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Der Pharma Chemica, 2010, 2(5): 419-425
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Formulation and *in vitro* characterization of lansoprazole floating gastroretentive microspheres by modified non aqueous solvent evaporation method

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ABSTRACT

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT is to control the gastric residence time (GRT) using gastroretentive dosage forms. The aim of the present study is to prepare the floating microspheres of lansoprazole and sustain the drug release for longer time to over come the short half life of the drug. Floating microspheres with four different ratios of polymer and drug were formulated by modified non-aqueous solvent evaporation method and in vitro evaluations were performed. The drug polymer dispersions were pressurized under CO_2 gas, which upon release of the pressure cavities formed on the polymeric surface, which helps the microspheres to remain buoyant for prolonged time. Drug: polymer 1:4 ratio showed the %buoyancy 98.4%.It was observed that as the polymer concentration increases the buoyancy of microspheres also extended proportionally. SEM studies of microspheres showed good topology and the size was 280 μ. The cumulative % drug release in simulated gastric fluids after 10 hours was 82.0%-94.80%. Model fitting analysis revealed the release pattern was following Higuchi model for all formulations by obtaining maximum R^2 value.

Key words: Lansoprazole, Hydroxypropylmethylcellulose**,** Ethylcellulose, Floating microspheres, kinetic assessment.

INTRODUCTION

Drugs with short half-life and easily absorbed from the gastrointestinal tract are eliminating quickly from the blood circulation, so they require frequent dosing. To avoid this drawback, the oral sustained- controlled release formulations have been developed in an attempt to release the

drug slowly into the GIT and maintain an effective drug concentration in the serum for longer period of time. However, such oral drug delivery devices have a physiological limitation of gastric retention time (GRT)[1], variable and short gastric emptying time can result in the absorption zone leading to diminished efficacy of the administered dose[2,3]. To overcome these limitations, gastroretentive dosage forms are designed on the basis of the several approaches like, formulating low density dosage form that remain buoyant above gastric fluid(floating dosage form)[4,5] or high density dosage form that retain at the bottom of the stomach[6], imparting bioadhesion to the stomach mucosa[7], reducing motility of the GI tract by concomitant administration of drugs or pharmaceutical excipients[8], expanding the dosage form by swelling or unfolding to a large size which limits emptying of the dosage form through the pyloric sphincter[9], utilizing ion-exchange resin which adheres to mucosa[10], or using modified shape system[11].

Stomach Specific FDDS have a bulk density less than gastric fluids so they remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS'). The recommended hydrocolloids for floating formulations, cellulose ether polymers are most popular, especially hydroxypropylmethylcellulose (HPMC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy [12]. Before the 19th centuary, peptic ulcer disease appears to have been a rare disorder, with the1st cases of perforated peptic ulcers designed in the early 1800s. Incidence increased through the 1st half of the 20th centuary until the late 1960s. A breach in the mucosa of the alimentary tract, which extends through the muscularis mucosae into the submucosa or deeper is called as ulcer [13].

In the present study lansoprazole was selected as the payload model drug to treat the peptic ulcer. Lansoprazole is a proton pump inhibitor with a bioavailability of 80% or more and protein binding of 97%. Its metabolism is mainly by liver and excretion by renal and fecal. It acts by irreversibly blocking the (H^+,K^+)-ATPase enzyme system of the gastric parietal cell. Its half life is 1-1.5 hrs with poor absorption may be because of degradation and poor solubility [14]. The solubility and absorption can be improved with an increase in the gastric residence time and also by creating basic pH with incorporation of carbondioxide.

MATERIALS AND METHODS

Lansoprazole was a generous gift sample from Dr. Reddy's laboratories Ltd, Andhra Pradesh; Ethylcellulose was purchased from S.d. fine- chem limited, Mumbai; HPMC- Yarrow chem. Products, Mumbai; Magnesium stearate- NR chem, Mumbai ;Acetone –Universal laboratories private limited, Mumbai; Liquid paraffin- Accord labs, Andhra Pradesh; Span 80-Central drug house private limited, Mumbai; Petroleum ether –Accord labs, Andhra Pradesh;. All the chemicals and reagents used were of high quality analytical grade.

