Research Article

# Development and Evaluation of Floating Microspheres of cephalexin as Gastroretentive Dosage Form

**A. Aejaz [1*] and A. Sadath [2]**

[1]CMJ University, shillong, Meghalaya, India.

[2]Himalayan institute of pharmacy &research,Dehradun, Uttrakhand, India.

**ABSTRACT**

Floating microsphere of cephalexin were prepared and evaluated with an objective to prolong the gastric residence time of the drug which may result in improved bioavailability, reducing dose frequency, improving solubility of drug and to provide stability of drug which are degraded by the higher pH of the intestine. The floating microspheres were prepared using different polymers like ethylcellulose, HPMC- Ethyl cellulose, cellulose acetate and Eudragit S-100 by solvent evaporation/ diffusion method.The major advantage of preparation technique includes short processing time, lack of exposure of the ingredients to high temperature and high encapsulation efficiency. The floating microspheres were evaluated for micrometric properties, particle size, percent yield, drug polymer compatibility (IR study), scanning electron microscopy and *in vitro* drug release. The micrometric properties were found to be good and scanning electron microscopy shows that spherical microsphere with porous surface were formed. The practical yield was more than 70% with a particle size range of 128.23-389.72□□m. the percent entrapment is about 65% and more in larger particle as compared to smaller particle. The percent buoyancy was more than 70% upto 12 hours. The particle size, percent yield, percent drug entrapment and percent buoyancy was increased significantly ($p<0.05$) with increase in . The *in vitro* release was slow and extended to more than 12 hours. *in vitro* release was significantly decreased ($p<0.05$) with increase in polymer concentration. Release obeys first order kinetics model and the drug release was diffusion controlled with Fickian or non Fickian transport depending upon the polymers. The prepared floating microspheres were stable. Hence it can be inferred that the floating microsphere of cephalexin may prolong drug release thereby improving bioavailability and enhance opportunity of absorption in stomach to prevent degradation of drug under alkaline pH.

**Keywords**: cephalexin, floating microspheres; buoyancy; *in vitro* release.

## INTRODUCTION

Oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations.However, it is a well accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12or even 24 hours is possible for many drugs that are absorbed uniformly from GI tract[1].

Cephalexin is a broad spectrum antibiotic used for the treatement of respiratory tract infection, skin and skin structure infection,genitourinary infections[2,3].In order to enhance bioavailability, the improvement of its solubility and dissolution characteristics is considered to be very effective. Floating drug delivery system is an effective technique which can easily enhance the bioavailability, reducing dose frequency, improving solubility of drug and to provide stability of drug which are degraded by the higher pH of the intestine .

In the present study, cephalexin loaded microspheres were prepared using different polymers like ethylcellulose, Hydroxyl propyl methylcellulose,cellulose acetate and eudragit S-100, to prolong the drug release in upper gastrointestinal tract, where absorption of cephalexin is well confined.

## MATERIALS AND METHODS

### Chemicals

Cephalexin was a gift sample from aurobindu pharmaceuticals,Hyderabad.Ethyle cellulose & HPMC purchase from SD Fine Che Ltd., Mumbai, Cellulose acetate from NR Chem, Mumbai, Eudragit S 100 fromEvonik industries. All the chemicals used in the present study were of AR Grade.

### Preparation of cephalexin loaded floating microspheres[4,5,6,7]

The floating microspheres loaded with

cephalexin were prepared by emulsion-solvent evaporation/ solvent diffusion method using different polymers as follows:

