

DESIGN AND EVALUATION OF INTRAGASTRIC FLOATING DRUG DELIVERY SYSTEM FOR OFLOXACIN

NISHA KABBUR, ASHWINI RAJENDRA*, SRIDHAR BK

Department of Pharmaceutics, National College of Pharmacy Shivamogga, Karnataka

Received: 24 Jun 2011, Revised and Accepted: 11 Sep 2011

ABSTRACT

A gastroretentive controlled release system of ofloxacin was formulated to increase the residence time in stomach and to modulate the release behavior of the drug. Rice bran oil entrapped zinc pectinate beads contained ofloxacin, capable of floating in the gastric condition were formulated and evaluated. The gel beads were prepared by emulsion gelation method by employing low methoxy pectin (LMP) alone and mixture of LMP and hydrophilic copolymers (natural gums) such as gellan gum (GG) and karaya gum (KG) in three different ratios. The beads were evaluated for percent drug entrapment efficiency, buoyancy and *in vitro* drug release. The percent entrapment efficiency was found to be 57.49% to 78.81%. The *in vitro* drug release study of the beads was carried out in simulated gastric media by conventional USP dissolution method. All the oil entrapped zinc pectinate beads floated if a sufficient amount of oil was used. Beads formulated employing LMP alone could not sustain the drug release for 8 hr, whereas beads formulated with mixture of LMP and copolymers demonstrated sustained release of ofloxacin for more than 8 hr. The drug release from the formulated beads followed first order kinetics with Fickian diffusion mechanism ($n < 0.5$). Thus gastroretentive floating beads of ofloxacin were successfully prepared by using low density oil and different proportions and combinations of rate controlling polymers.

Keywords: Ofloxacin; Floating drug delivery systems, Low methoxy pectin, Gellan gum, Karaya gum, Zinc pectinate beads, Rice bran oil, Gastric residence time.

INTRODUCTION

Floating Drug delivery system are designed 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. The hydrodynamic balanced system (HBS) also called floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).¹ Ofloxacin is an antibacterial fluoroquinolone. It is widely prescribed in gastric ulcers, duodenal ulcers, *Zollinger-Ellison syndrome* and gastro esophageal reflux disease. It is prescribed with proton pump inhibitor or antacids. Ofloxacin exhibit pH dependent solubility. It is more soluble in acidic pH and slightly soluble in neutral or alkaline pH conditions. However, precipitation of the drug occurs in intestine, which adversely affects the absorption in the lower sections of the intestine. So there is need for systems that reside in the stomach over a relatively long period and release the active compound in a sustained manner.²

The aim for the present study was to develop a delivery system wherein the retention of ofloxacin could be achieved for increasing local action in gastric region against *Helicobacter pylori*. Therefore the present investigation is concerned with the development of rice bran oil entrapped zinc pectinate beads containing ofloxacin, which after oral administration were designed to prolong the gastric residence time, thus to increase the bioavailability of the drug.

The *in vitro* drug release study of the beads was carried out in simulated gastric media by conventional USP dissolution method. Various formulations of floating beads of ofloxacin were developed using polymers like LMP alone and mixture of LMP with rate controlling polymers such as GG and KG. The beads were prepared

by emulsion gelation method. Rice bran oil was used to impart buoyancy to the beads due to its low density. The beads were spherical in nature and the evaluation of the drug content and entrapment efficiencies showed that beads formulated using LMP alone resulted in poor drug content and entrapment. Beads formulated with mixture of LMP and GG showed the highest drug content and entrapment compared to other formulations. The beads did not swell much or erode in the dissolution media, which suggested that drug release was dependent on the dissolution and diffusion of the drug through the polymer matrix. The buoyancy studies on the beads proved that a minimum of 25% w/w of rice bran oil was required to impart satisfactory buoyancy to the beads. The beads showed instantaneous and excellent buoyancy and remained afloat on the dissolution medium throughout the study period. The *in vitro* drug release study showed that LMP alone could not sustain the drug release for sufficient period of time whereas incorporation of rate controlling polymers such as GG and KG as copolymers can effectively sustain the drug release from the bead formulations. Here zinc chloride was used as cross linking agent as, calcium chloride reacted with ofloxacin and tend to solubilize the drug in the cross linking medium itself.³

MATERIALS AND METHODS

Materials

The following chemicals and solvents were used: Ofloxacin (a gift sample from Apex formulations Pvt. Ltd, India); Low methoxy pectin (LMP) (a gift sample from Krishna Pectins Pvt. Ltd, India); gellan gum (GG) (Sigma-Aldrich Chemicals, India); karaya gum (KG) (Morning Star Enterprises, India); Rice bran oil (RBO) (Sri Anjaneya Agrotech Pvt Ltd, India); Zinc chloride (High purity laboratory chemical, India) and hydrochloric acid (HCl) Ranbaxy Fine Chemicals, Chandigarh.

