Development and Evaluation of Gastroretentive Drug Delivery System of BCS Class-II Drug for an Peptic Ulcer

Anju Mishra*[1], Dr. Satish Kumar Sahu[2], Dr. Utpal Jana[3]

[1]Assistant Professor, School of Pharmacy Chouksey Engineering College, Bilaspur – 495001, Chhattisgarh, India
[2]Professor, J. K. College of Pharmacy, Bilaspur - 495550, Chhattisgarh, India
[3]Professor and Head, Dept. of Pharmaceutics, Anand College of Education, Kabilpur, Debra, Paschim Medinipur – 721126, West Bengal, India

***Corresponding author email -** phmanju90@gmail.com
Assistant Professor, School of Pharmacy Chouksey Engineering College, Bilaspur – 495001, Chhattisgarh, India

KEYWORDS
Peptic ulcer; BCS Class II drug; Microcapsules; Characterization

ABSTRACT
Peptic ulcer is one of the silently developed diseases characterized by abdominal pain, vomiting, poor appetite, weight loss and sometimes internal bleeding. The BCS class II drugs are commonly employed for the treatment of peptic ulcers. These drugs possess poor solubility, variable bioavailability and need frequent dosing that leads to poor patient compliance. The purpose of this study is to develop gastroretentive polymeric microcapsules of BCS class II drugs for the effective treatment of the peptic ulcer. The formulation will be characterized for drug content, particle size, entrapment efficiencies, zeta potential, in vitro and in vivo drug release and stability study. The developed microcapsules will help to release the drug for prolonged period of time and will also provide effective delivery system of BCS class II drugs for the treatment of peptic ulcer.

1. Introduction

Oral route has achieved the most attention and is quite successful. Oral delivery of drug by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. An oral sustained release drug delivery system should be primarily aimed at achieving more predicted and increased bioavailability of drugs. The administration of a medication by means of oral controlled release drug delivery system (CRDDS) should ideally produce the required plasma level for a prolonged period of time. The development of oral drug delivery involves the optimization of the dosage form and characteristics of GI physiology. The sustained drug delivery may be complicated by limited gastric residence time (GRT) when taken orally. Rapid gastrointestinal transit can prevent complete drug release in the absorbance zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in the stomach or the upper part of the small intestine. [1] One of the suitable approaches that overcome the obstacles associated with the oral and conventional controlled drug delivery is the use of gastroretentive Drug Delivery System (GRDDS). GRDDS retain the dosage form in the stomach for prolonged and predetermined period of time. Gastroretentive dosage forms overcome the limitation of conventional oral controlled drug delivery systems by prolonging the gastric residence time by retaining dosage form in stomach and upper part of GI tract. Giving sufficient time for drug to be released from dosage form and sufficient time for a drug to be absorbed through GI tract, protecting the drug to degrade in colon. Protecting the degradation of normal GI flora by restricting the dosage form in stomach and upper part of GI tract.Gastric emptying of dosage form is an extremely variable process and ability to reside a dosage form in stomach for prolonged period of time and prolong the emptying time compared to conventional dosage form. In case of CRDDS gastric retention is important aspect, because it helps to retain CRDDS in stomach for longer and predicted time. GRDDS include floating DDS, bio-adhesive system, swellable system, high and low density system. [2]

Gastroretentive dosage form

Gastroretentive drug delivery system is one of the oral controlled dosage forms in which the dosage forms are retained in the stomach or small intestine.

Physiology of stomach

The complex anatomy and physiology, variation in acidity, bile salts, enzyme content and mucosal absorptive surface of GI tract mouth to the rectum significantly influence the drug release, dissolution and absorption from orally administered dosage forms. There are two distinct modes of GI motility and secretory pattern in human and animals, in fasted and fed states. As a result, the BA of the orally administered drugs may be different depending on the state of feeding. Fasted state is associated with cyclic events regulating the GI motility patterns, commonly called as the migrating motor complex(MMC).The MMC is organized into alternating cycles of activity and quiescence and can be sub divided into basal, preburst and burst interval, also named as phase I,II and III, respectively. [3]

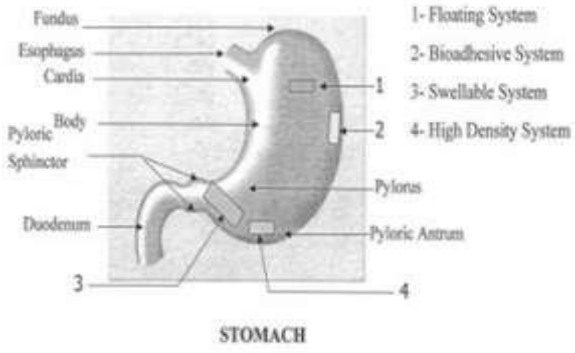

Fig.1. Physiology of the gastrointestinal tract.

