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Preparation and Evaluation of Lansoprazole Floating Micropellets

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A sustained release system for lansoprazole designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating micropellets by emulsion solvent diffusion technique. Floating micropellets of 1:1, 1:2 and 1:3 drug to carrier ratios were prepared using hydroxypropylmethylcellulose, methylcellulose and chitosan as a carrier. The yield of the micropellets was up to 82%. All floating micropellet formulations showed good flow properties expect formulation contain hydroxypropylmethylcellulose as coating material and packability. Drug loaded micropellets were found to float on simulated gastric fluid and simulated intestinal fluid for more than 12 h. The drug release studies were carried out in simulated gastric and intestinal fluid without enzymes at 37° for a period of 12 h. The Drug to chitosan ratio 1:1 showed good incorporation efficiency and high percentage *in vitro* release of lansoprazole from micropellets. The morphology and particle size analysis were analyzed by scanning electron microscopy and optical microscopy. The range of particle size is in between 327 to 431 μm. This method is simple, giving better yield and reproducible. The prepared lansoprazole floating micropellets can be used for sustained release in gastric media for more than 12 h, there by improving the oral bioavailability of lansoprazole by increasing gastric residence time because this helps to retained in stomach for a longer period.

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and having a short half-life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, a prominent site for the absorption of many drugs, will lead to lower bioavailability[1]. Therefore, prolonged gastric retention is important in achieving control over the gastric residence time (GRT) because this helps to retain the controlled release system in the stomach for a longer and predicted time[2].

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Several techniques[3-6] have been adopted for this purpose. However, the development of bioadhesive systems is one such method by which the controlled release system adheres to gastric mucosa to improve the GRT. There are some inherent problems associated with such systems since they will deliver a large amount of drug at a particular site of the GIT, there by leading to local irritation[3]. Another approach to improve the GRT is to incorporate the drug into a floating device that is less density than the gastric fluid. The traditional oral delivery system has certain disadvantages that needed to be overcome, such as the short retention time in the gastrointestinal tract (GI), protection of GI-labile drugs from the hostile intestine environment etc. Many attempts have been made in recent years to provide a dosage form with a longer transit time and therefore a more efficient absorption. These approaches include utilization of passage-delaying agents, use of large unit dosage forms, Compared to these approaches, the gastric floating drug

delivery systems (GFDDS) developed has provided several advantages. Furthermore, the buoyancy action provided by the GFDDS seems to offer a greater safety for clinical uses than some of the above- mentioned approaches. In fact, no adverse effects due to floating devices have been reported to date. The concept of floating microparticles can also be utilized to minimize the irritant effect of weakly acidic drugs on the stomach by avoiding direct contact with the mucosa and providing a mean of getting low dosage for prolonged period[7].

The development of oral controlled release drug delivery systems has been hindered by the fluctuation in gastric emptying time, the variation in pH, at different segments of the GIT and difficulty of localizing an oral delivery system in a selected region of the GIT[2]. A GFDDS[8-13] can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is being able to prolong the retention time of a dosage form in the GIT, thereby improving the oral bioavailability of the drug. Lansoprazole is selected as a model drug and it is a proton pump inhibitor, used in the treatment of ulcer and reflux oesophagits[14].

It has short plasma half life and elimination half-life. In the present study, the floating microparticle technique was adopted to achieve the floating multi-unit system for lansoprazole using three different polymers in different ratios. The characterization, *in vitro* degradation studies and *in vitro* release studies of drug from floating micropellets were evaluated.

MATERIALS AND METHODS

Lansoprazole was a gift sample from Cirex Pharmaceuticals, Hyderabad. Hydroxypropylmethylcellulose, Methylcellulose and Chitosan were obtained from Himedia Laboratories, Mumbai. Dichloromethane was commercially obtained from Cambrian Chemicals, Cambridge. Ethanol commercially available grade from Hayman Laboratories Ltd., England. Poly vinyl alcohol was obtained from Sigma Chemical Company, USA. All other chemicals used were of analytical grade.

