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Original Article

Preparation and *in-vitro* evaluation of microballoon drug delivery system of Lansoprazole

Sushil K. Raipuria *, Prithu Pathak, A.K. Pathak

[a] *Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India.*

Corresponding Author. Tel: +91 7389977096, *E-mail address:* sushil2004@gmail.com

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ABSTRACT

In present study an attempt was made to prepare hollow microspheres (microballoons) of Lansoprazole by emulsion solvent diffusion technique for sustained delivery by using polymers like Ethyl cellulose and Carbopol 934 in order to extend the drug release for about 12 h in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. The particle size was determined by optical micrometer and average particle size was found to be in range of 189.5± 2.63 to 124.33± 2.14. Formulation F2 containing Ethyl cellulose and Carbopol 934 polymer blend showed the best floating ability (97.5%) as compared with other formulations. From Scanning Electron Microscopy (SEM) it was observed that, microballoons were found to be spherical in shape with smooth surface texture with a hollow space within. Among all formulations, F2 showed appropriate balance between buoyancy and drug release rate of 88.65% in 12 h, which is considered as the best formulation.

1. INTRODUCTION

Microballoons have been widely accepted as a means to achieve oral release. The microballoons require a polymeric substance as a coat material or carrier [1-3]. A number of different substances both biodegradable as well as non- biodegradable have been investigated for the preparation of micro particles. It is only reduces the dose of the drug, reaching to the effective biological sites rapidly but also results in reduced in toxicity of the targeting [4,5]. But in the past few years, pharmacists have been focused their research in colloidal drug delivery system/colloidal carriers, like liposomes, microspheres and nanoparticles as a targeting carriers, which has given selective targeting. The main aim of the present work is to develop the lansoprazole micro particles by using ethyl cellulose/carbopol 934 as a polymer for prolonged, relatively constant effective level of lansoprazole and improve patient compliance [6-8]. The purpose of the present study is to develop an optimized gastric floating drug delivery system to prolong the gastric residence time after oral administration, at particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Floating dosage form (microballoons) containing Lansoprazole as drug is designed for the treatment of gastric ulcer [9, 10].

2. EXPERIMENTAL

Lansoprazole was obtained as a gift from Torrent Pharma Gujarat. Ethyl cellulose, carbopol 934. dichloromethane, ethanol and polyvinyl alcohol were purchased from Central Drug House Delhi, India. Rest all other chemicals were of analytical and HPLC grade.

2.1 Preparation of floating microballoons

Floating microballoons were prepared by the emulsion solvent diffusion method. Lansoprazole, ethyl cellulose and carbopol 934 were dissolved in a mixture of ethanol and dichloromethane (DCM). The resulting solution was added slowly to stirred 250 mL of aqueous solution of 0.50% (w/v) PVA at room temperature. The stirring was done for 2 h at 1000-1200 rpm by mechanical stirrer equipped with four bladed propellers. With continuous stirring solvent was allowed to evaporate. After evaporation of solvent, microballoons were filtered by

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Whatman filter paper collected washed with water and dried at room temperature in a desiccator for 24 h [11-16].

Table 1: Formulation of the prepared floating microballoons

Batch Code	Drug : polymer ratio	Solvent ratio (Ethanol : DCM)	Surfactant (PVA) 0.50% w/v in 250 ml aqueous solution
FM-1	1:1:1	1:1	0.50%
FM-2	1:1:2	1:1	0.50%
FM-3	1:1:3	1:1	0.50%
FM-4	1:2:1	1:1	0.50%
FM-5	1:2:2	1:1	0.50%

2.2 Evaluation parameters

2.2.1 Particle size and size distribution

Floating microballoons were studied microscopically for their size and size distribution using calibrated ocular micrometer. Least count of the ocular micrometer was calculated as 143.04µm. Around 50 particles from each formulation were observed and the data for each formulation were recorded.