There are various approaches to gastroretentive drug delivery systems such as FDDS, Swelling or expanding system, mucoadhesive system, modified-shape system, high density system and other delayed gastric emptying devices. Floating drug delivery system (FDDS) have bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuation in the plasma drug concentrations. Floating system can be classified into two distinct categories: effervescent and non-effervescent systems. [4]

Peptic ulcer

Peptic ulcer (PU) can be defined as the presence of a profound loss of substance affecting the mucosa of the stomach and/or duodenum, reaching beyond the muscularis mucosa, generally to the muscle layer due to the environmental gastric acid secretion.The two most common etiological causes are the chronic infection with Helicobacter pylori (Hp) and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid. There are other less common causes that can cause a PU, which are considered together, account for less than 5% of cases. Zollinger-Ellison syndrome or gastrinoma is one among them which is a neuroendocrine tumor, usually located at the head of the pancreas or in the duodenal wall, overactive and gastrin secretory. However, we must remember that approximately 5-15% of patients considered Hp negative, despite performing wide comprehensive etiological studies, do not get to find again the precise cause of PU, which are referred to as “idiopathic”. Tobacco abuse and O blood group, are considered as the risk factors for development of ulcer disease. The existence of genetic factors is unknown, although some cases with familial aggregation can occur. [5] Tobacco consumption, complicates ulcer healing and promotes its recurrences, especially in patients Hp (+) or in common NSAIDs takers. The digestive and extra-digestive diseases, most frequently associated with peptic ulcer, among which are included the concomitant presence of chronic gastroesophageal reflux disease (GERD), Barrett’s esophagus, chronic obstructive pulmonary disease, liver cirrhosis, chronic renal failure, while in other clinical situations, their presence is lower, as in the atrophic gastritis, Addison’s disease, autoimmune thyroiditis and hyperparathyroidism. The peptic ulcer is a curable disease and needs proper medication for complete cure. The drugs used are mainly BCS class II category with poor solubility and poor bioavailability. The maximum drug availability is essential to the absorption site in order achieve the maximum bioavailability. The present study has been designed to develop gastro-retentive system of BCS class II drug for effective management of peptic ulcer. [6]

2. Materials and methods

Chemicals and reagents

Lafutidine was purchased from Merck-Schuchardt, Mumbai, Maharashtra, India, Ciprofloxacin hydrochloride, HPMC- Hydroxy proply 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

Characterization of lafutidine

Nature - A Crystalline acicular shape with smooth surface
Color - yellowish white
Taste - Bitter
Melting point – the melting point of drug sample was determined by capillary method and found between 98.87-101.57 °C which complies with melting point reported in clarkes Index.
Solubility - It is freely soluble in glacial acetic acid, DMF, soluble in methanol, sparingly soluble in dehydrated ethanol, very slightly soluble in ether, practically insoluble in water with log p = 3.8

pH - pH of lafutidine drug found to be 5.6 ±0.2 [7]

Characterization of ciprofloxacin HCl

Nature - Ciprofloxacin hydrochloride (USP) is the mono hydrochloride monohydrate salt of ciprofloxacin
Taste - it is extremely bitter taste
Color - It is a faintly yellowish to light yellow crystalline substance.
Molecular weight - 385.8 g/mol.
Melting Point - 313°C to 322°C pH 3.0 – 4.5
Partition coefficient - partition coefficient values were obtained 1.3 [8]

Sodium alginate

Alginates are biodegradable hydrophilic polymers consisting of β-D-mannuronic acid and α-L-glucuronic acid residues joined by 1, 4-glycosidic linkages. [9] These polysaccharides found in brown seaweed and marine algae such as Laminaria Hyperborea, Ascophyllum nodosum, and Macrocystis pyrifera. Several alginate salts are commercially available as sodium alginate, calcium alginate, ammonium alginate, and potassium alginate. Specially; sodium alginate has been commonly used in the formulation of GRDDS. Alginates can be chosen in such formulations as it exhibits good characters as biocompatibility, biodegradable, nontoxic in addition to it experience mucoadhesive properties. [10] These polymers form a viscous gel layer upon contact with gastric fluids to form low-density dosage form. Alginate can form cross-linking with polyvalent cations which result in the formation of stable gellike matrices. Sodium alginate has been used as a polymer in the preparation of gastroretentive drug delivery tablet of domperidone. [11]

Formulation of microcapsules

Lafutidine microcapsules were prepared by Orifice ionic gelation technique using polymers Sodium alginate and HPMC, calcium chloride was used as crosslinking agent. [12]

