CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.21299552

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING MICROSPHERES OF LEVOFLOXACIN

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Abstract:

Levofloxacin floating microspheres were formulated and characterized for enhancing residence time of drug in GIT. Levofloxacin is a fluoroquinolone antibiotic. Floating microspheres of Levofloxacin with Hpmc, Sodium alginate were prepared by solvent evaporation method. Microspheres were characterized for their micromeritic properties, floating behavior, entrapment efficiency, scanning electron microscopy (SEM), in vitro drug release. Floating microspheres were successfully prepared by solvent evaporation method. SEM images showed that microspheres prepared with different concentrations of polymer and emulsifier were spherical shaped with a smooth surface. The prepared microspheres also showed good flow properties. Microspheres were capable to float for 8 h. As the polymer concentration increases in vitro drug release was decreased. However, the release was controlled by polymer concentration for a longer period. The optimized formulation showed good results for all the evaluation parameters. Hence, it can be concluded that the developed formulation is a potential dosage form for Levofloxacin.

Key words: *Levofloxacin, floating microspheres ,Polymers, Invitro kinetic studies.*

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Please cite this article in press ***J. Ramesh*** *et al.,* ***Formulation And Evaluation Of Gastroretentive Floating Microspheres Of Levofloxacin*** *Indo Am. J. P. Sci, 2026; 13(07).*

1.INTRODUCTION:

The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (gastro intestinal tract).[1] In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach.[2] Floating drug delivery 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.[3]While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the system is eliminated from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentrations. The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' (HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gel like barrier at the outer surface.[4] The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3–4 h) in the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.[5]Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect.[6]

2.1 MATERIALS

levofloxacin was collected as a gift sample from Hetero laboratories, Hyderabad, Synthetic polymers, super disintegrants and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY

Formulation development

Table-: 1 Preparation of Levofloxacin microspheres

Ingredients	F1	F2	F3	F4
Drug	60	60	60	60
Sodium alginate	100	200	-	-
Ethylcellulose	-	-	100	200
Methanol	5 ml	5 ml	5 ml	5 ml
Cacl 2	5 %	5 %	5 %	5 %

Method:

Alginate particulate system for Levofloxacin microspheres was prepared using sodium alginate and different combinations of Sodium alginate, ethylcellulose. In order to get the complete solution stirring is continued and after that it was added drop by drop into a solution containing calcium chloride. Microspheres, which were formed, were kept in original solution for 24hr for internal jellification followed by filtration for separation. The complete release was observed at pH 6.4-7.4 but the drug release was not observed in acidic formed during this phase.[8]

Compatibility studies Fourier transform infrared (FTIR) analysis[9]

The FTIR analysis of the Levofloxacin was carried out for qualitative compound identification. To check the compatibility of the drug with various polymers, IR spectra of drug, polymers, and combination of the drug and polymers were taken on an FTIR spectrophotometer in the wave number region of 4000-400/cm.

SEM Analysis[10]

Study of surface morphology by scanning electron microscope (SEM) The prepared formulations were dispersed in deionized water and sonicated for 30 minutes. A circular metal plate is taken onto which carbon double tape (1 mm×1 mm) is stickered; a drop of the resultant dispersion is placed onto the tape and allowed to dry for a while. Then, it is scanned under SEM for morphology.

Evaluation of Floating microspheres1[1,12,13,14]

Particle size

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope

Yield of microspheres:

Product yield The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Production yield is calculated using the following equation:

Floating Property of microsphere:

100 mg of the floating microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microsphere was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microspheres were dried in a desiccator over night.

The percentage of microspheres was calculated by the following equation :

% microsphere = Weight of microsphere/ Initial weight of microsphere x 100

Drug content:

The various batches of the formulations were subjected for drug content analysis. Accurately weighed microsphere samples were mechanically powdered. The powdered microspheres were dissolved in adequate quantity of pH 6.8 phosphate buffer in two-necked round bottomed flask. With the help of mechanical stirrer, it was allowed to stir for 3 hrs then filter. The ultraviolet (UV) absorbance of the filtrate was measured using a UV spectrometer at 292 nm. The drug content for the formulations was determined by calculating:

Drug content = Practical drug content × Entrapment efficiency/ Theoretical drug content *100

Entrapment efficiency

The various batches of the formulations were subjected for entrapment efficiency. Accurately weighed microsphere samples were added in adequate quantity of pH 7.4 phosphate buffer and were centrifuged in ultracentrifuge at 17,240 rpm at −4°C for 40 minutes. The free drug concentration was determined spectrophotometrically at 292 nm. The entrapment efficiency for all the formulations was calculated by:

% Drug Entrapment = Practical drug loading/ Theoretical drug loading X 100

In Vitro drug release

To carry out In Vitro drug release, accurately weighed 50 mg of loaded microspheres were dispersed in dissolution fluid in a beaker and maintained at 37±2° C under continuous stirring at 100 rpm. At selected time intervals 5 ml samples were withdrawn through a hypodermic syringe fitted with a 0.4 µm Millipore filter and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug.

