Preparation and Characterization of Lafutidine and Ciprofloxacin HCl Loaded Microcapsules by Orifice Ionic Gelation Method

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Abstract:

Microcapsules have been recognized as an effective method for achieving controlled release and targeted drug delivery. Additionally, the concepts of mucoadhesion and floating have garnered attention in the design of drug delivery systems, as they enhance intestinal residence time by promoting close contact between the dosage form and the absorption surface, thereby improving drug bioavailability. Lafutidine and Ciprofloxacin HCl microcapsules were synthesized utilizing Sodium Alginate as the coating material, in conjunction with various mucoadhesive and floating polymers, including HPMC, by Orifice-Ionic Gelation technique. Microcapsules are characterized by their discrete, spherical nature, ability to flow freely, encapsulation efficiency and drug release. To achieve an optimized microcapsule formulation, various modifications were examined, including cross-linking duration, the incorporation of magnesium stearate, and the drug-polymer ratio.

Keywords: Microcapsules; Lafutidine; Ciprofloxacin HCl; Orifice-ionic gelation; Controlled release

1. Introduction

Lafutidine and Ciprofloxacin HCl are commonly employed in the management of peptic ulcers. While Lafutidine serves as an antiulcer agent, it is combined with the antibiotic Ciprofloxacin to effectively eliminate ulcers associated with *H. Pylori*. Hence, combination of these two drugs in the form microcapsules can effective be treated the peptic ulcers. Microencapsulation is a process to achieve controlled release and drug targeting. Mucoadhesion has been a topic of interest in the design of drug delivery systems to prolong the residence time of the dosage form in GIT, which facilitates the intimate

contact with absorption surface to enhance the bioavailability of drugs. Several studies reported drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes. Amongst the polymers used for microencapsulation, alginate has gained much attention since it is non toxic, biodegradable and can be prepared by a safe technique avoiding organic solvents hence; orifice ionic gelation technique was developed as an alternative approach [1].

Major Advantages of microencapsulation:

Provide protection to the core material. Microcapsules allow for the transformation of gasses and liquids into solid particles. The surface can be modified based on need. The drug release can be modified

Disadvantages of microencapsulation:

The methods of preparation are expensive. Hygroscopic materials are mostly not stable. The release of encapsulated materials might be affected by the uniformity of coating [2]. Considering the various advantages of microcapsules, the present study has been designed to develop dual drug loaded microcapsules and their characterization for better therapeutic outcome.

2. Materials and Methods

Chemicals and reagents

Lafutidine was purchased from Merck-Schuchardt, Mumbai, Maharashtra, India, Ciprofloxacin hydrochloride, HPMC- Hydroxy propyl methyl cellulose was procured from Loba chemical Pvt. Ltd., Mumbai, Maharashtra, India, Sodium Alginate was procured from Sigma-Aldrich, Mumbai, Maharashtra, India. All chemical and reagents use in the study were of analytical grade.

Methods

Preformulation studies

The goal of preformulation studies are meant to gather all the important information, mainly about the physical, chemical, and biopharmaceutical characteristics of active pharmaceutical ingredients, adjuvant and packaging materials [3].

Organoleptic properties

Organoleptic properties like colour, odour and physical appearance of the APIs (Lafutidine and Ciprofloxacin) and excipients (HPMC and Sodium Alginate) were examined [4].

Solubility Analysis

The solubility of Lafutidine and Ciprofloxacin hydrochloride in various solvents (distilled water, methanol, chloroform, ethanol etc.) were examined in the pH range of 1 to 8. For solubility determination of both the drugs, 5mg of Lafutidine and 5mg of Ciprofloxacin hydrochloride were

added to 10 ml of each solvent separately in test tubes. The mixture was shaken in Mechanical Shaker for 24 hours at the temperature of 25.0 ± 1.5°C [5].

Melting point

The melting points of Lafutidine and Ciprofloxacin hydrochloride were examined using finely powdered sample of each drug, filled in a glass capillary tube. Then tubes were sealed at one end and tied to the thermometer, which was kept in Thiele's tube apparatus filled with silicone oil. The temperature was gradually raised, and the point at which the drug fully melted was documented. The melting point of the drug was analyzed in relation to the values reported in the literature [6].