Floating microspheres of lansoprazole were prepared by modified non-aqueous solvent evaporation method. Polymers(HPMC&EC) were weighed and completely dissolved in acetone at the polymer ratio 1:1, but the total concentration of the polymer was kept constant (10% w/w in acetone). Magnesium stearate and drug were then added and stirred in a magnetic stirrer.

Flocculation was generally recognized when no magnesium stearate was added. Especially with 5% magnesium stearate, the microspheres were nearly uniform and free flowing with a good reproducibility. The drug polymer dispersions were pressurized under CO2 gas, which upon release of the pressure formed cavities on the polymeric surface. The porous drug polymer dispersions were then slowly introduced into 70 ml liquid paraffin previously added with 1 % Span 80, while stirring at 1000 rpm held by a mechanical stirrer equipped with a three-blade propeller at room temperature. The whole system was stirred for 3 hours to allow complete evaporation of acetone. The oil layer was decanted and microspheres were washed several times with petroleum ether (40-60º). The washed microspheres were dried in an oven at room temperature not exceeding 25 ºC. Standard conditions in all batches of optimized formulations were surfactant concentration – 1 % Span 80, quantity of magnesium stearate – 5% w/w, volume of processing medium – 70ml liquid paraffin, stirring speed – 1000 rpm, concentration of total polymer solution 10% w/w in acetone [15].

Table no. 1: Formula for preparation of floating microspheres of lansoprazole

Formulation Code	Drug: polymer	Magnesium stearate(%w/w)	Acetone(ml)	Span 80	Liquid paraffin(ml)
F1	1:1	5	10	1%	70
F2	1:2	5	10	1%	70
F3	1:3	5	10	1%	70
F4	1:4	5	10	1%	70

Characterization

The %yield of microspheres were found by the formula [16]

% Yield = (Actual weight of product / Total weight of excipient and drug) × 100

DEE (Drug Entrapment Efficiency/Encapsulation efficiency)

Microspheres equivalent to 100 mg of the drug were calculated spectrophotometrically at 278 nm by determining the drug concentration [17].

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Percentage buoyancy

Fifty milligrams of the floating microspheres were spread over the surface of USP XXIV dissolution apparatus (type II) filled with 900 ml of 0.1N Hcl containing 0.02% w/v Tween 20. The mixture was stirred at 100 rpm for 12 hrs. The layers of buoyant microspheres was pipetted and separated by filtration. Microspheres in the sinking particulate layer were collected, separated by filtration. Microspheres of both types were dried in a dessiccator and weighed. The percentage buoyancy was determined by the formula [18, 19].

$$\text{Buoyancy (\%)} = Wf / (Wf + Ws) \times 100$$

Where Wf is the weight of floating microspheres after drying,
Ws is the weight of settled microspheres.

Micromeritic properties
The microspheres were characterized by their micromeritic properties, such as particle size, true density, tapped density, compressibility index, hausner ratio, angle of repose.

Tapped density = [Mass of microspheres / Volume of microspheres after tapping] ×100

% Compressibility index = [1- V/Vo] ×100

V and Vo are the volumes of the sample after and before the standard tapping [20, 21].

Hausner ratio = Tapped density/Poured density

Angle of repose = Tan^{-1} h/r. Where h is the heap, r is the radius.

FTIR Spectral analysis
FTIR spectra of pure drug, and its physical mixture were obtained in KBr pellets at scanning speed between 4000-500cm^{-1} using Perkin-Elmer FTIR spectroscope.