Preparation of microcapsules
Ionic gelation technique

Orifice ionic gelation method (syringe method): Orifice ionic gelation method is also been successfully used to prepare large sized alginate beads. In this method microcapsules are prepared by employing sodium alginate in combination with different mucoadhesive polymers like Hydroxy propyl methyl cellulose in the different polymer ratios like 1:1, 3:1, 5:1, 9:1& 4:1 are dissolved in purified water to form a homogenous polymer solution. 1 A homogenous polymer solution was prepared by coating material (sodium alginate) and mucoadhesive polymer was dissolved in 32 ml to form a homogenous polymer solution. The core material Lafutidine (100mg) plus Ciprofloxacin 500 mg was added to the polymer solution, it was properly stirred in homogenous solution at a 500 rpm. [13] The resulting dispersion was dropped drop wise to a calcium chloride (1% w/v) [40 ml] through a syringe fitted with a needle of 18 gauge. The added droplets were retained in the calcium chloride solution for 30 min to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation and the product was thus separated and washed repeatedly with water and dried at 45ºC for 12 hrs. Since the microcapsules prepared by the above method sustain the release up to 8 hrs to 9 hrs only, further modifications were made in this method. These modifications include (i) increasing the cross-linking time for further 3 to 6 hrs (Formulations F1 to F5). (ii) Addition of magnesium stearate (#200 mesh) in 2 to 4%w/w concentration after thoroughly mixing with the drug Lafutidine & Ciprofloxacin by spatulaion (on a butter paper). The prepared microcapsules were stored in a desiccator for further use. [14]

Angle of repose

The angle of repose is a parameter commonly used for the evaluation of interparticle force.[16] The simplest method for the determination of the angle of repose is the "poured" angle. A funnel with a wide outlet is affixed at a distance of 10 cm above the bench, where a piece of paper is placed directly beneath the funnel. Powder is added while the funnel is closed. The contents flow through and collect on the paper. The diameter of the cone (D) and two opposite sides ($l_1 + l_2$) are measured with rulers. The angle of repose (θ) is calculated from the equation arc cos $[D/(l_1 + l_2)]$. The relationship between flow properties and angle of repose has been established. When the angle of repose is less than 25 degrees, the flow is said to be excellent; on the other hand, if the angle of repose is more than 40 degrees, the flow is considered to be poor. [15]

$$\theta = tan^{-1}\,(h/r)$$

Swelling Study

The swelling index of microcapsule is an indication of the capacity of microcapsule to imbibe water and swell.Water uptake of the microcapsule loaded with the drug were determined by measuring the extent of swelling of the matrix in pH 1.2 acid buffer. The samples were allowed to swell in pH 1.2 acid buffer. The excess surface adhered liquid drops were removed by blotting with soft tissue papers and the swollen microspheres were weighed to an accuracy of 0.01 mg using an electronic microbalance. The microspheres were then dried in an oven at 50^0C for 5hr until there was no change in the dried mass of the samples. Dried microspheres were then weighed. Swelling study was calculated by using this equation. [16]

% swelling index = Where,

W_f - Weight of swollen microsphere

W_i- Weight of intial microsphere

Preparation of pH 1.2 acid buffers

To prepare 1.2 N HCl, 50 ml of 0.2M Solution of potassium chloride was taken in 200 ml of volumetric flask and 85ml of 0.2 M HCl was added and volume was make up to 200ml with distilled water. [17]

Preparation of standard calibration curve of lafutidine in 1.2 N acid buffers

Lafutidine (100 mg) was accurately weighed and dissolved in 100ml of pH 1.2 HCl buffer and sonicated for about 20 min till a clear solution was obtained.10 ml of 1st stock solution was diluted with 100 ml of pH 1.2 HCl buffer.1 ml of 2nd stock solution was diluted up to 10 ml of pH 1.2 HCl buffer to obtained 10 µg/ml and scanned between 200-400 nm. The resulting solution was serially diluted with 1.2 N HCl to get drug concentration of 5, 10, 15, 20, 25, 30, 35. The absorbance of solution was measured against 1.2 N HCl as blank at nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration (µg/ml) was plotted. [18]

Partition coefficient

The partition coefficient, abbreviated P, is defined as a particular ratio of the concentrations of a solute between the two solvents (a biphase of liquid phases), specifically for un-ionized solutes, and the logarithm of the ratio is thus log P. When one of the solvents is water and the other is a non-polar solvent, then the log P value is a measure of lipophilicity or hydrophobicity. The defined precedent is for the lipophilic and hydrophilic phase types to always be in the numerator and denominator respectively; for example, in a biphasic system of n-octanol (hereafter simply "octanol") and water. [19]

$$\log P_{\mathrm{oct/wat}} = \log_{10}\left(\frac{[\mathrm{solute}]^{\text{un-ionized}}_{\text{octanol}}}{[\mathrm{solute}]^{\text{un-ionized}}_{\text{water}}}\right).$$

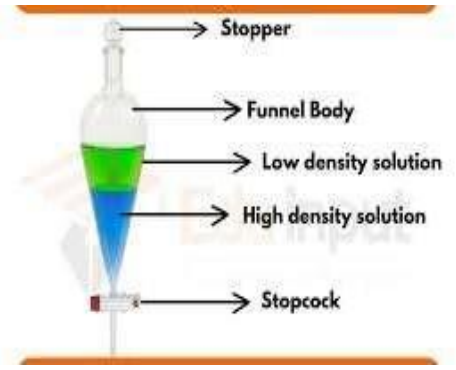

Fig.2. Partition coefficient of lafutidine.