Preparation of floating zinc pectinate beads

Ofloxacin, LMP, GG and KG were passed through sieve no 80 separately. Ofloxacin (20 % w/w of dry polymer weight) was dissolved in distilled water. LMP (3 % w/v) alone and polymer mixtures (3 % w/v) containing LMP and GG, and LMP and KG in three different ratios were dissolved in above dispersion and one formulation with polymer mixtures (3 % w/v) containing GG, KG and LMP. To the above mixture rice bran oil (25 %w/w) was added and stirred to form a homogeneous emulsion. The drug-loaded emulsion was extruded through a 23 G syringe needle into zinc

chloride solution (5 % w/v) maintained under gentle agitation. The beads were allowed to remain in the same solution for 30 min to improve their mechanical strength. The formed beads were separated, washed with water and allowed to dry at room temperature overnight. Table 1 lists the formulation variables for different formulations of ofloxacin loaded floating beads. Blank beads without ofloxacin were also prepared using the same technique.⁴⁻⁶

Table 1: Formulation variables of various ofloxacin bead formulations

Formulation code	LMP:GG (3% w/v)	LMP:KG (3%w/v)	Oil (%w/w)
F Blank	10:0	10:0	-
F	10:0	10:0	15
	10:0	10:0	20
	10:0	10:0	25
F1	9:1	-	25
F2	8:2	-	25
F3	7:3	-	25
F4	-	9:1	25
F5	-	8:2	25
F6	-	7:3	25

Drug Polymer Compatibility Studies

Differential scanning calorimeter (DSC)

Physical mixture of ofloxacin and other polymers were subjected to compatibility study using differential scanning calorimetry (DSC-60, Shimadzu, Japan). For DSC, aluminum pans were used to place the samples. The heating rate was kept at 10 °C rise per min up to 350 °C to better integrate the information. Nitrogen gas was used for purging at 30 ml/min.

Fourier transforms infrared spectra (FTIR)

The samples of pure drug and polymers and their physical mixtures were mixed with potassium bromide to form pellets. The samples were scanned over the wavelength range of 4000 cm⁻¹ to 400cm⁻¹ and the spectra were obtained (Perkin Elmer FTIR).

Determination of bead diameter

The diameter of a sample of gel beads (25 beads) of each formulation was determined using a dial thickness meter. Measurement for each sample was repeated ten times. Mean diameter and standard deviations were recorded.

Drug content

An accurately weighed sample of beads (100 mg) was crushed in a mortar and added to 100 ml of 0.1N hydrochloric acid (pH 1.2). This mixture was kept overnight under stirring to elute complete drug from the polymer matrix. The mixture was filtered and analyzed using spectrophotometer at a wavelength of 294.5 nm (UV spectrophotometer, 1601, Shimadzu, Japan) against blank bead mixture, which was treated similarly. The drug content of each formulation was recorded as mg/100 mg of gel beads.

Drug entrapment efficiency

The percentage drug entrapment efficiency (% EE) of each bead formulation was calculated using the following equation:^{7,8}

$$EE (\%) = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Determination of swelling index

The swelling behavior of the zinc pectinate beads was studied in 0.1 N Hydrochloric acid (pH 1.2).⁹ Approximately 100 mg of beads were taken in a dissolution basket and weighed (W₁); the baskets along with the beads were immersed in 0.1N Hydrochloric acid. The weight (W₂) of the basket along with the beads was determined for 8

hr, every 30 minutes for the first 2 hr, and then at every hour for remaining duration. The swelling index (SI) of each formulation was calculated using the following equation:

$$\% SI = \frac{W_2 - W_1}{W_1} \times 100$$

Buoyancy studies

The time between the introduction of the FDDS into the medium and its buoyancy to the upper one third of the dissolution vessel (floating lag time) and the time for which the formulation constantly floated on the surface of the medium (floating duration) were measured simultaneously as a part of dissolution studies by visual observation.^{2, 10}

In vitro drug release studies

In vitro release characteristics of ofloxacin floating gel beads (n=3) were evaluated employing USP XXIII dissolution testing apparatus 2 (Paddle method). The dissolution test was performed using 500 ml of 0.1 N Hydrochloric acid as dissolution medium maintained at 37±0.5 °C. The contents were stirred at 50 rpm. A 5 ml aliquot of the solution was withdrawn at predetermined time intervals for 8 hr and fresh 5 ml dissolution media was replaced to maintain sink condition. The sample aliquots were analyzed using spectrophotometer at a wavelength of 294.5 nm (UV spectrophotometer, 1601, Shimadzu, Japan).