1. Using EC polymer 46: The drug and ethyl cellulose were mixed in dichloromethane at various ratio and triethyl citrate (10%) was added as plasticizer. The slurry was slowly introduced into the solution of polyvinyl alcohol (0.25%, 200ml). The resultant solution was stirred at 500 rpm for 1 hrs. This formed microsphere was filtered and dried at room temperature.
2. Using HPMC and EC polymers[5]: Drug, HPMC and EC were dissolved in a mixture of ethanol and dichloromethane at room temperature. This was poured into 250 ml water containing 0.01%. Tween-80 maintained at 30-40ºC and subsequently stirred for 45 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water and dried overnight at room temperature.
3. Using cellulose acetate polymer[6]:Floating microsphere loaded with cephalexin were prepared by using solvent diffusion/ evaporation method. The polymer, cellulose acetate and drug was dissolved in ethyl acetate and acetone in different proportion. The resulting solution was added slowly to 150 ml of 0.1 M acidic solution containing 0.05% polyvinyl alcohol maintaining at 30- 400c.The emulsion was continuously stirred for 2 hours at the speed of 500 rpm. The floating microspheres were collected by decantation and then dried over night.
4. Using Eudragit S-100 polymer [7]:Eudragit S-100 and a drug were dissolved in 8 ml ethanol, followed by the addition of 2 ml isopropanol and 5 ml dichloromethane. The polymer solution was slowly introduced into 1000 ml of 0.4% poly (vinyl alcohol) aqueous solution with stirring at 250 rpm using a mechanical stirrer equipped with a 3 blade propeller. The solution was stirred for 10 min and the microspheres were collected by filtration. The collected microspheres were dried for 12h at 50ºC.

**Characterization of floating microspheres,**[5,6]

The prepared floating microspheres were evaluated for drug carrier interaction using scanning electron microscopy (SEM) and FTIR (Perkin Elmer 1600 series) spectral studies. For SEM studies The sample was prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300Aº under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electronmicroscope (Joel JSM-1600, Tokyo, Japan). : Fourier Transformation Infrared spectra of pure drug, polymer and drug loaded floating microspheres were obtained in KBr pellets at moderate scanning speed between 4000-200 cm–1 in a Perkin-Elmer Fourier Transformation Infrared spectroscope.

**Evaluation of floating microspheres**

**1. Yield of microspheres**[15]

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

**Practical yield**

$$= \frac{\text{Actual weight of product}}{\text{Weight of excipient \& drug}} \times 100$$

**2. Particle size**[9]

The size was measured using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer.

**3. Drug entrapment efficiency**[10,11]

Microspheres equivalent to 50 mg of the drug were taken for evaluation The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl and small quantity of methanol repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution with 0.1N HCl spectrophotometrically (UV-1700, Shimadzu, Japan) at 262 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated by using the following formula:

$$\text{Percentage drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{Theoretically expected drug loaded}} \times 100$$

**4. Micrometric properties**[12]

The microspheres were characterized by their micrometric properties such as angle of repose, tapped density,compressibility index and true density.

**a) Angle of repose**

The angle of reposeΘ of the microspheres, which measures the resistance to particle flow was calculated as:

$$\tan\Theta = \frac{2H}{D}$$

where 2H/D is the surface area of the free-standing height of the microsphere heap that is formed after making the microspheres flow from the glass funnel.

**b) Tapped density and compressibility index**

The tapping method was used to calculate tapped densities and compressibility index using tapped density:

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

$$\% \text{ compressibility index} = [1 - V/V_0] \times 100$$

Here, V and $V_0$ are the volumes of the sample after and before the standard tapping respectively.

**c) True density**

Density of hollow microspheres is determined by immersing the microspheres in 0.02% tween-80 solution in a metal mesh basket. The microspheres that are sunk after this process are used for density measurement as carried out by the displacement method.

**5. *In vitro* buoyancy**[8]

An *in vitro* floating study was carried out usi ng 0.1NHCl containing 0.02% tween-80 as a dispersing medium. Microspheres were spread over the surface of 900 ml of dispersing medium at 37±0.5ºC.A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collectedat a predetermined time point. The collected samples were weighed after drying.

$$\% \text{ floating microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

**6. *In vitro* dissolution studies**[4,13,14]

The *in vitro* release of drug from floating microspheres was carried out using paddle type Electrolab tablet dissolution tester USP XXIII. Drug loaded microspheres equivalent to 250 mg of drug was introduced into 900ml of the dissolution medium (0.1N HCl) maintained 37±0.5ºC with paddle rotating at100 rpm Aliquots were withdrawn at regular interval and analyzed spectrophotometrically using Shimadzu-1700 UV-visible spectrophotometer.The dissolution studies were carried out in triplicate in 0.1N HCl for 12 hours.The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5ml with same dissolution medium.