Formulation of microcapsules

Lafutidine and Ciprofloxacin HCl microcapsules were prepared by Orifice ionic gelation technique using polymers Sodium alginate and HPMC, calcium chloride was used as cross-linking agent [7]. Microcapsules were developed using previously reported orifice ionic gelation method with slight modification. This approach involved the preparation of microcapsules utilizing sodium alginate in combination with mucoadhesive and floating polymer Hydroxypropyl methyl cellulose (HPMC). Firstly, a homogenous polymeric solution (32 ml) was prepared by mixing coating material (sodium alginate) and HPMC in methanol. Then core material Lafutidine (100 mg) and Ciprofloxacin (500 mg) was incorporated to the polymer solution with continuous stirring at 500 rpm. The dispersion was introduced drop wise to the beaker containing 40 ml of calcium chloride solution with the help of a syringe fitted with a needle of 18 gauges. The additional droplets were preserved in the calcium chloride solution for 30 min. This stage facilitates the curing reaction to develop spherical microcapsules. Then the product was collected and washed repeatedly with water. The prepared microcapsules were dried at 45ºC for 12 hrs and 1% magnesium stearate was added to avoid sticking of microcapsules and stored in a desiccator for further use [8].

Characterization of microcapsule

Measurement of particle size (PS) and zeta potential (ZP)

Microcapsules were analysed for particle size with the help of Malvern particle size analyzer (Malvern S4700 PCS system, Malvern Instruments Ltd, UK). A suspension of microcapsules was prepared by suspending 50 mg of particles in 10 ml of MQ water and analysed with an obscuration index of about 5% (The obscuration index quantifies the extent of light lost caused by the presence particles along the light path). The experiment was carried out at a scattering angle of 90° and at a temperature of 25°C. Measurements were conducted thrice for each sample under similar conditions and mean values were reported. For measuring the Zeta potential (zetasizer, Litesizer DLSIF 501, Anton Paar, India) same suspension was used and values were recorded [9].

Encapsulation efficiency and drug loading

The encapsulation efficiency (% EE) and drug loading (% DL) were determined by previously reported HPLC method with some modifications. The microcapsule solution of 1 mg/ml was prepared in methanol and 20 µL of the sample was injected manually to HPLC equipped with Shimadzu VP HPLC System with LC-10AT pump and SPD-10AV vp UV/VIS detector. The separation through chromatography was performed utilizing a C18; 5µ, 4.6 x 250 mm, Thermo Hypersil BDS analytical column. The mobile phase, containing methanol and water in a ratio of 75:25 v/v, was subjected to filtration through a 0.45 µm membrane filter and subsequently degassed using ultrasonication. The flow rate was continually maintained at 1.0 ml/min, with analysis conducted at a wavelength of 280 nm. The quantification of Lafutidine and Ciprofloxacin in microcapsules was calculated from the peak area of HPLC chromatogram with the help of standard curve. The drug % EE and % DL were calculated using following equation [10].

$$\%\ \text{Encapsulation efficiency} = \frac{(\text{Actual drug content})}{(\text{Theoretical drug content})}\ x\ 100$$

$$\%\ \text{Drug Loading} = \frac{(\text{Wt. of the drug})}{(\text{Wt of microcapsules})}\ x\ 100$$

***In-vitro* drug release study**

The in vitro release of Lafuditine and Ciprofloxacin from selected microcapsule formulation was examined in pH 1.2 acid buffers for the time period of 12 h. These experiments were performed using dissolution testing apparatus (USP Type II) at a stirring speed of 100 rpm. Microcapsules were taken in muslin bag and added to 600 ml of dissolution media, maintained at temperature 37 ± 0.5 ^{o}C. An aliquot of 5 ml was pooled out at different time points and same quantity was replenished with fresh dissolution medium. The samples were then filtered using Whatman filter paper and drug content was estimated by HPLC. Percent drug released was calculated at each time interval and drug release was plotted against time [11].