2.2.2 Drug content and entrapment efficiency

The drug content was measured by extracting 78 mg of microballoons using 0.1 N HCl with agitation for 8 hrs. The dispersion was sonicated for 15 mins and filtered. After appropriate dilution with 0.1N HCl, absorbance was taken in UV spectrophotometer at λ_{max} **298 nm**. The % drug content was calculated from the formula:

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in floating microballoons}}{\text{Weight of drug in floating microballoons}} \times 100$$

Drug entrapment efficiency represents the proportion of the drug, which has been incorporated into the microballoons. It was calculated using the formula:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Entrapment efficiency}}{\text{Entrapment efficiency}} \times 100$$

2.2.3 *In-vitro* buoyancy

Floating microballoons to 78 mg calculated on the basis of single dose were dispersed in 900 ml of 0.1 N HCl solution (pH 1.2) containing simulated gastric fluid at 37°C. The mixture was stirred with a paddle at 100 rpm and after 12 hrs, the layer of buoyant microballoons (W_f) was pipetted out and separated by filtration simultaneously sinking microballoons (W_f) was also separated. Both microballoons types were dried at 40°C overnight. Weight of each were measured and buoyancy was determined.

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

W_f = weights of the floating microballoons

Ws = weights of the settled microballoons

2.2.4 Yield of floating microballoons

The prepared floating microballoons were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microballoons.

$$\text{\% Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipient and drug}} \times 100$$

2.2.5 Morphological characterization

The floating microballoons were examined by optical and scanning electron microscopy (Zeiss Germany). Floating microballoons were suspended in water and then a drop having microballoons was placed on a glass slide, covered with a cover slip and viewed under the optical microscope (Leica–Biomed, Germany) to examine their shape.

2.2.6 *In-vitro* drug release study in simulated gastrointestinal fluid

Best formulation of floating microballoons was evaluated on the basis of above tests were selected for the *in-vitro* drug release study by the paddle type dissolution apparatus specified in USP XXIII. 78mg of Lansoprazole loaded floating microballoons was weighed accurately and gently spread over the surface of 900 ml of dissolution medium. The content was rotated and thermostatically controlled at 37±0.5°C condition was prevailed during the drug dissolution. The release was determined in dissolution medium of pH 1.2. Aliquot was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were analyzed spectrophotometrically.

3. RESULTS AND DISCUSSION

The microballoons of Lansoprazole were prepared by solvent diffusion evaporation method. The effect of formulation variables e.g. drug concentration, solvent ratio of internal phase (ethanol/dichloromethane), surfactant concentration and process variables e.g. stirring speed were studied in order to optimize the formulation. The results suggested that these variables influence the shape, size and size distribution, total drug loading efficiency and *in-vitro* drug release. Hence, these parameters were optimized to prepare microballoons of small size with narrow size distribution, good drug loading efficiency, good release at the gastrointestinal pH and good surface morphology. As the formulation code **F2S2R3D2 Drug** and polymer weight was initial and optimal according to the matrix which encapsulated the drug.

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Table 2: Effect of polymer ratio on particle size of floating microballoons

Batch Code	Drug and Polymer ratio [Lansoprazole Ethyl cellulose: Carbopol)	Particle size (µm)
F1	1:1:1	89.09
F2	1:1:2	143.04
F3	1:1:3	167.64
F4	1:2:1	194.26
F5	1:2:2	271.06

Formulation F1 effect of polymer concentration was found to influence the particle size by decreasing concentration of polymer. It was observed that size of microballoons were **89.9 (**µm**)** found to be decreased and irregularly distributed. Formulation **F3, F4, F5** effect of polymer concentration increasing it was obtained particle size **167.64, 194.26, 271.06 (**µm**)** increasing and aggregating.

3.1 Optimization of formulation and process variable

Various formulation and process variables i.e. drug concentration, surfactant concentration and stirring speed which could affect the preparation and stability of floating microballoons that were further identified and studied by optimization which was done on the basis of particle size.

3.2 Optimization of polymer mixture concentration

For optimization of polymer mixture concentration, different floating microballoons formulations were prepared by taking different polymer concentration and keeping all the other parameters constant. The effect of ratio of polymer on the particle size was reported.

Table 3. Effect of polymer ratio on particle size of floating microballoons

Batch Code	Drug and polymer ratio [Lansoprazole: Ethyl cellulose: Carbopole 934	Particle size (µm)
F1	1:1:1	89.09
F2	1:1:2	143.04
F3	1:1:3	167.64
F4	1:2:1	194.26
F5	1:2:2	271.06

3.3 Optimization of surfactant concentration

For optimization of surfactant concentrations, different formulation was prepared were analyzed by keeping the other parameters constant. Formulations having different surfactant concentration were optimized on the basis of particle size and surface morphology through optical micrometer.