Scanning electron microscopy (SEM)

Morphological examination of the surface and external structure of the dried beads of formulation F1 (Both drug loaded and blank beads) was performed using a scanning electron microscope (SEM) (model JEOL, JSM-840A). The samples were gold coated prior to the scanning.

Stability studies

Stability studies were carried out according to ICH guidelines by storing the formulation F1 at 40±2°C and relative humidity 75±5 % for a period of two months in a programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). The samples were withdrawn at 30 and 60 days and analyzed for the drug content, floating behavior and *in vitro* drug release.^{11,12}

Statistical analysis

The statistical analysis on the dissolution data obtained from the prepared beads (only LMP, LMP-GG and LMP -KG) was carried out by single factor Anova. The probability value of P < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

An attempt was made formulate oil entrapped floating zinc pectinate beads of ofloxacin, since it is required to act locally in the stomach and proximal region of small intestine. The drug and polymers were subjected for compatibility studies to ensure drug polymer compatibility. The gel beads were prepared by emulsion gelation method. The prepared beads were evaluated for various physicochemical parameters such as size and morphology, drug entrapment efficiency, floating characteristics, swelling studies, and *in vitro* release studies by conventional method.

The DSC thermograms of physical mixture of ofloxacin and the polymers showed characteristic peaks of ofloxacin with slight shift in their original positions (Table 2) (Figure 1).

Table 2: Characteristic peaks for DSC samples

SI No	Sample combinations	Characteristic peaks
1	Ofloxacin	274.5 °C
2	Ofloxacin and pectin	274.5 °C
3	Ofloxacin, pectin and gellan gum	270.0 °C
4	Ofloxacin, pectin and karaya gum	274.5 °C

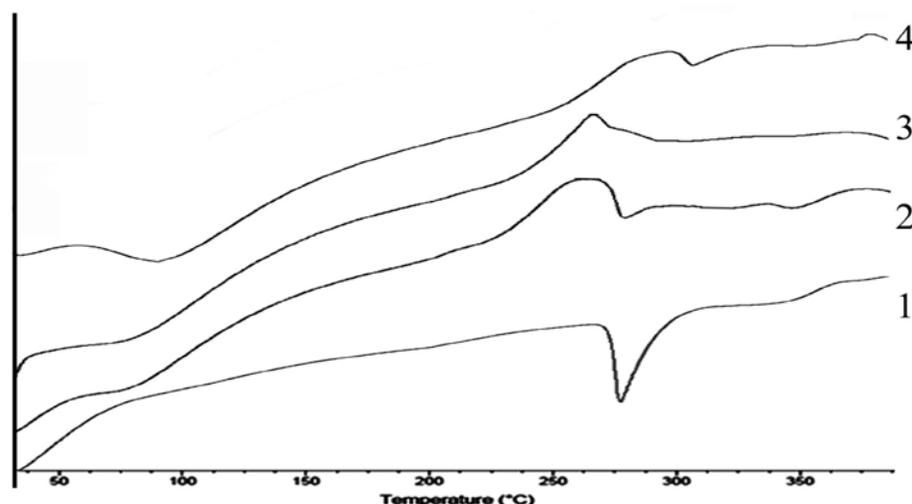


Fig. 1: DSC thermogram of (1) pure ofloxacin, (2) ofloxacin and LMP (physical mixture), (3) ofloxacin, LMP and GG (physical mixture), (4) ofloxacin, LMP and KG (physical mixture)

The following characteristic bands O-H stretching band at 3300 cm^{-1} , C-H stretching (aliphatic) 2936.17 cm^{-1} , C-H stretching (aromatic) 2785.3 cm^{-1} and C=O stretching at 1712.89 cm^{-1} were observed in the spectra of pure ofloxacin. (Figure: 2)

All the above bands associated with the pure drug were present in the FTIR spectra of drug in combination with gellan gum and karaya gum. This shows that there is no chemical interaction taking place

between drug and excipients. The findings indicate that the drug and polymers are compatible with each other.