Preparation of floating micropellets:

Lansoprazole micropellets were prepared by modification of the method described by Kawashima *et al.* (1992)[15]. The drug to carrier ratios of 1:1, 1:2 and 1:3 of different carriers such as hydroxypropylmethylcellulose, methylcellulose and chitosan were used for the preparation of nine formulations of micropellets. The composition of each formulation is listed in Table 1. Lansoprazole and carrier were dissolved in 20 ml of mixture of ethanol and dichloromethane of 1:1 ratio. The above mixture was dropped into 200 ml of 1 % w/v of poly vinyl alcohol solution with stirring at 500 rpm for one hour. The formed floating micropellets were filtered, washed with water and dried at room temperature in a desiccator. The floating micropellets were sieved and fractions were collected corresponding to particle size.

TABLE 1: FORMULATION CODE, COMPOSITION, YIELD AND DRUG ENTRAPMENT IN FLOATING MICROPELLETS OF LANSOPRAZOLE

Formulation code	Drug to carrier ratio	Percentage yield*	Drug entrapment (% w/w)
H1	1:1	84.52	92.4
H2	1:2	73.91	62.6
H3	1:3	74.17	70.5
M1	1:1	82.73	83.2
M2	1:2	70.44	72.1
M3	1:3	67.53	79.3
C1	1:1	85.59	93.1
C2	1:2	72.19	91.3
C3	1:3	66.23	93.2

Average of three preparations. Floating micropellet formulations of lansoprazole with hydroxypropylmethylcellulose (H), methylcellulose (M) and chitosan (C).

Analysis of Micropellets:

UV spectrophotometric method was employed to verify the presence of drug in the micropellets. A study was performed in the percentage yield of micropellets when drug, polymer ratios were changed. Drug was extracted from the micropellets with 0.1N HCl and absorbance was measured using UV/Vis spectrophotometer at 410 nm. The amount of lansoprazole in the micropellets was estimated with the help of standard graph.

Determination of the shape and size of the micropellets:

The surface morphology and the internal texture of lansoprazole micropellets were observed by a scanning electron microscope[16] as shown in the fig.1. The mean particle size and size distribution were carried out by optical microscopy under 200 X magnification. An average of about 200 particles were counted and determined.

Micromeritic studies:

The prepared micropellets are characterized by their micromeritic properties, such as particle size, tapped density, compressibility index, true density and flow property[17]. The results are shown in Table 2.

Stability Studies:

The prepared micropellets were placed in screw capped glass containers and stored at ambient humidity conditions, at room temperatures (27±2°), oven temperature (42±2°) and in refrigerator (5-8°) for a period of 45 days. The samples were assayed for drug content at regular intervals of two weeks[18].

Fig. 1: Scanning electron microscopy (SEM) of lansoprazole floating micropellets

Figure showing morphology of lansoprazole floating micropellets containing chitosan in the drug and coat ratio of 1:1(C_1).

TABLE 2: MICROMERITIC PROPERTIES OF FLOATING MICROPELLETS OF LANSOPRAZOLE

Formulation code	Average particle size (μm)	Angle of repose (ϕ)	Percentage compressibility index (I)	Tapped density (g/cm³)	True density (g/cm³)
H1	431	59°19'	15.2	0.186	0.863
H2	428	54°82'	12.5	0.184	0.851
H3	413	56°13'	13.1	0.185	0.849
M1	372	36°71'	15.8	0.171	0.746
M2	355	31°82'	10.2	0.169	0.732
M3	327	29°74'	9.3	0.173	0.717
C1	359	32°81'	14.6	0.163	0.910
C2	331	29°75'	11.9	0.158	0.915
C3	329	25°94'	8.1	0.160	0.918

All the values are average of three preparations. lansoprazole floating micropellet formulations H_1, H_2 and H_3 are drug and hydroxypropylmethylcellulose ratio of 1:1, 1:2 and 1:3. M_1, M_2 and M_3 are drug and methylcellulose ratio of 1:1, 1:2 and 1:3. C_1, C_2 and C_3 are drug and Chitosan ratio of 1:1, 1:2 and 1:3.