**RESULTS AND DISCUSSION**

All the floating Microspheres were prepared by solvent evaporation/ diffusion methods. Ethylcellulose floating microspheres were prepared by solvent evaporation method as shown in table-4 In this method, o/w emulsion was formed stabilize by ethylcellulose and after evaporation of organic solvent cephalexin get encapsulated by ethylcellulose**.** EC-HPMC floating microspheres were prepared by solvent evaporation method as shown in table-5. In this method, the emulsion was stabilized by tween-80 and the volatile solvent get evaporated leaving a solidified thin film at the interface between aqueous
phase and organic phase, where cephalexin gets encapsulated in the core-coat of polymers[5]. Cellulose acetate floating microspheres were prepared by solvent diffusion/ evaporation method as shown in table-6**.** When the polymer solution pour into aqueous phase, all the methanol or acetone will diffused along with small amount of ethyl acetate resulting in an interfacial polymer deposition leading to the formation of floating microspheres[16]. eudragit S-100 floating microspheres were prepared by solvent diffusion method as shown in table-1. In this method, the organic solvent ethanol gets diffused out of dispersed droplets with controlled rate in presence of dichloromethane or propanol. The acrylic polymer eudragit instantly solidified as thin film at the interface between aqueous and organic phase where cephalexin get encapsulated in core-coat of polymer76. The ratio of mixture of solvent was kept constant and the concentration of respective polymer was varied in all the preparation methods.

Physical characteristics of cephalexin floating microspheres were measured according to the

methods describe above. The results and listen in Table 2.

The invitro dissolution studies were performed by over a period of 12 hours and results are shown in figure 1&2. *in vitro* release was significantly decreased with increase in polymer concentration. Release obeys first order kinetics model and the drug release was diffusion controlled with Fickian or non Fickian transport depending upon the polymers. scanning electron microscopy shows that spherical microsphere with porous surface were formed

IR studies indicated that during the process of formulation no chemical reaction has been taken place. . At the end of 12 hours all the formulation were found to be satisfactory in terms of excellent micrometric properties, percent yield ,percent drug entrapment efficiency ,*in vitro* buoyancy and highest *in vitro* drug release of 89.75% in sustained manner with constant fashion over a extended period of time of12 hours . The results proved that the cephalexin loaded floating microspheres Were better in releasing the drug in the sustained fasion for extended period of 12 hours.

## CONCLUSION

The in vitro evaluation study of cephalexin loaded floating micro spheres was greatly improved when compared with those of conventional tablet dosageform. Among all formulations C1 with the drug: polymer ratio of (1:2) was found to be satisfactory in terms of excellent micrometric properties, percent yield (87.28%), percent drug entrapment efficiency (81.66%), *in vitro* buoyancy (88.59%), and highest *in vitro* drug release of 89.75% in sustained manner with constant fashion over a extended period of time of 12 hours .

The study reveals satisfactory results with a further scope of pharmacokinetic and pharmacodynamic evaluation.

**Table1: Formulations of cephalexin loaded floating microspheres prepared using ethyl cellulose, EC and HPMC, cellulose acetate &Eudragit S-100**

| | DISPERSED PHASE | | | | |
|---|---|---|---|---|---|
| **FORMULATION CODE** | **Drug (mg)** | **EC(gm)** | **DICLORO METHANE (ml)/ Triethyl citrate (%)** | | **CONTINUOUS PHASE** |
| **E1** | 500 | 0.50 | 15 | 10 | 0.25% PVA aqeous solution |
| **E2** | 500 | 1 | 15 | 10 | |
| **E3** | 500 | 1.5 | 15 | 10 | |
| | **DRUG** | **HPMC/EC** | **ETHANOL:DOCHLOROMETHANE** | | **CONTINUOUS PHASE** |
| **HE1** | 500 | 0.5/ 1.0 | 1:2 | | 250 ml water containing 0.01% w/v tween-80 |
| **HE2** | 500 | 0.5/2.0 | 1:2 | | |
| **HE3** | 500 | 0.5/3.0 | 1:2 | | |
| | **DRUG** | **CELLULOSE ACETATE** | **ETHYLE ACETATE:ACETONE** | | **CONTINUOUS PHASE** |
| **C1** | 500 | 1 | 1:1 | | 250 ml 0.1 M acidic solution containing 0.05% w/v polyvinyl alcohol |
| **C2** | 500 | 2 | 1:1 | | |
| **C3** | 500 | 3 | 1:1 | | |
| | **DRUG** | **Eudragit – S100** | **ETHANOL:DICHLOROMETHANE:PROPANOL** | | **CONTINUOUS PHASE** |
| **EU1** | 500 | 0.5 | 8:5:2 | | 250 ml water containing 0.4% w/v polyvinyl alcohol |
| **EU2** | 500 | 1 | 8:5:2 | | |
| **EU3** | 500 | 1.5 | 8:5:2 | | |