3. Results and Discussion

Preformulation studies

Organoleptic properties

The organoleptic properties of active pharmaceutical ingredients are crucial in designing the new dosage forms. Organoleptic properties of Lafutidine and Ciprofloxacin hydrochloride were analyzed and compared (Table 1). Both compounds exhibited no odor and possessed a bitter taste. Lafutidine

was observed as a yellowish-white crystalline substance with an acicular shape and a smooth surface, while Ciprofloxacin hydrochloride was characterized as a faintly yellowish to light yellow crystalline powder. No noticeable changes in color or appearance were observed during the examination of the physical mixing of the drug and excipients.

Table 1: Organoleptic properties of lafutidine and ciprofloxacin hydrochloride.

S. No.	Properties studied	Results of lafutidine	Results of ciprofloxacin hydrochloride
1.	Colour	Yellowish white	Faintly yellowish to light yellow
2.	Odour	Odorless	Odorless
3.	Taste	Bitter	Bitter
4.	Appearance/ morphology	Crystalline acicular shape with smooth surface	Crystalline powder

Solubility studies

The aqueous solubility of a drug is a crucial physicochemical characteristic for the better drug absorption in the human physiological systems (Indian pharmacopeia, 2007). For better therapeutic outcome of a drug substance, it must have some solubility in the physiological pH range of 1 to 8. The solubility profiles of Lafutidine and Ciprofloxacin hydrochloride in various solvents revealed distinct differences in their properties. Lafutidine is generally soluble in glacial acetic acid, methanol, DMSO, and 0.1 N HCl but no solubility was observed in water (Table 2).

Table 2: Solubility of lafutidine and ciprofloxacin hydrochloride in various solvents.

Solvents	Solubility of lafutidine	Solubility of ciprofloxacin hydrochloride
Water	Not Soluble	Soluble
Acetic acid (Glacial)	Soluble	Freely soluble
DMSO	Soluble	Poorly soluble
Acetone, Ethyl alcohol	Sparingly soluble	Practically insoluble
Methanol	Soluble	Slightly soluble
0.1 N HCl	Soluble	Freely soluble

The solubility of Lafutidine was less in acetone and ethyl alcohol. In contrast, Ciprofloxacin hydrochloride is soluble in water, glacial acetic acid, and 0.1 N HCl, while it showed poor solubility in DMSO, very slight solubility in methanol, and is practically insoluble in acetone and ethyl alcohol. These solubility differences highlight the diverse chemical characteristics of the two drugs and have

important implications for their formulation and bioavailability in different pharmaceutical applications.

Melting point

The melting points of Lafutidine and Ciprofloxacin HCl were 98 to 102 °C and 313 to 322 °C, respectively as revealed by literature. The melting points of Lafutidine and Ciprofloxacin, determined by the capillary method, were 101 °C and 312 °C, respectively.

Preparation of Microcapsules

The microcapsules of Lafutidine and Ciprofloxacin HCl were developed by orifice ionic gelation method. The sodium alginate polymer taken together with mucoadhesive and floating polymer Hydroxypropyl methyl cellulose (HPMC) was used for developing gastro retentive microcapsules. In order get optimized microcapsule formulation, modifications like cross-linking time, addition of magnesium stearate and drug-polymer ratio was investigated.

Table 3: Preparation of microcapsules of lafutidine and ciprofloxacin HCl.

S. No.	Lafutidine	Ciprofloxacin HCl	Sodium alginate	HPMC	Magnesium stearate (mg)	Calcium chloride
F1	100	500	100	250	2%	1%
F2	100	500	100	500	4%	1%
F3	100	500	100	750	2%	1%
F4	100	500	200	250	4%	1%
F5	100	500	200	500	2%	1%
F6	100	500	200	750	4%	1%
F7	100	500	300	250	2%	1%
F8	100	500	300	500	4%	1%
F9	100	500	300	750	2%	1%
F10	100	500	400	250	4%	1%
F11	100	500	400	500	2%	1%
F12	100	500	400	750	4%	1%
F13	100	500	500	250	2%	1%
F14	100	500	500	500	4%	1%

Total 14 formulations (F1 to F14) were investigated (Table 3). The yield of the microcapsules was in the range of 60 % to 84 %. The lowered yield in certain instances may be associated to losses that take place throughout multiple stages of processing, including the adhesion of the polymeric solution to the wall of glass container and the consequent effects of the washing procedures.