The prepared beads were almost spherical and translucent. The mean surface diameter of all the formulations was between 1.691 ± 0.022 and 2.099 ± 0.041 (mean \pm SD). The percent drug entrapment efficiency for various ofloxacin floating bead formulations was found to vary between 57.49% and 78.81% (Table 3).

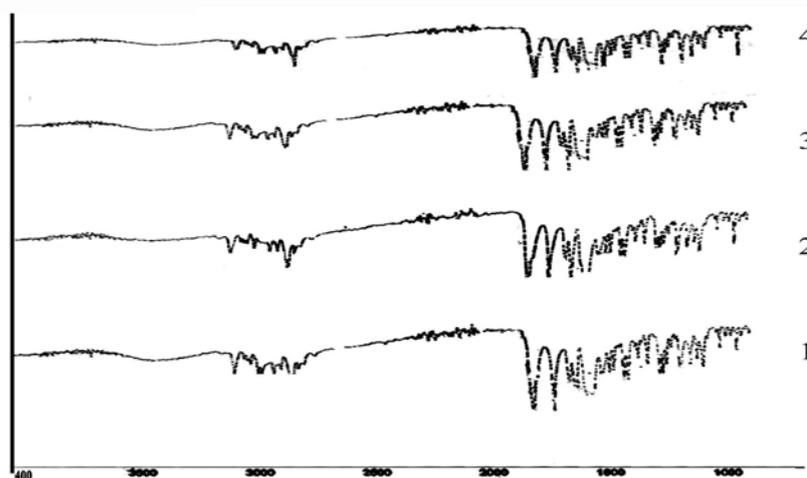


Fig. 2: FTIR spectra of (1) pure ofloxacin, (2) ofloxacin and LMP (physical mixture), (3) ofloxacin, LMP and GG (physical mixture), (4) ofloxacin, LMP and KG (physical mixture)

Table 3: Characterization of floating zinc pectinate beads

Formulation code	Mean Diameter \pm SD (mm)	Drug content (mg)	%EE	%Swelling Index
F blank	1.691 ± 0.022	-	-	0.74
F	1.693 ± 0.015	2.437 ± 0.037	57.49	2.42
F1	1.751 ± 0.023	1.236 ± 0.017	78.81	1.79
F2	1.841 ± 0.022	1.620 ± 0.054	69.16	2.21
F3	1.898 ± 0.018	1.551 ± 0.114	72.13	1.22
F4	2.057 ± 0.069	1.362 ± 0.035	74.28	2.10
F5	2.009 ± 0.027	1.713 ± 0.111	65.40	1.74
F6	2.099 ± 0.041	1.417 ± 0.027	62.98	

%EE= encapsulation efficiency

The floating ability of prepared beads was evaluated along with dissolution studies. The beads without oil sink immediately in 0.1 N Hydrochloric acid (pH 1.2), while beads containing sufficient amount of rice bran oil (25%) demonstrated instantaneous and excellent floating ability.

In vitro drug release study of ofloxacin floating beads was carried in 0.1N Hydrochloric acid (pH 1.2), for a period of 8 hr. In the 0.1N Hydrochloric acid, the beads exhibited a biphasic release profile as an initial rapid drug release phase (burst effect) was followed by a

sustained, gradually increasing drug release phase after 1 hr extending up to 8 hr. Formulation F contained only LMP could not sustain the ofloxacin release up to 8 hr. It showed complete drug release at the end of 4 hr. The formulations containing GG; F1, F2 and F3 released 87.51%, 74.33 and 74.76% of drug respectively at the end of 8 hr and the release profile is shown in figure 3 (a). The formulations containing KG; F4, F5 and F6 released 76.41%, 68.52% and 66.00% of the drug at the end of 8 hr respectively. The release profile from these beads is shown in figure 3 (b).

