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Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF FLOATING MICROSPHERES OF ANTIULCER DRUG USING NOVEL SYNTHETIC AND NATURAL POLYMERS

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Abstract:

The aim of this work was to develop natural and synthetic polymer based microspheres of Dexlansoprazole in different drug-to-polymer ratios to avoid the dose frequency of drug. HPMC, EC, and Guar gum microspheres have outstanding floating capabilities, according to in vivo and in vitro buoyancy experiments. The result indicates that with an increase in the concentration of polymers, HPMC, EC and Guar gum slight decrease the floating time. Formulations F4 of prepared microspheres were found to be the best compare to other formulation. The Floating Lag Time (Sec.) lag time of formulation F4 was also found less (52±6), compare to other formulation. The drug release from the floating microspheres was sufficiently sustained, and zero order drug diffusion was verified. Dexlansoprazole floating microspheres may thus offer a practical dose form for providing the optimum results in terms of flow, release, and floating characteristics. Further research is required to determine whether they have the ability to increase human Dexlansoprazole bioavailability.

Key words: *Dexlansoprazole, Microspheres, Natural and synthetic polymer, Formulation, Evaluation.*

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INTRODUCTION:

Floating oral drug delivery system (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration [1].

Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation [2].

Microspheres are defined as “Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles” (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations³. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation.

In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single-unit dosage forms such as non-disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the

polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided [4].

Dexlansoprazole is used to treat gastroesophageal reflux disease. Efficacy is similar to that of other Proton Pump Inhibitors (PPIs). It is taken orally. Dexlansoprazole is used to treat and maintain healing of erosive esophagitis and to treat stomach acid associated with Gastroesophageal Reflux Disease (GERD). It lasts longer than lansoprazole, with which it is chemically related, and should be taken less frequently. There is no concrete evidence that it works better than other PPIs. Dexlansoprazole permanently binds to the proton pump and blocks it, preventing the formation of gastric acid. In the treatment of healing of Erosive Esophagitis (EE) 60 mg orally once a day Duration of treatment Up to 8 weeks, In the treatment of stomach acid associated with symptomatic Gastroesophageal Reflux Disease (GERD) 30 mg orally one once a day Duration of therapy 4 weeks Use.

The low bioavailability (40-45%) and the short biological half-life (2.5- 4.0 hours) of Dexlansoprazole after oral administration favor the development of a prolonged release formulation. The aim of this work was to develop natural (i.e. chitosan, or sodium alginate) and synthetic (i.e. HPMC, Eudragit L 100, Eudragit RSPO and RLPO) polymerbased microspheres of Dexlansoprazole in different drug-to-polymer ratios to avoid the dose frequency of drug.

MATERIAL AND METHODS:**Preparation of floating microsphere of Dexlansoprazole:**

Floating microspheres loaded with Dexlansoprazole were prepared using solvent-evaporation method using HPMC, EC and Guar gum in different ratio table 1. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at $27 \pm 2^\circ\text{C}$. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at $40 \pm 2^\circ\text{C}$ and stored in desiccator [5].

Table 7.1: Formulations of the floating microspheres prepared

S. No.	Formulation Code	Dexlansoprazole (mg)	HPMC (mg)	EC (mg)	Guar gum (mg)
1.	F1	75	100	25	-
2.	F2	75	100	50	-
3.	F3	75	100	75	-
4.	F4	75	150	25	10
5.	F5	75	150	50	20
6.	F6	75	150	75	30

Evaluation of microspheres:**Percentage Yield**

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres [6].

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

Drug Entrapment:

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed⁷. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior:

Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer⁸. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Measurement of mean particle size:

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement [9].

Determination of zeta potential:

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate [10].

Shape and surface characterization of microspheres by scanning electron microscopy (SEM):

From the formulated batches of microspheres, formulations (F3) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000 [11]. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

In-vitro release studies:

The *in vitro* drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly [11]. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 282nm to determine the concentration of drug present in the dissolution medium.

RESULTS AND DISCUSSION:

Floating microspheres loaded with Dexamethasone were prepared using solvent-evaporation method using HPMC, EC and Guar gum in different ratio polymers. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane.

Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 65.52 ± 0.25 – $75.56 \pm 0.15\%$. The maximum percentage yield was found in formulation F4, 75.56 ± 0.15 as compare to all formulation. The drug entrapment of all formulations was determined spectrophotometrically. The drug entrapment efficiencies of different formulations were in range of 63.25 ± 0.45 - $73.32 \pm 0.15\%$ w/w. Results demonstrated that increase in concentration of polymer increased the entrapment of the drug. The

drug entrapment efficiency was found to be good in all the formulations. The maximum drug entrapment was found in formulation F-4 (73.32 ± 0.15).