Table 4. Effect of surfactant concentration on particle size of floating microballoons

Batch code	Surfactant conc. PVA (%w/v)	Particle size (nm)	Surface morphology
F2S1	0.25	164.67	Rough surface
F2S2	0.50	143.21	Uniform surface
F2S3	0.75	127.65	Irregular, rough

3.4 Optimization of stirring speed

Stirring speed of the stirrer was varied from 300 to 500 rpm for floating microballoons preparation having formulation code F2S2 using the optimized formulation parameters which was previously optimized for surfactant concentration.

Table 5. Effect of stirring speed on particle size of floating microballoons

Formulation code	Speed (nm)	Particle size (µm)
F2S2R1	300	189.96
F2S2R2	350	147.64
F2S2R3	400	143.02

3.5 Optimization of drug polymer concentration

The optimization of drug and polymer concentration of the floating microballoons was done by preparing floating microballoons formulations with varying the percentage of drug and polymer concentration, while keeping other parameters constant. Optimization was done on the basis of particle size. The observations are recorded.

Table 6. Effect of drug polymer concentration on particle size of floating microballoons

Formulation code	Drug and polymer concentration	Particle size (µm)
F2S2R3D1	1:1:1	89.09
F2S2R3D2	**1:1:2**	**143.04**
F2S2R3D3	1:1:3	167.64
F2S2R3D4	1:2:1	194.26
F2S2R3D5	1:2:2	271.06

Table 7. Optimized formulation on the basis of formulation & process variables

S. No.	Optimized parameter	Formulation	Final code for
1.	Polymer ratio (1:2)	**F2**	**F2S2R3D2**
2.	Surfactant concentration (0.50%)	**F2S2**	
3.	Stirring speed (400 rpm)	**F2S2R3**	
4.	Drug polymer concentration(1:1:2)	**F2S2R3D2**	

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The percentage yield of microballoons was found to be **97.5%** which shows good efficiency to get good productivity of microballoons. The entrapment efficiency of the optimized formulation was found to be **80.0%** and similarly In *vitro* buoyancy was found to be **67.5 % (Table 8).**

Table 8. Parameter of evaluation of microballoons

Formulation code	% Yield	Entrapment efficiency %	% Buoyancy
F2S2R3D2	97.5%	80.0%	67.5%

3.6 Scanning Electron Microscopy (SEM)

The surface and particle morphology (SEM) confirmed the shape of microballoons. The particle size was found to be less than **300** µm as shown in Fig. **1.32kx, 20.kx** and **72.16kx** by magnifying it acts **300kX.** Similarly surface morphology was found be plain and spherical.

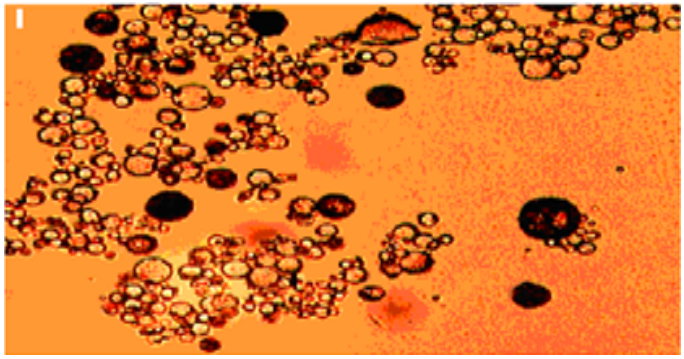

Fig. 1. Morphology of Microballoons (Leica –Biomed, Germany)