**Table 2: mean particle size, Practical yield, *in vitro* buoyancy and Drug entrapment efficiencyof floating microspheres of Cephalexin**

| | Mean particle size (mean±SD) (□m) | Practical yield (mean±SD) (%) | Drug entrapment efficiency (mean±SD) (%) | *In vitro* buoyancy (mean±SD) (%) |
|---|---|---|---|---|
| E1 | 316.15±22.25 | 72.56□ 0.67 | 78.33□□ 1.52 | 81.42□□ 2.45 |
| E2 | 342.89±24.45 | 80.83□□ 0.63 | 83.11□□ 2.07 | 85.23□□ 2.80 |
| E3 | 371.28±18.14 | 83.28□0.57 | 86.31□□ 1.05 | 88.33□□ 3.14 |
| HE1 | 262.50±23.81 | 81.26□□ 0.69 | 68.17□□ 2.05 | 72.05□□ 2.58 |
| HE2 | 297.70±16.21 | 86.67□□ 0.45 | 74.11□□ 1.07 | 76.66□□ 2.60 |
| HE3 | 335.39±21.00 | 88.59□□ 0.38 | 78.22□□ 1.82 | 80.83□□ 3.18 |
| C1 | 328.49±19.80 | 87.28□□ 0.76 | 81.66□□ 2.08 | 88.59□□ 1.52 |
| C2 | 357.21±20.26 | 91.53□□ 2.02 | 84.00□□ 1.26 | 89.70□□ 2.02 |
| C3 | 389.72±17.50 | 94.39□□ 1.50 | 88.66□□ 1.52 | 91.24□□ 2.28 |
| EU1 | 128.23±15.65 | 67.48□□ 2.07 | 65.74□□ 4.04 | 78.07□□ 0.98 |
| EU2 | 185.15±22.25 | 74.73□□ 1.54 | 69.24□□ 1.52 | 86.78□□ 2.30 |
| EU3 | 248.63□21.53 | 79.18□□ 1.97 | 74.57□□ 3.05 | 89.32□□ 2.06 |