The percentage buoyancies of formulations F1–F3 at the end of 10 h were found to be $72.25 \pm 0.32\%$, $69.95 \pm 0.42\%$ and $73.32 \pm 0.25\%$, and for the formulations F4-F6 at the end of 10 h were $73.25 \pm 0.42\%$, $79.92 \pm 0.36\%$, and $71.15 \pm 0.41\%$. The result indicates that with an increase in the concentration of polymers, HPMC, EC and Guar gum slight decrease the floating time. Formulations F4 of prepared microspheres were found to be the best compare to other formulation. The Floating Lag Time (Sec.) lag time of formulation F4 was also found less (52 ± 6), compare to other formulation.

The maximum percentage yield, drug entrapment, percentage buoyancy and less floating lag time was found to be formulation F4 in floating microsphere. The optimized formulation of batches subjected to further studies. The results of measurement of mean particle size of optimized formulation F4 of floating microsphere was found to be 210.25 nm. Results of zeta potential of optimized formulation F4 of floating microsphere was found -38.58 mV. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum Zero order release i.e 0.988 hence indicating drug releases from formulations was found to follow Zero order release kinetics for floating microsphere.

Table 2: Results of evaluation of different formulation

Formulation	Percentage Yield	Drug entrapment (% w/w) of prepared microsphere	Percentage Buoyancy
F1	67.78 ± 0.35	63.25 ± 0.45	65.58 ± 0.36
F2	65.52 ± 0.25	64.45 ± 0.25	69.98 ± 0.25
F3	68.98 ± 0.21	67.78 ± 0.36	64.58 ± 0.15
F4	75.56 ± 0.15	73.32 ± 0.15	74.45 ± 0.23
F5	69.74 ± 0.14	68.85 ± 0.41	65.85 ± 0.14
F6	68.85 ± 0.23	69.95 ± 0.32	69.15 ± 0.45