Characterization of microcapsules

Measurement of particle size and zeta potential

The stability and efficacy of the microcapsule formulations can be greatly impacted by the results of the zeta potential and particle size studies, which offer important insights into their features. The microcapsules formulations have zeta potentials ranging from -16.8 mV to -31.6 mV and particle sizes ranging from 10.3 µm to 39.7 µm (Figure 1). The microcapsules exhibited distinct characteristics, being discrete, free-flowing, and spherical in shape.

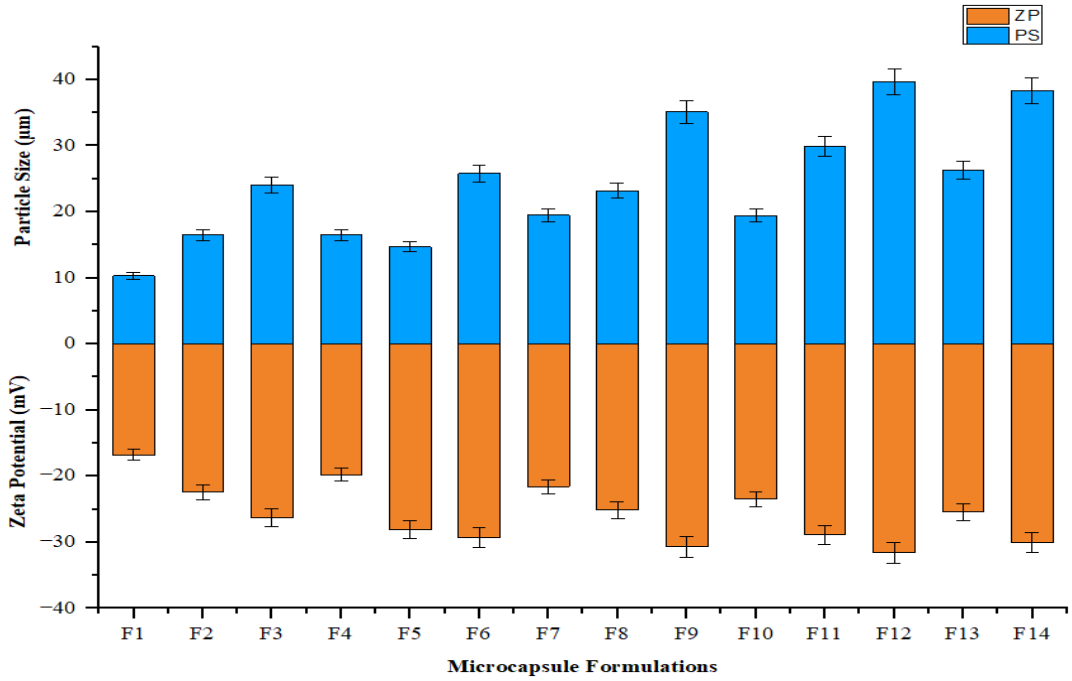

Figure1. Particle size and zeta potential of microcapsule formulations.

The higher viscosity of the solution used for the coating led to an increase in the diameters of the microcapsules, which appeared to increase in proportion to the polymer ratio. Modulation in the processing factors was not successful in reducing the particle size or the size range of the particles. Smaller particles tend to have enhanced bioavailability, as they generally exhibit better penetration and dispersion in biological systems. These smaller formulations may be especially beneficial in applications like drug delivery, where increased surface area and faster dissolution rates are advantageous. The zeta potential of all formulations showed negative values, indicating that the particles are likely to experience electrostatic repulsion, which helps prevent aggregation and enhances stability.

Table 4: Particle size, zeta potential, encapsulation efficiency, drug loading and % yield of drug loaded microcapsules.