Stability studies[15]

The stability protocol was designed based on the ICH 'Q1AR2' guidelines. The microspheres formulations chosen were stored at 30 ± 2 0 C and 65 ± 5% RH for a period of 3 months and at 40 ± 20 C and 75 ± 5% RH for a period of 3 months. The stored samples were tested for their drug release and for any physical change.

3.RESULTS AND DISCUSSION:

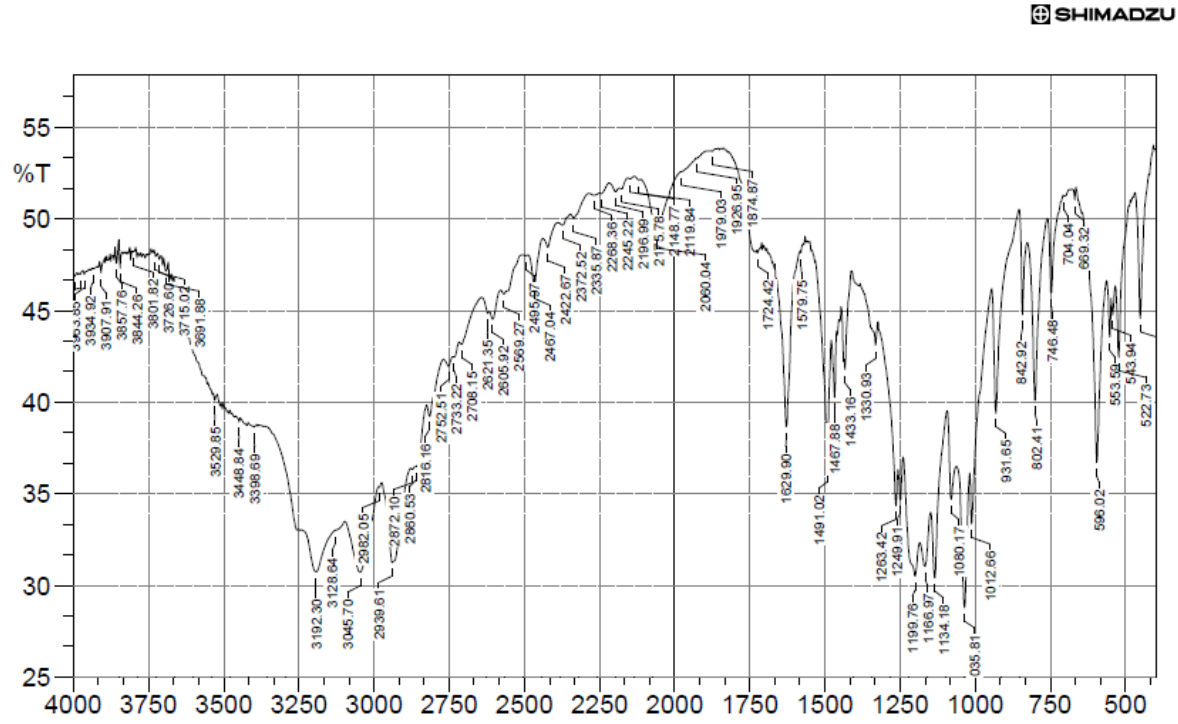

Fig-:1 FTIR Studies of Levofloxacin

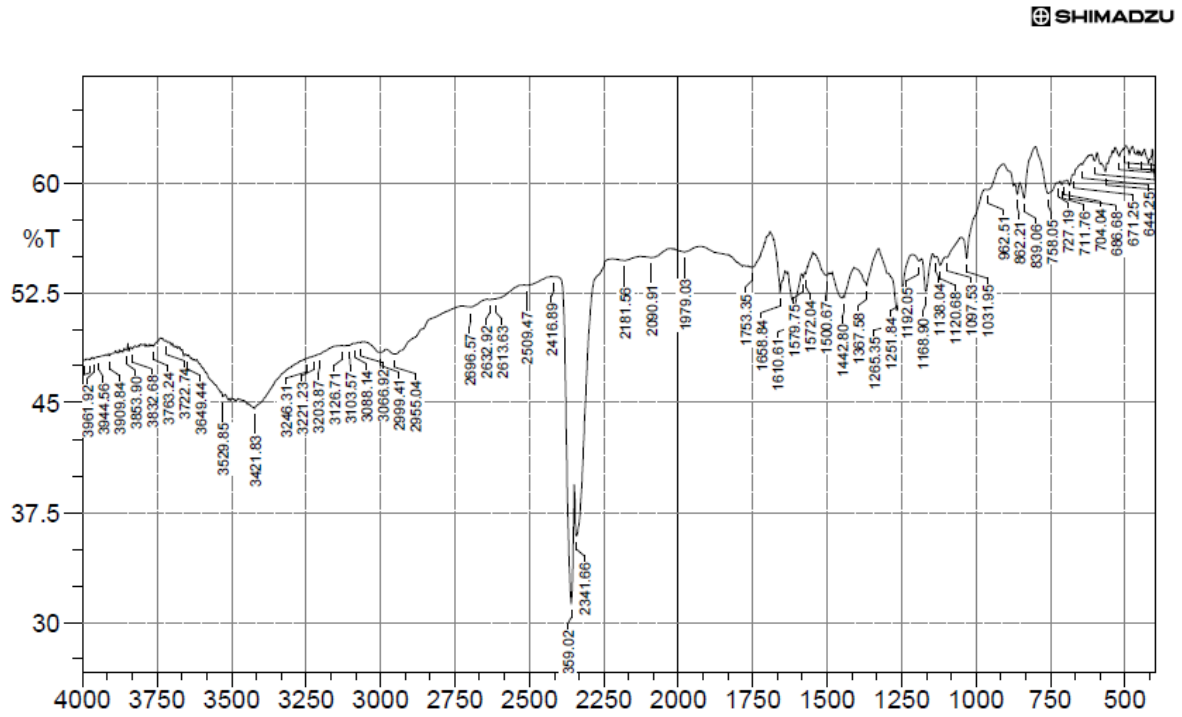

Fig-:2 FTIR Studies of optimized formulation

Formulation and Evaluation of sustained release Microspheres of Levofloxacin

Optimization of formulation variables

Therefore, the optimized conditions for the formulation of sustained release microspheres were:

Results of the evaluation parameters of formulated sustained release microspheres

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and in vitro drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of cyclobenzaprine hydrochloride from sustained microspheres were also studied.

Table-:2 Effect of drug polymer ratio on Yield of microspheres, Particle size, Drug entrapment efficiency

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	82.45	276.32	85.92
F2	84.51	247.45	82.42
F3	91.35	258.21	84.23
F4	81.52	228.46	83.69

Floating Property of microsphere

Floating Microsphere were dispersed in 0.1 N HCl to simulate gastric fluid. Floating ability of different formulation were found to be differed according to polymer ratio.

Table-: 3 Percentage buoyancy for different formulation

Formulation	1 hour	2 hours	4 hours	6 hours
F1	97.20	96.15	92.49	95.25
F2	96.15	96.46	95.23	93.25
F3	97.55	95.51	90.96	91.49
F4	96.62	92.42	92.68	93.16

Drug release studies

Table-:4 Drug release studies all formulations

TIME (hours)	F1	F 2	F3	F4
0	**0**	**0**	**0**	**0**
1	09.36	10.23	12.25	12.25
2	22.36	21.05	24.58	23.68
3	30.15	29.56	31.29	30.28
4	41.25	40.25	40.28	42.35
5	52.36	51.26	51.28	50.26
6	65.26	64.25	60.46	63.28
7	74.56	70.25	72.35	70.25
8	92.45	89.46	92.12	96.88