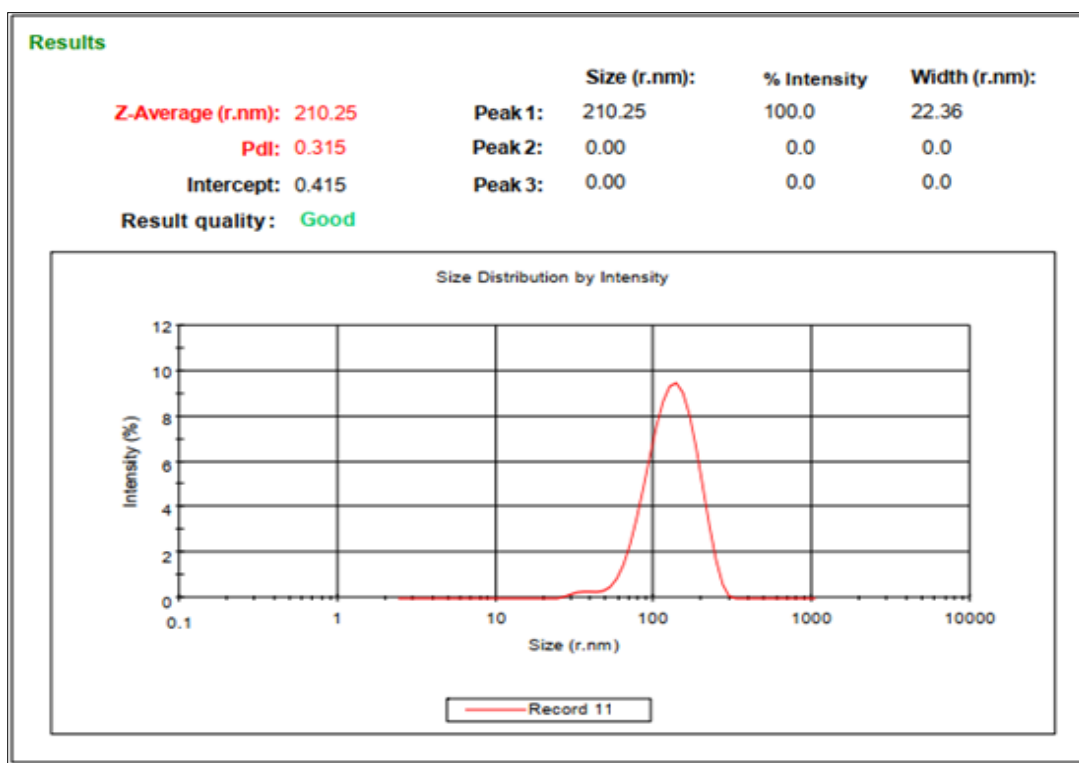


Figure 1: Particle size data of optimized microsphere formulation F4

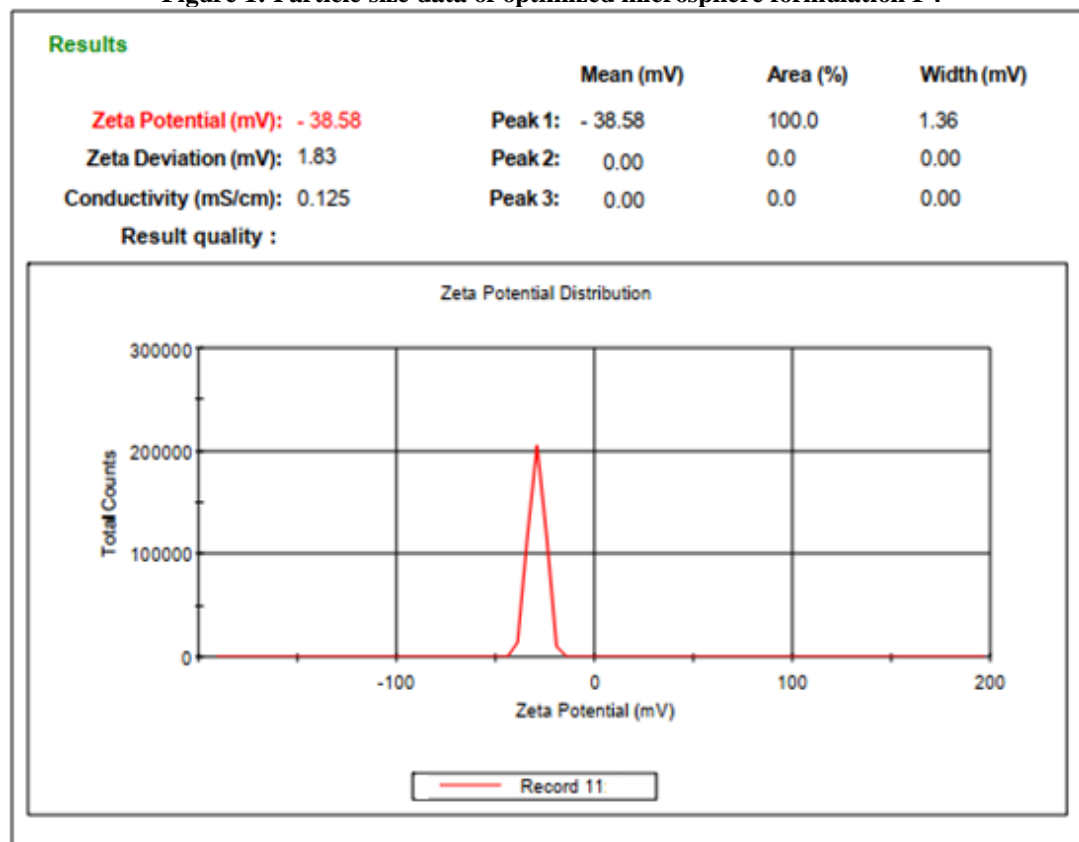


Figure 2: Zeta potential data of floating microsphere F4

Table 3: Release Study data of formulation F1-F6

Time (Hrs)	% of Drug Release						
	F1	F2	F3	F4	F5	F6	Marketed Formulation (Dexlansoprazole 60mg Tablet)
0.5	35.56	32.25	28.85	30.25	19.85	13.32	36.65
1	52.23	48.85	35.65	42.23	25.56	20.25	65.58
2	69.98	65.56	55.65	61.14	35.65	29.98	93.32
4	76.65	79.85	69.98	73.32	48.85	36.65	99.74
6	96.41	89.95	75.56	85.45	59.95	45.58	-
8	99.12	96.65	89.95	92.25	68.87	59.98	-
10	99.45	99.12	97.74	98.85	79.95	74.45	-
12	99.85	99.45	99.45	99.78	99.41	91.15	-

Table 4: Release Kinetics of optimized formulation of microsphere F4

Time (h)	Square Root of Time(h) ^{1/2}	Log Time	Cumulative% Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	19.85	1.298	80.15	1.904
1	1	0	25.56	1.408	74.44	1.872
2	1.414	0.301	35.65	1.552	64.35	1.809
4	2	0.602	48.85	1.689	51.15	1.709
6	2.449	0.778	59.95	1.778	40.05	1.603
8	2.828	0.903	68.87	1.838	31.13	1.493
10	3.162	1	79.95	1.903	20.05	1.302
12	3.464	1.079	99.41	1.997	0.59	-0.229

Table 5: Comparative study of regression coefficient for selection of optimized Formulation F4

Release Kinetics	Zero order	First order	Higuchi	Korsmeyerpeppas
R ²	0.988	0.668	0.974	0.987

CONCLUSION:

Floating microspheres of Dexlansoprazole were prepared by a solvent diffusion-evaporation method. The nature of polymer influenced the physical

characteristics as well as floating behaviour of the microspheres. *In vitro* buoyancy and *in vivo* studies confirmed the excellent floating properties of HPMC, EC and Guar gum microspheres. The drug release

was sufficiently sustained and zero order diffusion of the drug from floating microspheres was confirmed. Hence the floating microspheres of Dexlansoprazole, may provide a convenient dosage form for achieving best performance regarding flow, release and floating properties. Further, their potential to improve Dexlansoprazole bioavailability in humans needs to be investigated in further studies.

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