 5: *In vitro* release patterns of formulations

Release kinetics

The release kinetics of all formulations was checked by fitting the release data to various kinetic models. The kinetic release of F1, F3, F4, F5, F6, F7 formulations were best fitted to Zero order release model and F2 was best fitted to Hixson-Crowell release as shown in table 7. F8 and F9 followed Korsmeyer-Peppas release kinetics. It was further confirmed by fitting data to the Korsmeyer-Peppas equation and the 'n' values for the all nine formulations obtained were in the range of 0.847 to 1.060.

Table 7: Kinetic release study profile of formulation F1 – F9.

Formulation Code	R^2						N Values
	Zero order	First order	Hixson Crowell	Higuchi	Baker Lonsdale	Korsmeyer Peppas	
F1	0.994	0.815	0.919	0.918	0.801	0.981	0.847
F2	0.969	0.960	0.988	0.948	0.921	0.942	1.060
F3	0.974	0.895	0.935	0.955	0.817	0.968	0.833
F4	0.987	0.715	0.856	0.887	0.716	0.966	0.895
F5	0.994	0.879	0.953	0.930	0.856	0.993	0.905
F6	0.989	0.810	0.932	0.953	0.837	0.985	0.893
F7	0.995	0.827	0.919	0.900	0.798	0.989	0.932
F8	0.973	0.881	0.957	0.937	0.888	0.982	0.850
F9	0.988	0.852	0.949	0.948	0.851	0.992	0.871

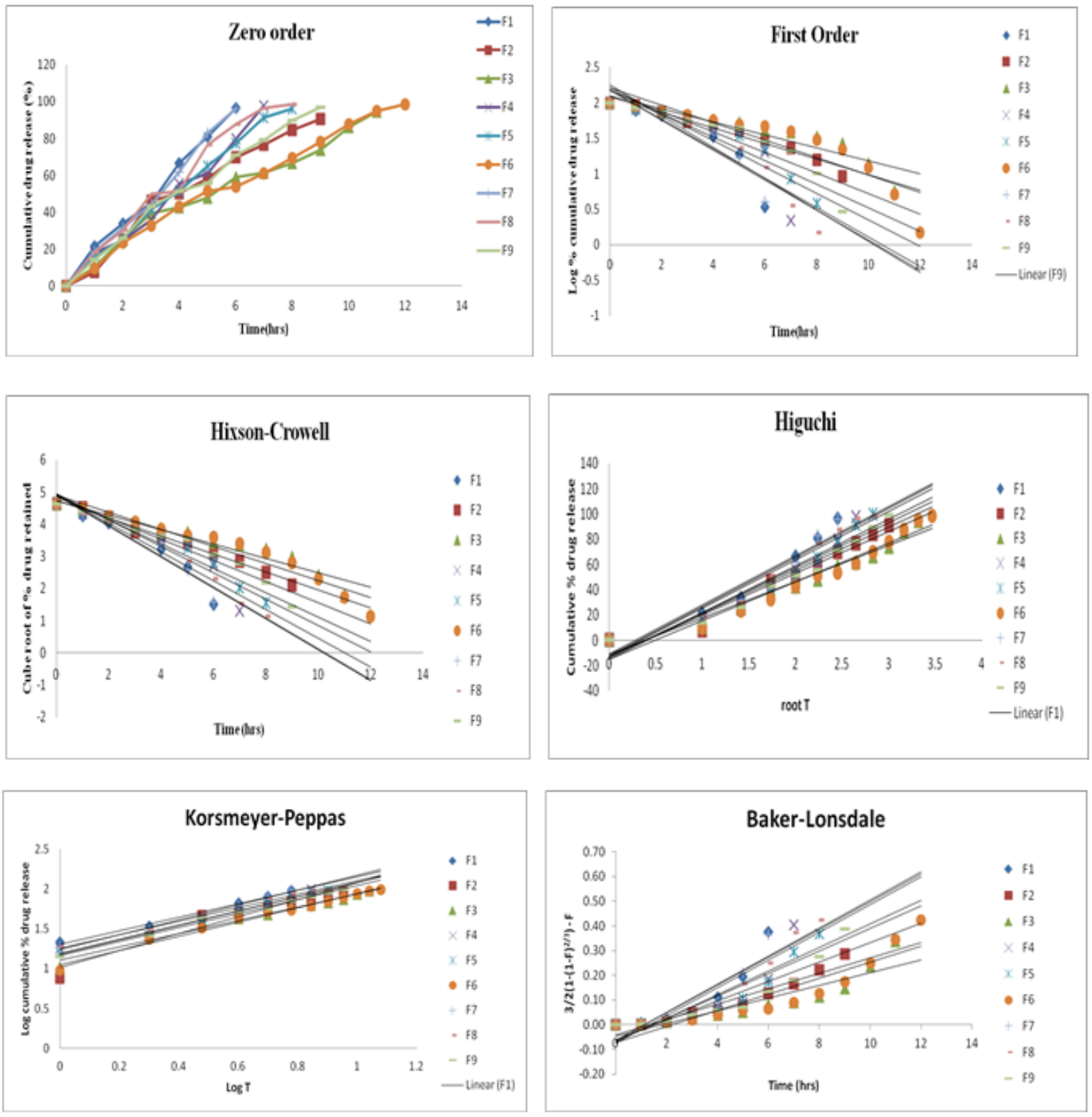

Figure 6: Release kinetics of F1 - F9

STABILITY STUDIES

Stability studies were carried out for formulations F6 as per ICH guidelines for 3 months in 40^0C/75% RH. Table 8 showed there was no significant change in appearance, drug content, microencapsulation efficiency and cumulative %drug release of the mucoadhesive microbeads of all formulations at the end of 3months. It was found that the formulations were stable throughout the study period.