In vitro Drug release:

In vitro release profile of lansoprazole from micropellets was determined in pH 1.2 and in pH 6.8 for the period of 12 h using the rotating basket method specified in USP XXVII at 100 rpm. Micropellets equivalent to 50 mg of drug were suspended in the dissolution medium and the medium was maintained at 37±2°. Five milliliters of samples were withdrawn periodically at intervals of one hour and same volume of fresh medium was replaced into the beaker. The concentration of drug release at different time intervals was then determined by measuring the absorbance using UV/Vis spectrophotometer at 410 nm and with the help of standard graph.

RESULTS AND DISCUSSION

Nine formulations of lansoprazole loaded micropellets were prepared using hydroxypropylmethylcellulose, methyl cellulose and chitosan as carriers by emulsion-solvent diffusion technique. Each carrier, three drugs to carrier ratios 1:1, 1:2 and 1:3 were prepared. Among the three different polymers and three drugs to carrier ratios, drug to chitosan 1:1 ratio showed maximum percentage yield of 85% and drug to chitosan 1:3 ratio showed highest drug entrapment of 93% w/w as shown in the Table 1. The particle size of micropellets was determined by optical microscopy and the size of the micropellets was found to be ranging between 327-431 μm. The formulations were free

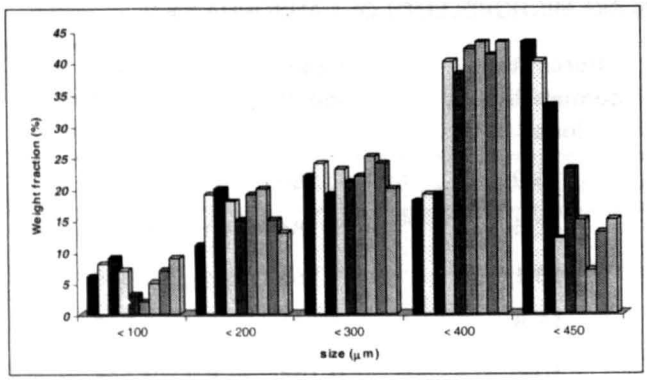

Fig. 2: Particle size distribution of lansoprazole floating micropellets

Particle size distribution of various lansoprazole floating micropellets formulation in the drug and HPMC ratio of 1:1, 1:2 and 1:3 such as H_1(■), H_2(□) and H_3(■), drug and methylcellulose ratio of 1:1, 1:2 and 1:3 such as M_1 (▨), M_2 (▨) and M_3 (▨), drug and chitosan ratio of 1:1, 1:2 and 1:3 such as C_1(▨), C_2 (▨) and C_3 (▨).

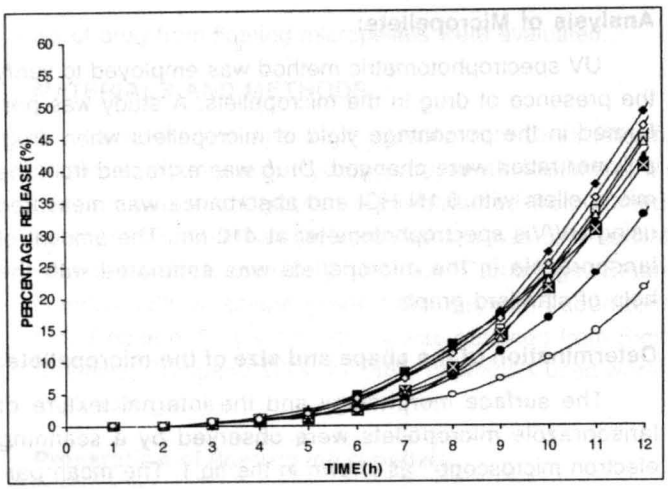

Fig. 3: *In vitro* release profile of floating micropellets of lansoprazole in pH 1.2

***In vitro* release profiles of lansoprazole from floating micropellets formulation in the drug and HPMC ratio of 1:1, 1:2 and 1:3 such as, H_1 (-◆-), H_2 (-□-) and H_3 (-▲-), drug and methylcellulose ratio of 1:1, 1:2 and 1:3 such as, M_1 (-□-), M_2 (-□-) and M_3 (-□-), drug and chitosan ratio of 1:1, 1:2 and 1:3 such as C_1 (-◇-), C_2 (-•-) and C_3 (-□-) were studied in simulated gastric fluid pH 1.2, samples drawn at regular time intervals and lansoprazole content was measured at 410 nm.**

flowing in nature except H_1, H_2, H_3 formulations in which hydroxypropylmethylcellulose is used as a coating material. The particle size distributions of micropellets were determined by optical microscopy under 200X magnification as shown in fig. 2.