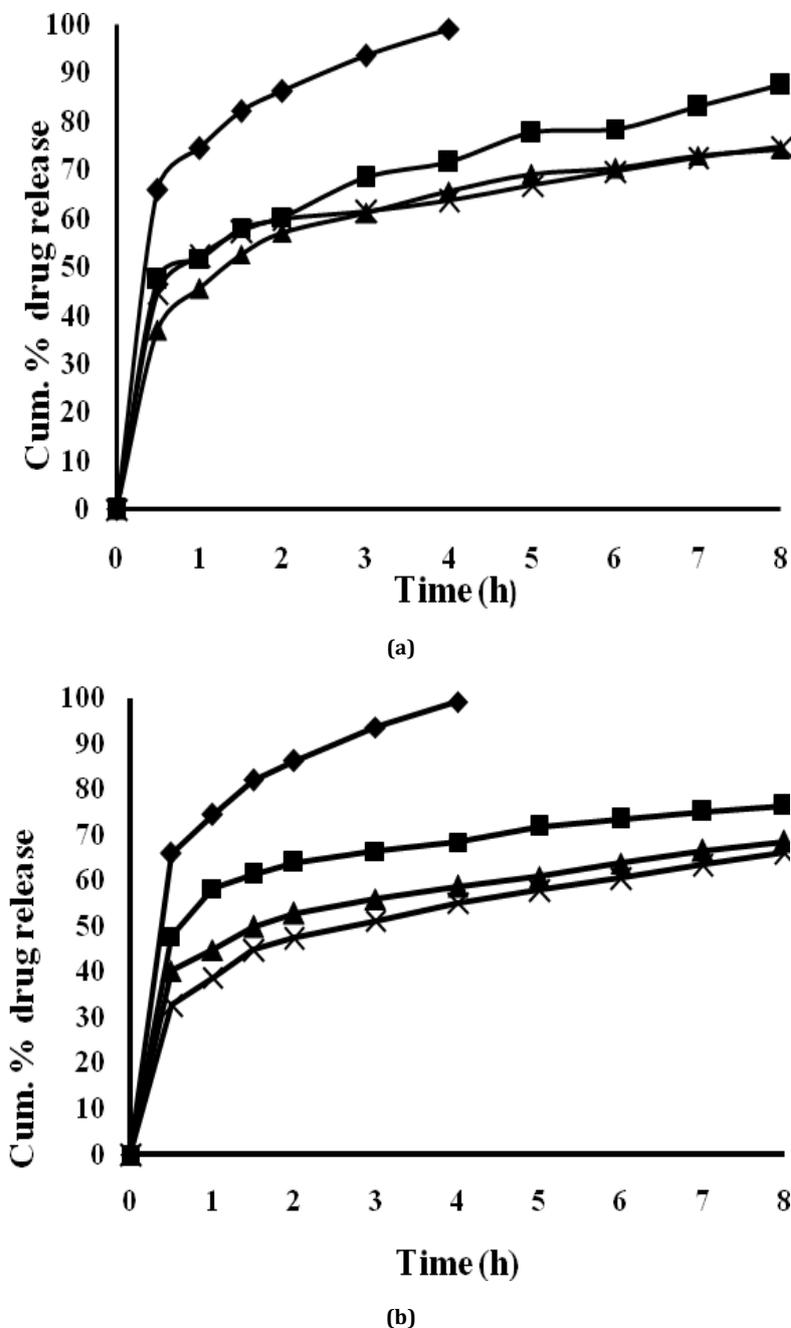


Fig. 3: Comparison of *in vitro* dissolution characteristics of (a) F (◆), F1 (■), F2 (▲), F3 (×) (n = 3); (b) F (◆), F4 (■), F5 (▲), F6 (×) (n = 3)

The *in vitro* release data of all the batches were fitted to zero order, first order, Higuchi and Korsmeyer and Peppas equations. It was observed that for the formulation F, F1 and F2, the r^2 values were higher when fitted to first order equation ($r^2 = 0.944$), which indicates that a first order release from these

formulations, whereas all the other formulations, F3 to F6 followed Higuchi model. The release exponent 'n' values of the Korsmeyer-peppas model for all the formulations were found to be less than 0.5 ($n < 0.5$), thus the drug release from the beads followed Fickian (case I) diffusion (Table 4).

Table 4: Kinetics of release pattern

Sl no	Formulation code	r ² for zero order equation	r ² for first order equation	r ² for higuchi equation	n value for peppas equation	r ² value for peppas equation
1	F	0.606	0.944	0.870	0.198	0.998
2	F1	0.683	0.922	0.887	0.225	0.986
3	F2	0.657	0.980	0.880	0.246	0.983
4	F3	0.567	0.762	0.793	0.170	0.979
5	F4	0.503	0.715	0.753	0.154	0.967
6	F5	0.604	0.779	0.832	0.189	0.995
7	F6	0.692	0.840	0.899	0.247	0.995

The scanning electron microscopy of blank and drug loaded beads (both external and internal structure) are shown in figure 4 and 5.