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

The release of lafuditine from microcapsule of different batches was investigated in pH 1.2 acid buffer for 12 hours. These experiments were performed using dissolution on apparatus USP Type I at a stirring speed of 100 rpm. Microcapsule Lafuditine were taken in muslin bags and added to 600 ml of pH 1.2 acid buffer, maintained at temperature 37± 0.5^0 C. [20] During dissolution study 10 ml aliquot was withdrawn at different time interval and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatman filter paper no 42 and analysed for Lafuditine content at 290 nm using double beam UV spectrophotometer. Percent drug released was calculated at each time interval and graph was plotted between Percent drug released Vs time in hours. [21]

Evaluation of % drug loading and entrapment efficiency

Encapsulation efficiency and loading efficiency study

Accurately weighed 100 mg of microcapsule were crushed in mortar and small quantity of pH 1.2 acid buffers and then mixture was transferred to 100 ml volumetric flask and volume made upto 100ml with pH 1.2 acid buffer. After that mixture was stirred for 24 hours on magnetic stirrer and filtered through Whatman filter paper no. 42 and analysed spectrophotometrically at 290 nm. The encapsulation efficiency and Drug loading was calculated by using this equation. [22]

% Encapsulation Efficiency =

$$\frac{Total\ drug\ added - Drug\ in\ \ Supernatant}{total\ drug\ added} \times 100$$

% Drug Loading Efficency =

$$\frac{Actual\ drug\ content}{Wt\ of\ microspheres} \times 100$$

Evaluation of microcapsule

Measurement of particle size and zeta potential

The particle size of a pharmaceutical preparation is strictly maintained in order to get optimal biological activity. Methods to estimate particle size are a. Optical Microscopy b. Sieving Method c. Sedimentation Method d. Elutriation Method e. Centrifugal refractometry f. Permeability Method g. Light scattering Method. [23]

Determination of drug content

The percent drug content of drug is determined by dissolving 100mg powder of drug in 25ml pH 1.2 acid buffer using the mechanical shaker for 20 min and to this solution pH 1.2 acid buffer is added and volume is made up to 100 ml the resulting solution has then filtered through Whatman filter paper no 42 and required dilution is made and absorbance is taken at defined wavelength. [24]

Entrapment efficiency (Floating lag time and floating duration)

Floating properties of dry microspheres will be performed in dissolution USP Type I apparatus. Dissolution basket is filled with 600 ml pH 1.2 acid buffer. The rotation speed is maintained at 100 rpm with

temperature maintained at 37 ° C. [25] Microspheres will be placed in dissolution basket. The time taken by formulation took to emerge on the formulation on the medium surface (floating lag time) and the time the formulation constantly floated on the dissolution medium surface were noted. [26]

Fourier transform infrared spectroscopy (Surface morphology study)

The Surface photography of the micro-particles is examined using scanning electron microscopy. Microspheres will be spread on a double-sided adhesive plate, one side of which is stuck to glass slide. Excess microspheres will be removed and the slide is kept on the sample holder and scanning electron micrograph is taken using an electron microscope. [27]

UV Spectroscopy

The scanning of drug is performed in 1.2 N HCl. Accurately weighed 100 mg of drug is dissolved in 100ml 1.2 N HCl and 10 ml of this solution is diluted up to 100 ml and 1 ml of this solution is diluted up to 10 ml to get 10 µg/ml concentrations. [28]

Fourier transform infrared spectroscopy

Infrared spectrum is obtained with FT-IR spectrophotometer in the range of 4000 to 400 cm^{-1} by using potassium bromide method. [29]

Differential scanning calorimetry

Thermal analysis is carried out using a differential scanning calorimeter (DSC).The samples will be placed in an aluminum sealed pan and preheated to 200°C.The samples will be cooled to room temperature and then reheated from 40 to 450°C at a scanning rate of 10ºC/min. [30]

X- ray diffraction

It is a technique used in material science to determine the crystallographic structure of a material. XRD work by irradiating a material with incident X rays and then measuring the intensities and scattering angles of the X rays that leave the material. [31]

Assay of drug

An assay is a process of analyzing a substance to determine its composition or quality. Three techniques – fire assay, wet chemistry, and instrumental analysis are mainly used to analyze and determine purity of metal. [32]

3. Results

Table 1. Solubility of lafutidine.

S. No.	Different Solvent	Solubility Expression
1.	Glacial Acetic Acid	Soluble
2.	DMF	Soluble
3.	Methanol	Soluble
4.	Dehydrated Ethanol	Sparingly Soluble
5.	Ether	Very Slightly Soluble
6.	Water	Pratically Insoluble

Table 2. Solubility of ciprofloxacin hydrochloride.