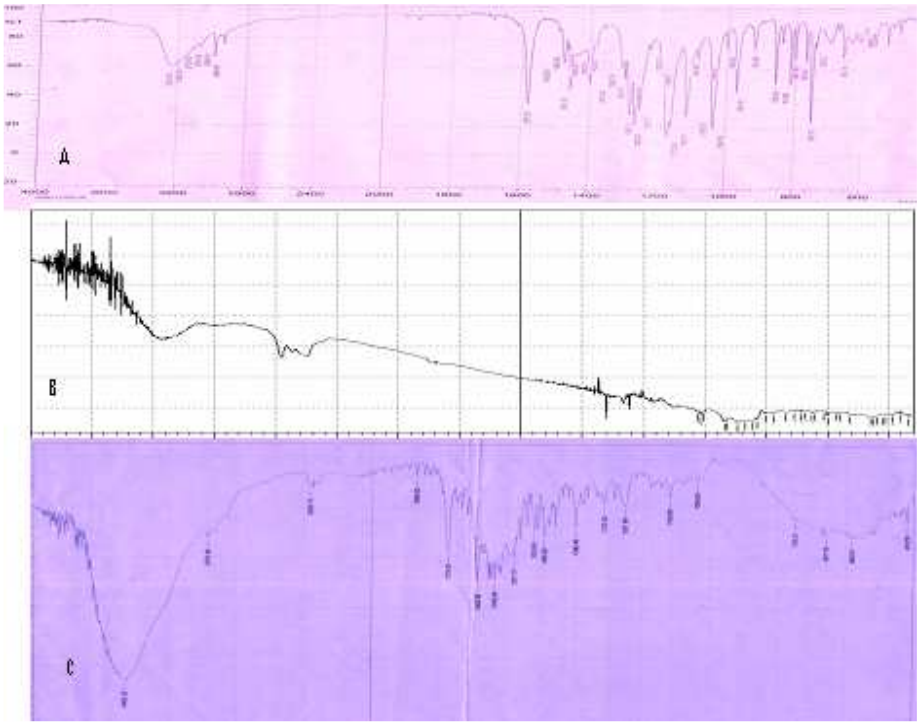

Fig.1. FTIR Spectral analysis of Lansoprazole alone (A) Physical mixture (B) and microspheres (C)

Shape and Surface characterization by SEM
Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 5.0KV during scanning [14].

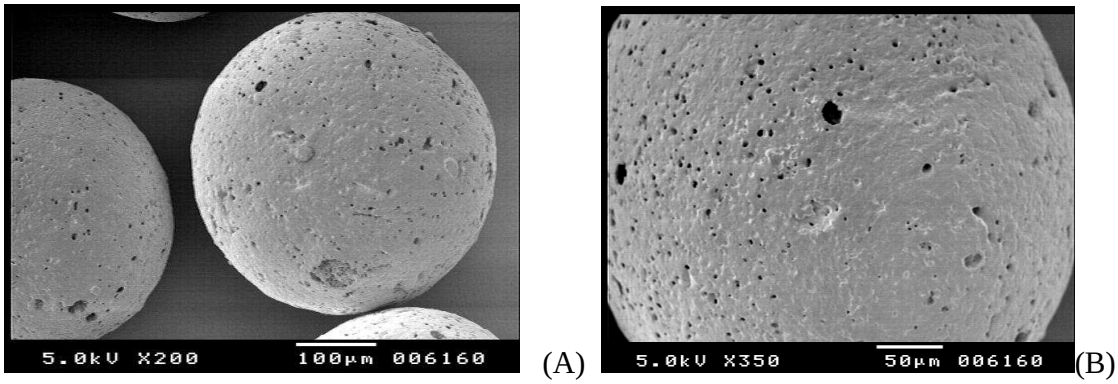

Fig.2 Surface morphological studies by SEM of selected formulation [F2] under lower and higher magnifications

In vitro drug release study
In vitro drug release studies were carried out for all formulations and pure drug by using USP type I dissolution test apparatus. Aliquots amount of 2ml was withdrawn at predetermined intervals and filtered. Equal volume of the dissolution medium was replaced to maintain sink condition (n=3). The required dilutions were made with 0.1N Hcl and the solutions were analyzed by spectrophotometer at 278 nm against suitable blank. From this, the %drug release was calculated and plotted against function of time to study the pattern of drug release [20].