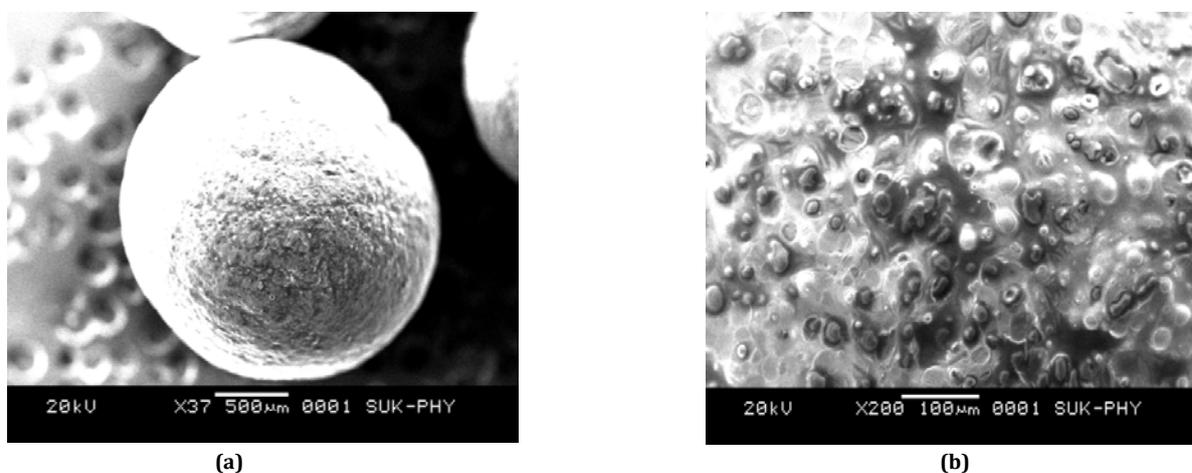


Fig. 4: Scanning electron microscopy of (a) external and (b) surface morphology of drug unloaded floating beads of formulation F1 (LMP:GG, 9:1)

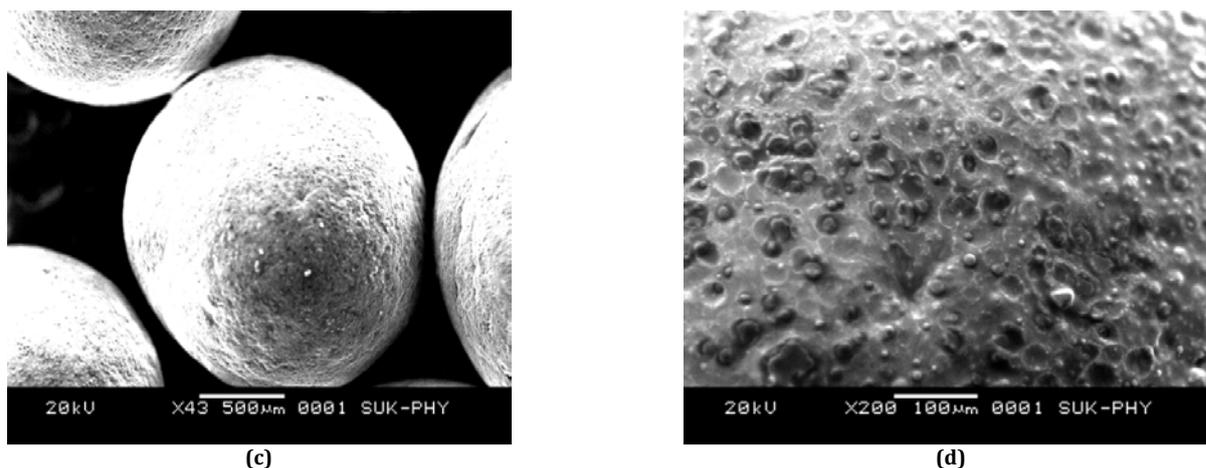


Fig. 5: Scanning electron microscopy of (c) external and (d) surface morphology of drug loaded floating beads of formulation F1 (LMP:GG, 9:1)