S. No.	Different Solvent	Solubility Expression
1.	Water	Soluble
2.	Acetic acid	Freely soluble
3.	Methanol	Very slightly soluble

4.	Acetone, Ethly alcohol	Pratically insoluble
5.	DMSO	Poorly soluble

Table 3. Formulation of microcapsule.

Ingredients			**Formulation**			
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Drug-β-CD complex (mg)	472.06	472.06	472.06	708.10	708.10	708.10
Eudragit RS100 (mg)	200	150	100	200	150	100
Carbopol 940 (mg)	100	150	200	100	150	200
Dichloromethane (ml)	5	5	5	5	5	5
Ethanol (ml)	5	5	5	5	5	5

Partition coefficient

Partition coefficient = conc. of solute in organic layer / conc. of solute in aqueous layer

1. Concentration of solute in organic layer = 0.004N
Concentration of solute in aqueous layer = 0.006N
Partition coefficient of lafutidine = 0.004 = 0.6
= 0.006

2. Concentration of solute in organic layer = 0.004N
Concentration of solute in aqueous layer =0.003N
Partition coefficient of ciprofloxacin hydrochloride = 0.004 = 1.3
= 0.003

UV Analysis

The scanning of drug was performed in 1.2 HCL. Accurately weighed 100 mg of drug was dissolved in 100 ml 1.2N HCl and 10 ml of this solution was diluted up to 100 ml and 1 ml of this solution was diluted up to 10 ml to get µg/ml concentration. Scanning was done in the range of 200 to 400 nm. The λ_{max} was found to be 290 nm which comply with specification given in pharmacopoeia. Given drug Sample passes the UV scanning test for lafutidine.

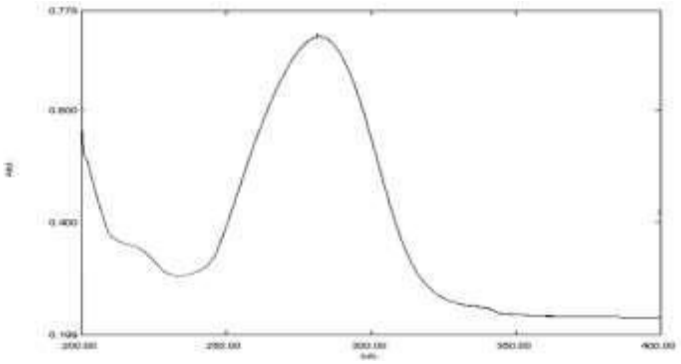

Fig.3. UV absorbance spectra of lafutidine in 1.2 HCl.

Table 4. Standard calibration curve of lafutidine in 1.2 N HCl.

S. No.	Concentration(µg/ml)	Absorbance
1.	0	0
2.	5	0.108±0.002
3.	10	0.200±0.002
4.	15	0.284±0.006
5.	20	0.386±0.001
6.	25	0.482±0.003
7.	30	0.692±0.005

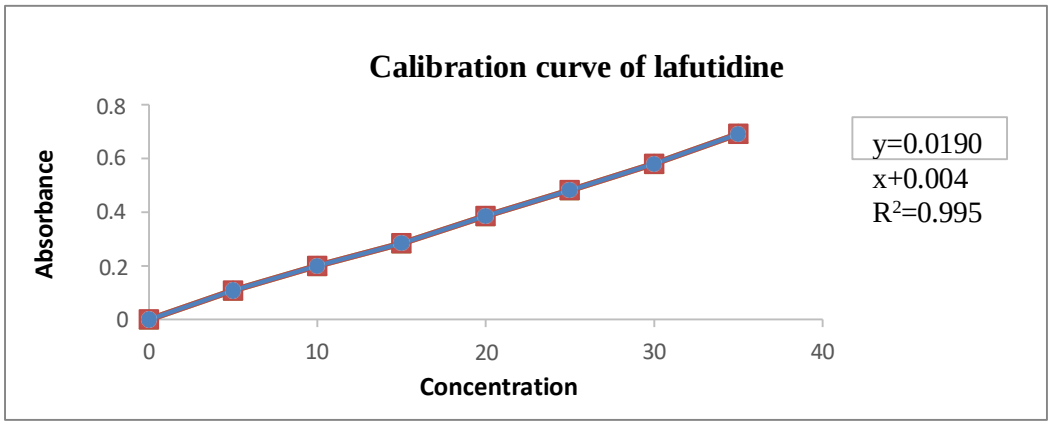

Fig.4. Graph of standard calibration curve of lafutidine in pH1.2 HCL.