The entrapment efficiency of nine formulations of micropellets were determined and is shown in Table 1. In general, the incorporation efficiency of micropellets prepared with chitosan was higher than those prepared with Hydroxypropylmethylcellulose and methylcellulose. Micromeritic studies of all formulations were performed and reported in Table 2. The surface morphology and internal texture of micropellets were determined by scanning electron microscope (SEM) as shown in fig. 1.

In vitro release studies of lansoprazole floating micropellets were carried out in pH 1.2 (0.1N Hydrochloric acid) and pH 6.8 (Phosphate buffer) for a maximum period of 12 h, the results are shown in fig. 3 and fig. 4. The release of lansoprazole from formulation containing drug to hydroxypropylmethylcellulose ratio of 1:3 and drug to chitosan ratio of 1:1 showed highest release of 66% and

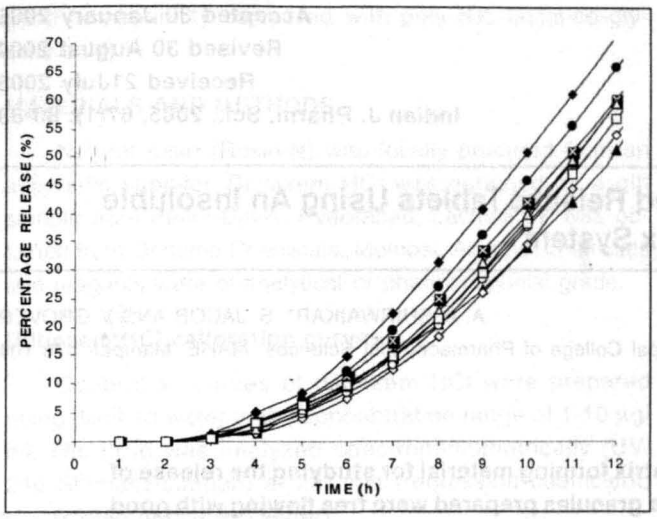

Fig. 4: *In vitro* release profiles of floating micropellets of lansoprazole in pH 6.8

***In vitro* release profiles of lansoprazole from floating micropellets formulation in the drug and HPMC ratio of 1:1, 1:2 and 1:3 such as H_1 (-◆-), H_2 (-□-) and H_3 (-▲-), drug and methylcellulose ratio of 1:1, 1:2 and 1:3 such as M_1 (-□-), M_2 (-◇-) and M_3 (-□-), drug and chitosan ratio of 1:1, 1:2 and 1:3 such as C_1 (-•-), C_2 (-□-) and C_3 (-▫-) were studied in phosphate buffer pH 6.8, samples drawn at regular time intervals and lansoprazole content was measured at 410 nm.**

72% w/w, respectively in simulated intestinal medium (pH 6.8).

To assess the floating properties, the prepared micropellets were placed in 0.1N hydrochloric acid containing 0.02%v/v Tween80 surfactant to simulate gastric conditions. Despite the solution being stirred for more than 12 h, the micropellets still floated, indicating the micropellets exhibit an excellent buoyancy effect.

The present study reports the development of drug-loaded floating micropellets of lansoprazole using polymers such as hydroxypropylmethylcellulose, methylcellulose and chitosan. The micropellets produced using chitosan exhibited better encapsulation efficiencies, micromeritic properties and *in vitro* release profile.

The microspheres, having lower densities, exhibited buoyancy and may be retained in the gastric environment for more than 12 h. This helps to improve the bioavailability of basic drugs like lansoprazole. The present studies demonstrated that the prepared micropellets floated more than 12 h. From the above data, it may be concluded that drug-loaded micropellets are a suitable delivery system for lansoprazole, and may be used for effective management of ulcer and reflux oseophagitis.

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