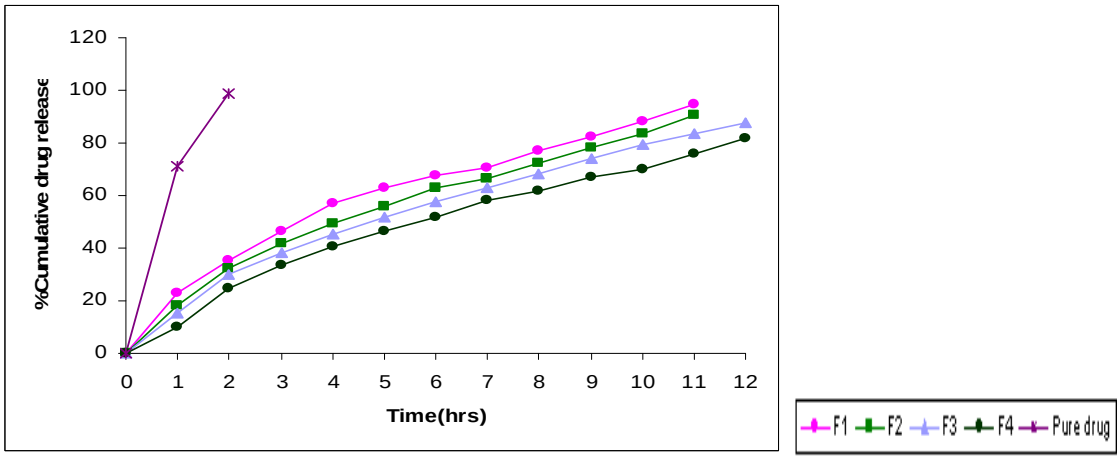

Fig 3: *In vitro* Drug release profile of Lansoprazole from formulations and pure drug

Kinetic Assessment
To study the nature and release pattern of the drug, model fitting curves were used.
Zero order model [22]: $M_t = M_c + k_0 t$, First order model [22]: $M_t = M_0 e^{-k_1 t}$
Higuchi model [23]: $M_t = M_0 + k_H t^{0.5}$, Korsmeyer- Peppas model[24]: $M_t / Ma = k_k t^n$

Where M_t is the amount of drug released in time t
M_0 is the initial amount of the drug
k_o is the zero order release constant
k_1 is the first order release constant
k_H is the Higuchi rate constant
k_k is the Korsmeyer- Peppas release constant and n is the release exponent that characterizes the mechanism of drug release.

RESULTS AND DISCUSSION

The percentage yields of different formulations were in the range of 88.33%-95.55%. Percentage drug entrapment efficiency of different formulations of floating microspheres was in the range of 88.82%-95.65%. F1 shows good entrapment efficiency. The percentage buoyancy was carried out to investigate the floating ability of the prepared microspheres. Floating ability of different formulations was found to be differed according to polymer ratio. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation because of porous cavities on the surface of the microspheres. Percentage buoyancy of the microspheres was in the range of 90.4%-98.4%. The F4 formulation shows good floating ability than other formulations. The compressibility index between 4.45%-9.086%. Hausner ratio between 1.04-1.09. All the formulations showed excellent flowability as expressed in terms of angle of repose in the range 30º -32º. From the results of FTIR studies it was found that lansoprazole is compatible with all the other ingredients (fig.2). The SEM photographs showed that the fabricated microspheres were spherical with a smooth surface and within each batch and particle size was 280µ (fig.1). Ethyl cellulose is low permeable and water insoluble polymer, HPMC is the swelling polymer which improves the buoyancy. The drug release from the floating microspheres matrix was controlled by the polymer. As the polymer content was increased, the release of drug was decreased significantly. The F1 shows good drug release than the other formulations. From *in vitro* drug release profile of all the formulations could be better expressed by Higuchi's model as they showed a good linearity with R^2 value of 0.9850-0.9964.The 'n' value for the Higuchi's model were between 0.5-0.8.It indicates that non-fickcian diffusion is the mechanism of drug release mechanism.

Table no. 2: Evaluation parameters of floating microspheres of lansoprazole

Formulation code	%yield	Drug content (mcg/mL)	Drug entrapment efficiency (%)	Percentage buoyancy	%Cummulative drug release	Micromeritic properties		
						Carr's index	Hausner ratio	Angle of repose
F1	88.33	44.10	95.65	90.4	94.8	4.45	1.04	32°75'
F2	90.90	46.68	93.37	93.2	90.5	2.68	1.02	30°34'
F3	92.57	45.70	91.40	95.6	87.5	8.03	1.08	31°46'
F4	95.55	47.82	88.82	98.4	82.0	9.08	1.09	32°54'

CONCLUSION

Fabricated floating microspheres showed excellent buoyancy, which is depending on the polymer ratio. Drug release was found to follow non-fickcian diffusion type. It may be concluded that the fabrication of lansoprazole microspheres by modified non-aqueous solvent evaporation method were promising in the treatment of peptic ulcer.

Acknowledgement
The authors express their heart felt gratitude to Nalanda College of pharmacy for providing information sources, library, internet and electronic facilities.

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