Fourier transform infrared spectroscopy (FTIR)

Possible interactions between drug and polymer were investigated by FT-IR. FT-IR of pure LAFT characteristic sharp peaks of alkene stretching (C–H and CH2) vibration at 3324.32–3016.48 cm−1 and alkane stretching (–CH3, –CH2 and –CH) vibration at 2853.73 cm−1. Also exhibited C O stretch at 1738.2 cm−1 due to saturated ketone and C O–NH stretching at 1635.90 cm−1. A selective stretching vibration at 1561.57 cm−1 and 1525.80 cm−1 for primary and secondary amine was also observed. For functional groups like S O stretch and –C–S stretch showed vibrations at 1041.78 cm−1 and 729.57 cm−1 respectively. Overall there was no alteration in peaks of lafutidine pure drug and optimized formulation, suggesting that there was no interaction between drug & excipients. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug , indicating absence of any interaction.

Characterization of drug, polymer, excipients and physical mixture using fourier transform infrared spectroscopy

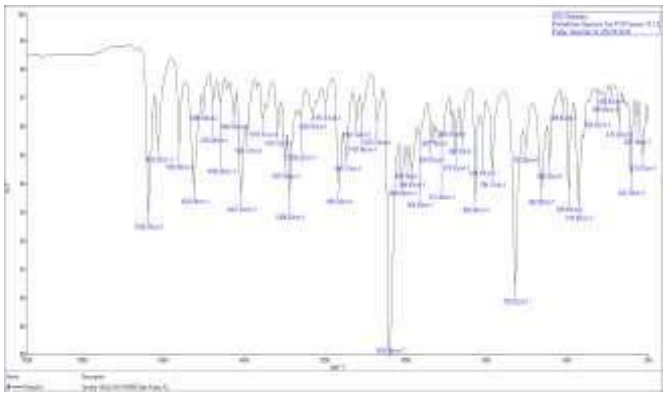

Fig.5. FTIR spectra of lafutidine.

Table 5. FTIR spectral analysis.

SL. No.	FREQUENCY RANGE (cm^{-1})	FUNCTIONAL GROUP
1	3675.36	Amide
2	2353	C–O bond
3	2260–2100	C=C Stretching bond of alkynes molecule
4	1535–1640	Diketones
5	1440–1470	Nitrosamine
6	1368	Iso propyl group
7	1270–1150	Ester carbonyl
8	1045, 1048	C–O bond
9	1035–1149	Polysaccharide
10	835–805	Aromatic compound
11	500–730	Halogen compound [Chloro-compound] (C-Cl)
12	490–620	Halogen compound [Iodo-compound](C–I)

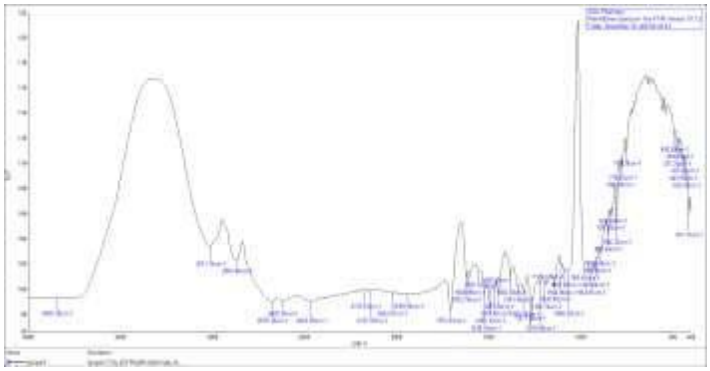

Fig.6. FTIR spectra of ciprofloxacin hydrochloride.

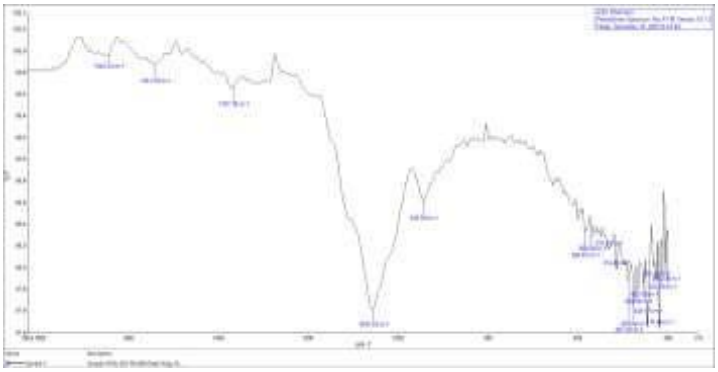

Fig.7. FTIR spectra of HPMC.

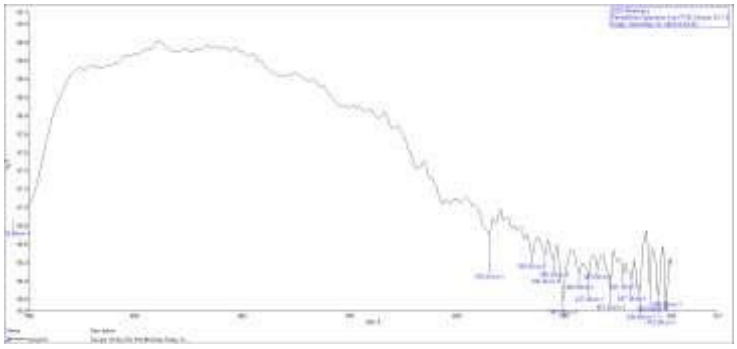

Fig.8. FTIR spectra of sodium alginate.