Formulation	PS (µm)*	ZP (mV)*	EE (% w/w)*	Drug loading (%w/w)*	% Yield
F1	10.37 ± 0.20	-16.77 ± 0.05	52.66 ± 0.85	27.94 ± 0.46	59.8
F2	16.53 ± 0.35	-22.40 ± 0.26	63.43 ± 0.31	24.43 ± 0.58	64.6
F3	24.17 ± 0.30	-26.47 ± 0.20	72.87 ± 0.25	18.55 ± 0.37	60.1
F4	16.67 ± 0.25	-19.50 ± 0.36	53.77 ± 1.23	47.59 ± 0.81	69.8
F5	15.50 ± 0.36	-28.17 ± 0.25	84.30 ± 0.65	16.33 ± 0.43	83.9
F6	25.77 ± 0.60	-29.43 ± 0.41	74.43 ± 0.72	17.54 ± 0.28	68.2
F7	19.60 ± 0.26	-21.53 ± 0.35	58.63 ± 0.42	38.37 ± 0.13	66.3
F8	23.23 ± 0.28	-25.37 ± 0.45	80.73 ± 0.65	15.79 ± 0.31	74.8
F9	35.23 ± 0.45	-29.97 ± 0.30	66.17 ± 0.75	34.27 ± 0.47	71.9
F10	19.37 ± 0.41	-23.67 ± 0.37	76.33 ± 0.55	22.66 ± 0.52	74.5
F11	29.93 ± 0.15	-28.77 ± 0.15	70.87 ± 1.08	27.32 ± 0.17	68.2
F12	39.63 ± 0.20	-31.53 ± 0.23	64.83 ± 0.35	31.39 ± 0.53	63.7
F13	26.30 ± 0.17	-25.33 ± 0.25	82.63 ± 0.31	13.84 ± 0.77	80.6
F14	38.13 ± 0.25	-30.03 ± 0.20	66.67 ± 0.55	26.82 ± 0.40	67.4

* The values represent as mean ± SD for n=3

Encapsulation efficiency (EE) and drug loading

Entrapment efficiencies of both drugs were in the range of 52.6 ± 0.85 % to 84.3 ± 0.65 % and loading of drug inside microcapsules was in the range of 13.8 ± 0.77 % to 47.59 ± 0.81 %. The uniformity of drug content in microcapsules is indicated with low values of standard deviation in % drug loading (Table 4). The result showed that high proportion of polymer influence the encapsulation efficiency of the drug. As the drug possesses lipophilic property, diffusion of drug is not possible through polymer. This showed good percentage of drug entrapment inside the microcapsule formulation. It was also observed that the drug entrapment was less with the increase of drug loading, which results in enhanced drug leakage, leading to wastage of drug. This occurs due to the channels developed within the polymer structure that facilitate the escape of the drug. However, the optimized formulation F5 was selected as best formulation based on the particle size and entrapment efficiency for the further studies.

In-vitro drug release

The release of the drug from any dosage form serves as an indication of the dissolution process. The aim of in vitro drug release studies, commonly referred to as dissolution testing, is to provide a possible prediction or correlation with the bioavailability of the product in vivo. The rate of drug release in vitro was affected by the composition of the drug and polymer. Nonetheless, a multifaceted interaction could take place within drug and the polymer, encompassing the entrapment of the drug within the polymer and absorption on the polymer matrix due to electrostatic adhesion. The *in vitro* release of drugs was performed for F5 formulation (Figure 2). The release of Lafutidine and Ciprofloxacin from the microcapsules was determined from the peak area of individual HPLC chromatogram. After 12 h study, the results showed that Lafutidine was released almost 85 % and Ciprofloxacin was released 90%. The formulation F5 prolonged the drug release up to 12 h due to water soluble polymer HPMC that hydrates in aqueous environments, resulting development of gel-like matrix. The swelling may establish a diffusion barrier, thereby regulating the drug release rate. The viscosity of formulation may also be enhanced, contributing to the modulation of the release rate. Sodium alginate enhances the mucoadhesion of formulations, thereby increasing drug retention on the site of application. The formation of gel in the gastric environment develops a barrier that regulates drug release, thereby contributing to the extended release of the drugs from the F5 formulation. The release of Lafutidine and Ciprofloxacin from microcapsules (F5) was also compared with native drugs. During the initial hour, a notable release of approximately 38% was recorded for Lafutidine intact powder, while Ciprofloxacin exhibited a release of 28%. The occurrence of burst release is a typical characteristic observed during the early phase of numerous drug release systems.