The scanning electron micrographs of external and surface morphology of both blank and drug loaded beads of formulation F1 are shown in figure 4 and 5. The beads (both blank and drug loaded) were spherical and the external surface was smooth with slightly rougher surface/shrinkage which could be due to drying. The internal surface of the blank beads shows sponge-like nature with little droplets of entrapped oil which imparts buoyancy to the beads. In the drug loaded beads the surface morphology is slightly sponge like which is due to the drug and rate controlling polymer are uniformly dispersed in the polymer matrix.^{4, 9, 13, 14}

The statistical analysis carried out on the formulations containing only LMP, LMP-GG and LMP-KG showed significant difference in their dissolution profiles whereas formulations F2 and F3 did not

show any significant difference in their dissolution profiles at the probability value $p < 0.05$.

In view of potential utility of the formulation, stability studies were carried out on formulation F1 for two months according to ICH guidelines. At the end of each month, the formulations were subjected to drug assay, floating behavior and *in vitro* release studies. The formulations showed no significant changes in drug content, floating time and duration and *in vitro* release profile after storage.

CONCLUSION

All the bead formulations showed satisfactory floating characteristics. From the dissolution data it is concluded that LMP alone cannot sustain the drug release but mixture of LMP with other

copolymers can sustain the drug release for more than 8 hr. The release of the drug from prepared beads followed Higuchi model and the mechanism of drug release was Fickian diffusion.

Thus, gastroretentive controlled release dosage form of ofloxacin was formulated by using low density oil and different proportions and combinations of controlling polymers.

ACKNOWLEDGEMENT

The authors thank the management of National education society, Shivamogga for providing facilities to carry out this work.

REFERENCE

- Bhowmik D, Chiranjib B, Chandira M, Jayakar B, Kumar S, Floating Drug Delivery System- A Review, *Der Pharmacia Lettre* 2009; 1(2): 199-218.
- Janardhan D, Sreekanth J, Bharat V, Subramaniyan PR. Formulation and Evaluation of Gastroretentive Drug Delivery System for Ofloxacin. *Int. J. Pharm Sci Nanotech* 2009; 2(1): 428-434.
- Benigno MS, Marta MC, Amparo SN and Alfonso DG. A physico-chemical study of the interaction of ciprofloxacin and ofloxacin with polyvalent cations. *Int J Pharm.* 1994; 106(3): 229-235.
- Sriamornsak P, Thirawong N, Puttipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. *Eur J Pharm Sci.* 2005; 24: 363-373.
- Shishu, Gupta N, Aggarwal N. Stomach specific drug delivery of 5-fluorouracil using floating alginate beads. *AAPS Pharm Sci Tech.* 2007; 8(2): E1-7.
- Gohel MC, Mehta PR, Dave RK, Bariya N. A more relevant dissolution method for evaluation of floating drug delivery systems. *J Disso Tech.* 2004; 11: 21-25.
- Mishra SK, Pathak K. Formulation and evaluation of oil entrapped gastroretentive floating gel beads of loratidine. *Acta Pharm.* 2008; 58: 187-197.
- Sriamornsak P, Thirawong N, Puttipatkhachorn S. Emulsion gel beads of calcium pectinate capable of floating on the gastric fluid: effect of some additives, hardening agent or coating on release behavior of metronidazole. *Eur J Pharm Sci.* 2005; 24: 363-373.
- Halder A, Maiti S, Sa B. Entrapment efficiency and release characteristics of polyethylene imine treated or untreated calcium alginate beads loaded with propranolol resin complex. *Int J Pharm* 2005; 302: 84-94.
- Stops F, Fell JT, Collett JH, Martini LG. Floating dosage forms to prolong gastro retention- the characterization of calcium alginate beads. *Int J Pharm.* 2008; 350: 301-311.
- Rahman Z, Ali M, Khar RK. Design and evaluation of bilayer floating tablets of captopril. *Acta Pharm.* 2006; 56: 49-57.
- Mazzo DJ. International stability testing. 1st ed., Illinois: Interpharm Press; 2005.
- Elmowafy EM, Gehanne AS, Mansour S, Elshamy AE. Ionotropically emulsion gelled polysaccharides beads: preparation, in vitro and in vivo evaluation. *Int J Pharm.* 2009; 75: 135-142.
- Sriamornsak P, Thirawong N, Puttipatkhachorn S. Morphology and Buoyancy of oil entrapped calcium pectinate beads. *AAPS PharmSciTech.* 2004, 6(3):65-71.