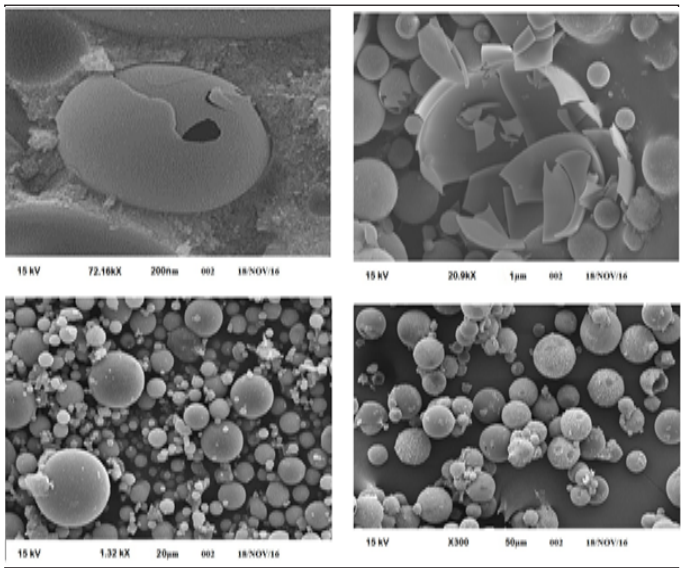

Fig. 2. Scanning electron microscopic image

3.7 *In-vitro* drug release study

The *in-vitro* drug release study performed in 1.2pH, confirmed that floating microballoons resulted in sustained and prolonged release of drug in the GIT fluids and they release up to **88.65%** in 12 hrs.

Table 9. Percentage drug release of formulation

Time (hours)	% Drug Release
0	0
1	10.8
2	17.44
3	29.74
4	37.08
5	42.3
6	48.6
7	54.36
8	62.86
9	69.3
10	78.6
11	82.8
12	88.65

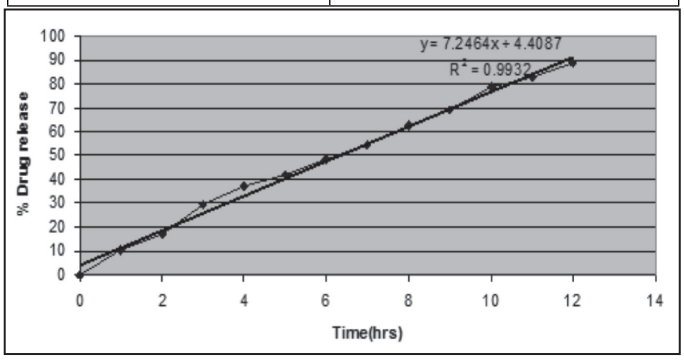

Fig. 3. Percentage drug release

3.8 Relaese kinetics

The release kinetic was studies by using various kinetics model such as zero order, first order, Higuchi model, Korsmeyer Peppas release kinetics.

Table 10. Kinetics of drug release

Time	Log time	Square root of time	% CD release	% CD retained	Log % CD release	Log % CD retained
1	0	1	10.8	89.2	1.033	1.950
2	0.301	1.414	17.44	82.56	1.241	1.911
3	0.477	1.732	29.74	70.26	1.473	1.846
4	0.602	2	37.08	62.92	1.569	1.798
5	0.699	2.236	42.3	57.7	1.626	1.758
6	0.778	2.449	48.6	51.4	1.686	1.710
7	0.845	2.646	54.36	45.64	1.735	1.659
8	0.903	2.828	62.86	37.14	1.798	1.572
9	0.954	3	69.3	30.7	1.840	1.487
10	1	3.162	78.6	21.4	1.895	1.330
11	1.041	3.316	82.8	17.2	1.918	1.235
12	1.079	3.464	88.65	11.35	1.947	1.054

*% CD = Cumulative Drug Release

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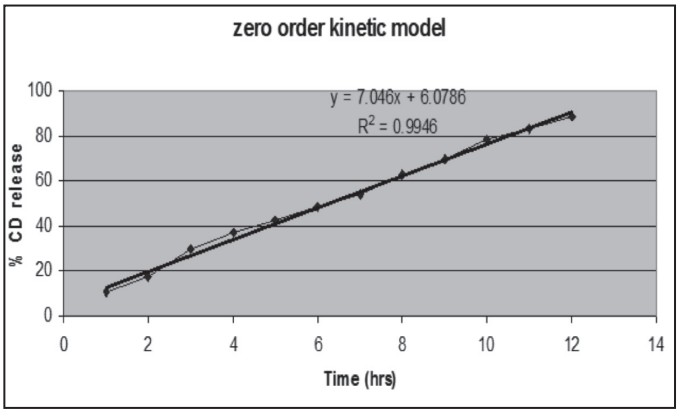