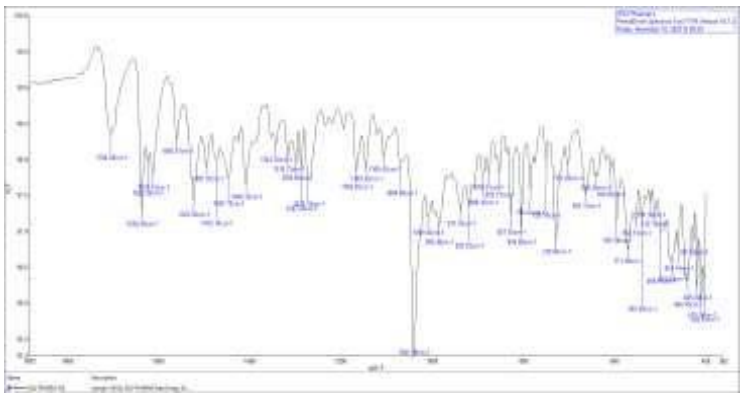

Fig.9. FTIR spectra of physical mixture of lafutidine, ciprofloxacin hydrochloride and HPMC.

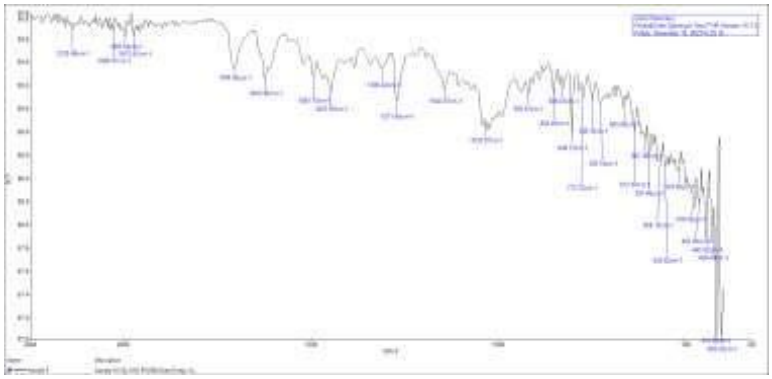

Fig.10. FTIR spectra of physical mixture of lafutidine, ciprofloxacin hydrochloride and sodium alginate.

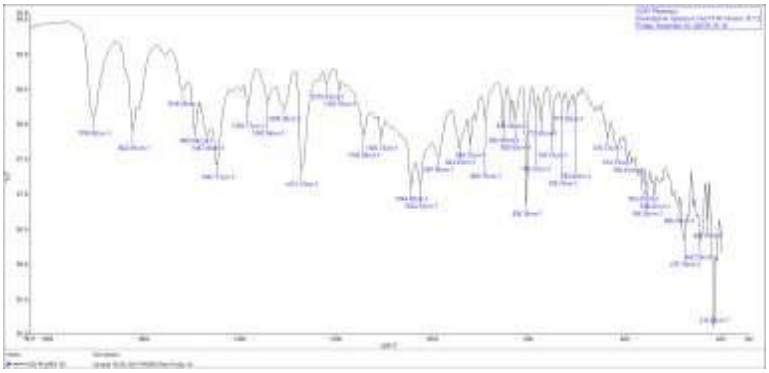

Fig.11. FTIR spectra of physical mixture of lafuditine, ciprofloxacin hydrochloride, HPMC and sodium alginate.

Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a differential scanning calorimeter (DSC).The samples were placed in an aluminum sealed pan and preheated to 100°C. In DSC the amount of heat put into the system is exactly equivalent to the amount of heat absorbed or liberated during a specific transition (transition energy). Differential scanning calorimetry was carried out to determine the possible interaction between drug and polymer. The DSC of lafutidine shows a endothermic peak at 101.57 °C corresponding to its melting transition temperature. While the DSC of physical mixture still show a endothermic peak for lafutidine at 100°C and show exothermic peak at 30°C.

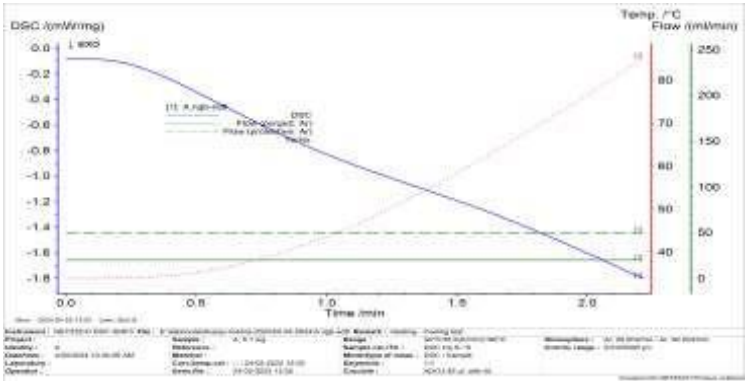

Fig.12. DSC thermogram of lafutidine.