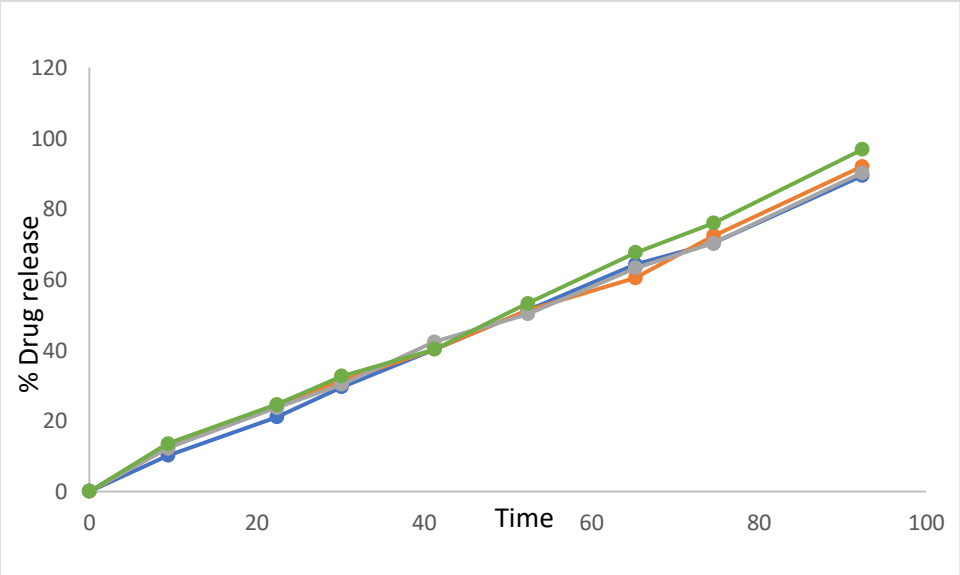

Fig-:3 In vitro drug release studies of all formulation

Characterization of microspheres

A. Surface topography by scanning electron microscopy (SEM)

Figure 4.13 A shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.

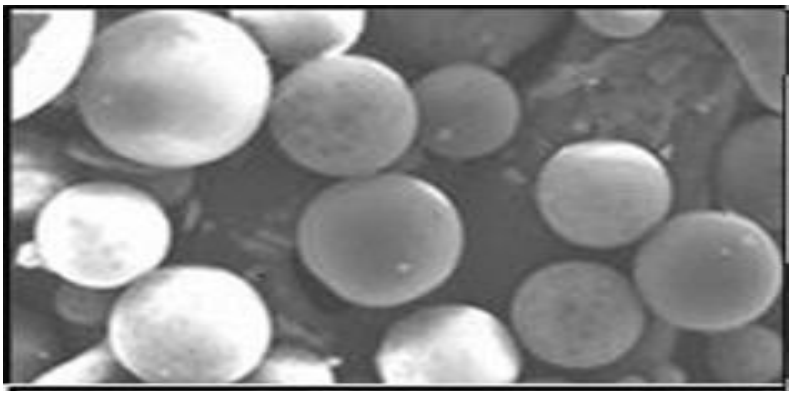

Fig-:4 SEM photograph of Levofloxacin microspheres

Stability studies

There was no significant change in physical and chemical properties of the Microspheres optimized formulation after 90 days. Parameters quantified at various time intervals were shown;

Table-:5 Results of stability studies of optimized formulation

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	96.88	96.62	96.12	95.36	Not less than 85 %
F-4	30^0C/75% RH % Release	96.88	96.51	96.06	95.35	Not less than 85 %
F-4	40^0C/75% RH % Release	96.88	96.56	96.14	95.28	Not less than 85 %

4. SUMMARY AND CONCLUSION:

Emulsion Solvent diffusion method used for preparation of Gastroretentive Floating microspheres FT-IR studies indicated that there was no chemical interaction between the drug and the polymers used. The morphology of floating microspheres was examined using SEM. The view of microspheres showed a floating spherical structure with rough surface morphology. It was also evident that the floating microspheres exhibited porous surfaces. Results of drug content determination from floating microsphere inferred that there was proper and uniform distribution of drug. The percentage encapsulation efficiency of microspheres also showed that the drug loading was optimum and increased with increasing number of polymers. The prepared microspheres exhibited good micromeritic properties.From the results of particle size analysis, it is clear that all the process variables were within the limits and the process was reproducible. The study of micrometric properties indicated fair to good flow of microspheres. All the formulations floated for more than 8 hours. In vitro test showed that larger the particle size, longer the floating time. The microspheres of all the formulations were spherical and free flowing. The in vitro release data showed maximum drug release of more than 90 % in 8 hours. Among the formulated microspheres, those prepared from a blend of polymers showed optimum release. Drug was released in 0.1N HCl buffer. Results of the stability studies showed that there was no significant change in the drug content and physical appearance.

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