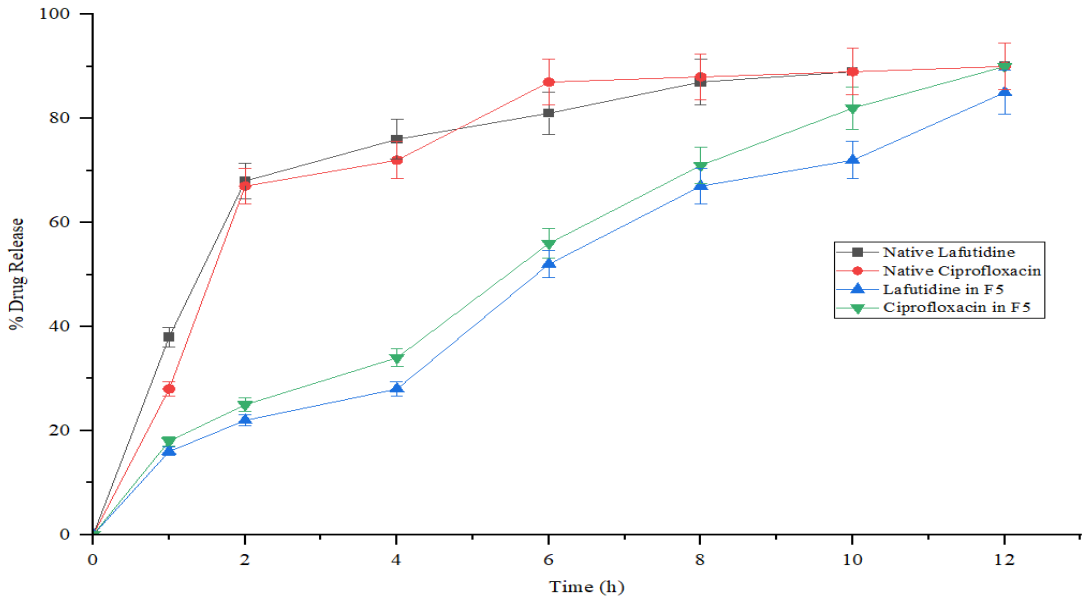

Figure 2: In vitro drug release from pure drug and microcapsule formulation (F5).

The initial burst release was reduced to 16 % and 18 % for Lafutidine and Ciprofloxacin respectively. A gradual release was noted from the microcapsules over a period of at least 12 hours, attributed to the polymer's formation of a protective wall around the drug. It indicates that they exhibit properties of sustained release. After 4 hours, a rapid drug release was observed. It is due to polymer erosion at the surface of the microcapsules, leading to the release of the drug that was loaded in the close vicinity of the surface. The combination of dissolution, diffusion, and erosion may serve as the mechanisms for drug release from the microcapsules.

4. Conclusion

The research focused on the formulation, development, characterization and evaluation of microcapsules containing Lafutidine and Ciprofloxacin hydrochloride for prolonged drug delivery, aiming for a sustained release profile to enhance therapeutic outcomes. The organoleptic properties revealed that both drugs were bitter in taste, odorless, and had distinct appearances; Lafutidine was yellowish-white, while Ciprofloxacin hydrochloride had a faint yellowish hue. These properties are useful for quality control and identification in pharmaceutical formulations. The solubility profiles indicated that Ciprofloxacin hydrochloride is soluble in water, glacial acetic acid, and 0.1N HCl, while Lafutidine is insoluble in water. However, Lafutidine showed solubility in organic solvents including methanol and DMSO. These differences in solubility were taken into account in formulation design. The melting points of Lafutidine (101 °C) and Ciprofloxacin hydrochloride (312 °C) further confirmed their distinct crystalline structures. The pH values of the drugs showed that Lafutidine is slightly alkaline (pH 5.6 ± 0.2), while Ciprofloxacin hydrochloride is more acidic (pH 3.5 ± 0.4), suggesting possible differences in their dissolution and absorption characteristics in different physiological environments.