Fig. 4. Zero order kinetic of drug release from Formulation F2

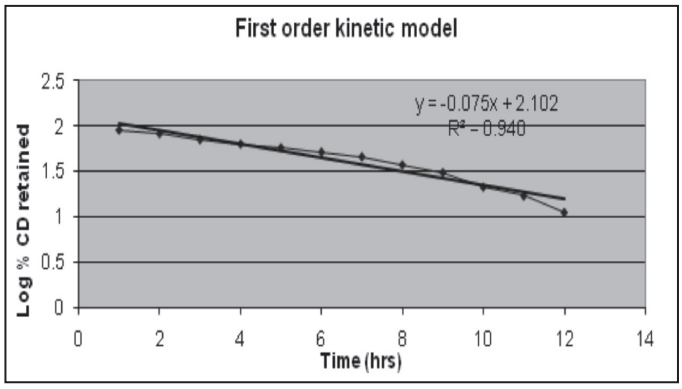

Fig. 5. First order kinetic of drug release from Formulation F2

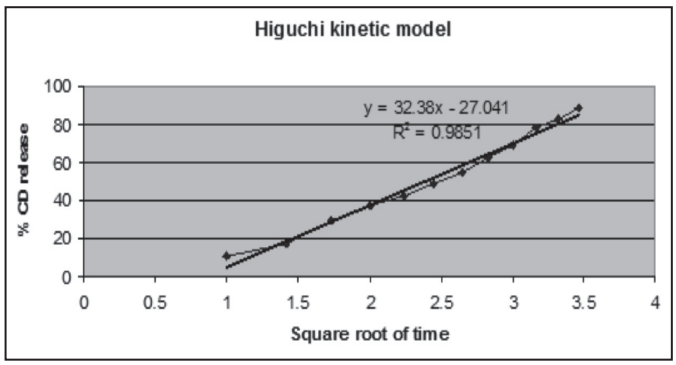

Fig. 6. Higuchi kinetic of drug release from Formulation F2

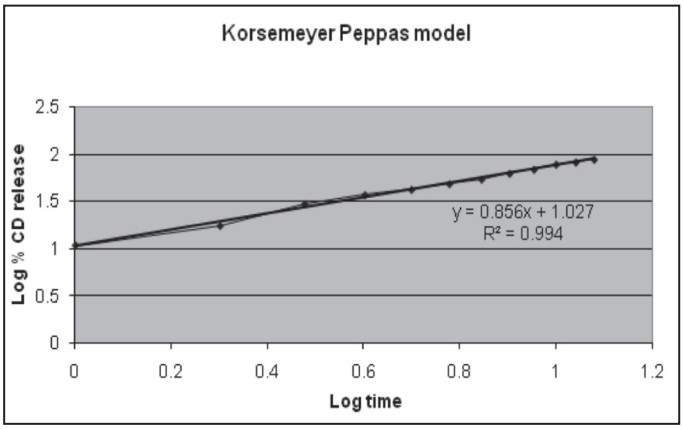

Fig. 7. Korsmeyer Peppas of drug release from Formulation F2

Table 11. Regression coefficient values of different release order kinetic

S. No.	Release order kinetic model	Regression coefficient R2
1.	Zero order kinetic Model	0.9946
2.	First order kinetic Model	0.9409
3.	Higuchi kinetic Model	0.9851
4.	**Korsmeyer Peppas kinetic Model**	**0.9948**

As per data of regression coefficient, it was interpreted that release kinetics of drug from formulation F2 was according to Korsmeyer Peppas kinetic model.

Peppas model equation given by % R = Kt_n or log % release = Log k + Log t Where R = drug release, K = constant, n = slope and t = time.

As per equation obtained during the Korsmeyer Peppas release kinetic

$$y = 0.8561x + 1.0276$$

Where y = drug release, x = constant and n = slope which is = 1.01.

4. CONCLUSION

Microballoons of Lansoprazole was successfully prepared by solvent diffusion evaporation method. These prepared microballoons shows good size, surface morphology that is smooth surface which is always an important factor to check the stability and strength of microstructure formulation. The *in-vitro* release data of floating microballoons of Lansoprazole exhibited good buoyancy up to 12 hrs and released the drug and desired fashion for prolong duration of time. It can be easily concluded from above mentioned parameters that floating microballoons of Lansoprazole are most acceptable and premising formulation to get better drug release and good therapeutic effect.

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