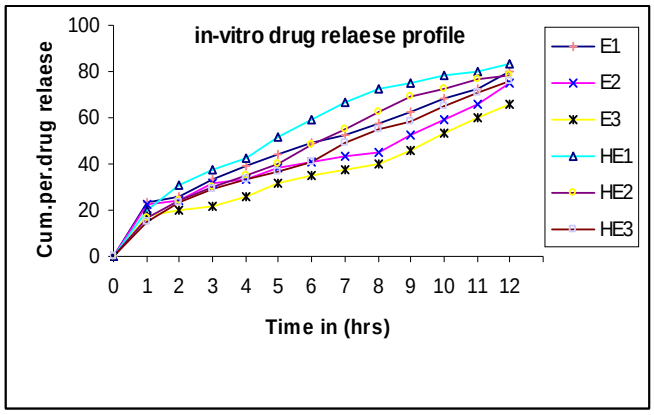


**Fig. 1: *In vitro* release data of cephalexin loaded floating microspheres of ethyl cellulose ,HPME & EC**

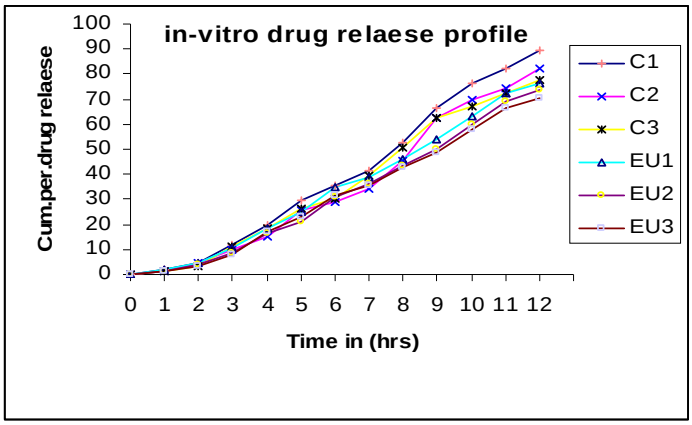


**Fig. 2: *In vitro* release data of cephalexin loaded floating microspheres of cellulose acetate &eudragit S-100**

**REFERENCES**


1. Chein YW. Oral Drug Delivery and Delivery systems. In, Novel drug delivery systems. Marcel Dekker, Inc., New York, 1992;50:139-177.
2. Florey K. Analytical profiles of drug substances. Academic press; 2005;4:23-43.
3. Rao BP, Kottan NA, Snehith VS and Ramesh C. Development of Gastro retentive drug delivery system of cephalexin by using factorial design. 2009; 50(1):8-24.
4. Patil HS, Patil MP, Tekade BW, Thakare BW, Thakare VM and Patil VR. Formulation and *In vitro* evaluation of floating microsphere of Acyclovir. Arch pharm Sci & Res. 2009;1(1): 194-198.
5. Pande AV, Vaidya PD, Arora A and Dhoka MV. *In vitro* and *in vivo* evaluation of ethyl cellulose based floating microspheres of cefpodoxime proxetil. Int J Pharm Biomed Res. 2010 ;1(4):122-128.
6. Jain AK, Jain CP, Tanwar YS and Naruka PS. Formulaltion, characterization and *in vitro* evaluation of floating microspheres of famotidine as a gastro retentive dosage form. Asian J pharm. 2009;3(3):222-226.
7. Lee JH, Park TJ and Choi HK. Development oral drug delivery system using floating microspheres. J Microencaps. 1999;16(6):715-29.
8. Pande AV, Vaidya PD, Arora A and Dhoka MV. *In vitro* and *in vivo* evaluation of ethyl cellulose based floating microspheres of cefpodoxime proxetil. Int J Pharm Biomed Res. 2010;1(4):122-128.
9. Srivastava AK, Ridhurkar DN and Wadhwa S. Floating microspheres of cimetidine: Formulation and characterization and *in vitro* evaluation. Acta Pharm. 2005;55:277-285
10. Patel MP, Patel MM, Patel KN, Patel DR and Patel UL. Designing and Evaluation of Floating Microspheres of Verapamil Hydrochloride: Effect of Methocel. Res J Pharma Dosage Forms Tech. 2009;1(1):22-28.
11. Malay KD and Kalakuntala RR. Evaluation of zidovudine encapsulated ethylcellulose microspheres prepared by water-in-oil-in-oil (w/o/o) double emulsion solvent diffusion technique Acta poloniae pharmaceutica and drug research. 2006;63(2):141-148.
12. Jain SK, Agrawal GP and Jain NK. Evaluation of porous carrier based floating orlistat microspheres forgastric delivery APPS PharmSciTech. 2006;7(4).
13. Gattani YS, Bhagwat A and Maske AP. Formulation and evaluation of intragastric floating drug delivery system of dilitiazem hydrochloride.Asian J pharm 2008;228-231.
14. Costa P and Lobo JM. Review – modeling and comparison of diffusion profiles. Eur J Pharm Sci. 2001;13:123-133.
15. Karthikeyan D, Karthikeyan M and Ramasamy C. Development of floating microsphere to improve oral bioavalibilty of cefpodoxime proxetil. Acta pharmaceutical sciencia. 2010;52: 101-104.
16. Soppimath KS, Kulkarni AR and Aminabhavi TM. Development of Hollow Microspheres as Floating Controlled-release System for Cardiovascular Drugs – preparation and release characteristics. Drug Dev Ind Pharm. 2001;27(6):507-515.