Microcapsules were developed using the orifice ionic gelation technique with various excipients ratios, and formulations (F1 to F14) were characterized for particle size, zeta potential, % EE, and swelling index, The microcapsules formulations have zeta potentials ranging from -16.8 Mv to -31.6 Mv and particle sizes ranging from 10.3 μm to 39.7 μm. The microcapsules were uniform in size, discrete and free flowing. This suggests that microcapsules were developed in stable colloidal dispersions. Encapsulation efficiency of both drugs was within the range of 52.6 ± 0.85 % to 84.3 ± 0.65 % and drug loading was 13.8 ± 0.77 % to 47.59 ± 0.81 %. Based on the particle size and encapsulation efficiency the optimized formulation F5 was considered as best one and selected for further studies. It was also noted that drug retention within the microcapsules was highly formulation-dependent. The *in-*

vitro release of drug from microcapsules exhibited that F5 had highest cumulative drug release at 12 hours, demonstrating its potential for sustained drug delivery.

Declaration of competing interest

The author declares no conflict of interest, financial or otherwise.

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References

1. Alipour S, Montaseri H, and Tafaghodi M. Preparation and characterization of biodegradable paclitaxel loaded alginate microparticles for pulmonary delivery. Colloids and Surfaces B: Biointerfaces, 2010. 81(2): p. 521-529.
2. Hwang S. J., Park H and Park K (1998).“Gastric Retentive Drug Delivery Systems,” Critical Reviews in Therapeutic Drug Carrier Systems,15 (3), pp. 243-284.
3. Albert A.A., and Serjeant E.P. Ionization Constants of Acids and Bases.Wiley, Newyork. 1984.
4. Singh B.N and Kim. Floating drug delivery systems: an approach to controlled drug delivery via gastric retention. J. Control. Release, 2000. 63: 235-239.
5. Kumar K Ranjiti, Bhikshapathi DVRN, Sandhyarani B. Preparation and *In Vitro* Evaluation of Lafutidine floating microspheres, Research Journal of Pharmaceutical, Biological and Chemical Sciences, ISSN: 0975-8585
6. Najmuddin M, Sachin S, Asgar A, Patel V, Khan T. Formulation and In vitro Evaluation of Floating Microspheres of Ketoprofen Prepared by Emulsion Diffusion Method. Int J Pharmacy and Pharma Res 2010; 2: 13-19.
7. Phutane P,Shindhane S,Lotlikar V,Ghule and lotlikar V.In vitro evaluation of novel sustained release microsphere of Glipizide by the evaluation of novel sustained release microspheres of Glipizide by the emulsion solvent diffusion evaporation method. J Young pharm.2010; 2(1):35-41.
8. Muthusamy K, Govindarazan G, Ravi T.K. Preparation and evaluation of Lansoprazole -floating micropellets. Indian J.Pharm.sci.2005; 67(1):75-79.
9. Mahajan, N.M., Sakarkar, D.M., Manmode, S. Preparation and Characterization of Meselamine Loaded PLGA Nanoparticles. Int. J. Pharm. Pharm. Sci. 2011 ;3(4): 208-214.
10. Dong W, Bodmeier R.Encapsulation of Lipophilic Drugs within Enteric Microparticles by A Novel Coacervation Method. Int. J. Pharm. 2006; 326(1–2): 128–138.

11. Sandile M, Khamanga N.P , Tsitsi N, Hendrina H, Roderick, B.W. The Evaluation of Eudragit Microcapsules Manufactured by Solvent Evaporation Using USP Apparatus 1. Dissolution Technologies. 2009. 16(2): 15-22.