Table 8: Stability studies data of best formulation

Sample timings (in months)	Physical appearance	Microencapsulation efficiency	Cumulative % drug release
F6 Formulation			
0	Off white	69.74	98.56
1	Off white	69.12	98.32
2	Off white	68.92	97.95
3	Off white	68.79	97.66

CONCLUSION

In the present study an attempt has made to formulate pantoprazole sodium as a micro particulate intestinal mucoadhesive dosage form and prolong its intestinal residence time, thus improving the oral bioavailability of drug. For the formulation, four biocompatible synthetic polymers sodium alginate, sodium carboxymethylcellulose, methylcellulose and hydroxylpropyl methylcellulose were chosen in varying proportions with the drug. Micro orifice-ionic gelation method was used to prepare mucoadhesive microbeads of pantoprazole sodium. Physico-chemical properties were highly influenced by the type of polymer and polymer concentration. According to the results of FTIR, there was no interaction between polymers and drug. In vitro dissolution profile of formulation F6 of showed a prolonged release in the intestine with greater mucoadhesion. Fitting of the curve in various release models showed that F6 followed zero order release kinetics. Thus F6 was considered as the best formulation among the formulated batches. Thus, it was concluded that ion tropic gelation technique is best suited for the preparation of mucoadhesive microcapsules of pantoprazole sodium for oral controlled release. The present study suggested that microencapsulation by ion tropic gelation is inexpensive compared with other techniques and also advantageous to prevent the drug related adverse effects of conventional dosage forms and maintain the sustained drug release over an extended period of time. This work can be extended for intestinal site specific drug release of drugs having low solubility, poor absorption or degradation in upper gastrointestinal tract and short biological half-life.

REFERENCES

[1]. Longer MA, Ching Seng Hung, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery III: Oral Delivery Chlorothiazide using a bio adhesive polymer. J.Pharm. Sci. 74, 1985, 406-411.

[2]. Smart, J. D. The basics and underlying mechanisms of mucoadhesion. *Adv.Drug Del. Rev***.** Nov v. 57(11), 2005, 1556-1568.

[3]. S. K. Prajapati, Purnima Tripathi, Udhumansha Ubaidulla, and Vikas Anand; Design and Development of Gliclazide Mucoadhesive Microcapsules: *In Vitro*and *In Vivo* Evaluation. AAPS PharmSciTech, M 9(1), 224-230.

[4]. Sumit C, Sibaji S, Sujit D, Formulation Development and Evaluation of Pantoprazole Enteric Coated Tablets, Int. J. Chem Tech Res. 1(3), 2009, 663-666.

[5]. Anita Patel, Khushbu Patel, Dr. Jayvadan Patel, Development and evaluation of mucoadhesive vaginal tablet of sertaconazole for vaginal candidiasis. International Journal of Pharm Tech Reseach. 3(4), 2011, 2175-2182.

[6]. Parmar H, Bakliwal S, Gujarathi N, Rane B, Pawar S. Different method of formulation and evaluation of mucoadhesive microsphere. International Journal of Applied Biology and Pharmaceutical Technology 1(3), 2010, 1157-1167.

[7]. Sharma D, Singh M, Kumar D. Novel paradigms in mucoadhesive drug delivery system. Int J Pharm Sci Res 3, 2012, 2455-2471.

[8]. Vimal kumar Yadav, A.B. Gupta, Raj kumar, Jaideep S. Yadav, Brajesh kumar; Mucoadhesive polymers: Means of improving the Mucoadhesive Properties of Drug delivery system. J Chem. Pharm. Res., 2(5), 2010, 418-432.

[9]. Gavin P. Andrews, Thomas P. Laverty, David S. Jones; Mucoadhesive polymeric platforms for controlled drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 71, 2009, 505–518.

[10]. Chowdary KPR, Srinivas Rao Y. Design and *in vitro* evaluation of mucoadhesive microcapsules of glipizide for oral controlled release: A technical note. AAPS of Ethyl cellulose coated nimesulide microcapsules: influence of solvent on microcapsules of nimesulide. Ind drugs 45(5), 2008, 370-375.

[11]. Balaji Maddiboyina, Abhay Asthana,Gyati Shilakari Asthana,Sima Singh, Ramya Krishna Nakkala, Omprakash Sunnapu, Niranjan Kotla. Formulation and Characterization of Polycarbophil Coated Mucoadhesive Microspheres of Repaglinide. J. Pharm. Sci. & Res. 7(11), 2015, 972-977.

[12]. Chun MK, Cho CS, Choi HK. Mucoadhesive microspheres prepared by interpolymer complexation and solvent diffusion method. Int J Pharm 288, 2005, 295-303.

[13]. Liua Z, Lua W, Qianb L, Zhanga X, Zenga P In vitro and in vivo studies on mucoadhesive microspheres of amoxicillin. J Control Release 102, 2005, 135-144.

[14]. B. Stephen Rathinaraj, Ch. Rajveer, S. Sudharshini, A. Kishore Reddy; Preparation and evaluation of mucoadhesive microcapsules of Nimodipine; International journal of research in pharmaceutical sciences 1(2), 2010, 219-224.

[15]. ICH Q1A (R2), Stability Testing Guidelines: Stability Testing of New Drug Substances And Products. The European Agency for the Evaluation of Medicinal Products, CPMP/ICH/2736/99: 2003, 4-20.