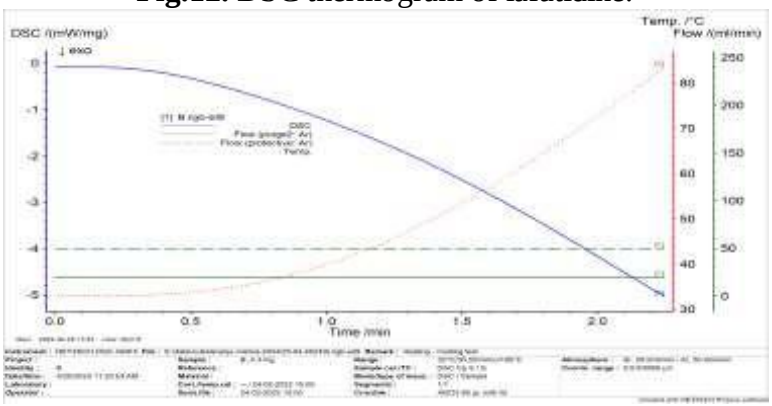

Fig.13. DSC thermogram of ciprofloxacin hydrochloride.

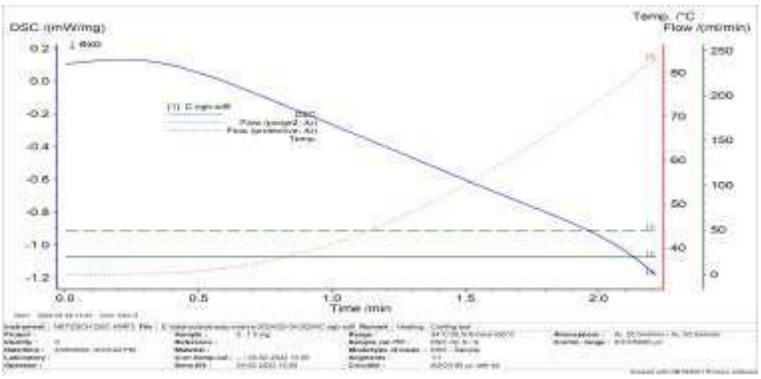

Fig.14. DSC thermogram of HPMC.

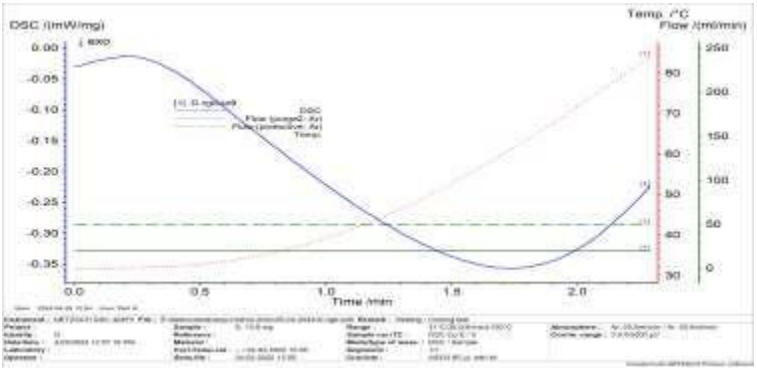

Fig.15. DSC thermogram of sodium alginate.

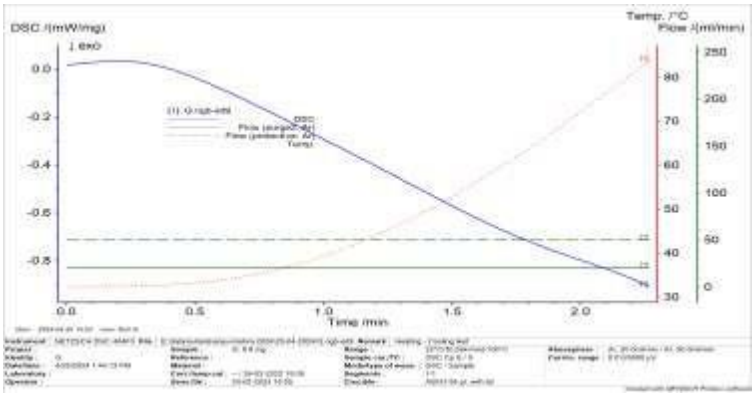

Fig.16. DSC thermogram of physical mixture of lafutidine, ciprofloxacin hydrochloride, HPMC and sodium alginate.

X-Ray diffraction analysis

X-Ray diffraction analysis (XRD) is a nondestructive technique that provides detailed information about the crystallographic structure, chemical composition, and physical properties of a material. It is based on the constructive interference of monochromatic X-rays and a crystalline sample.

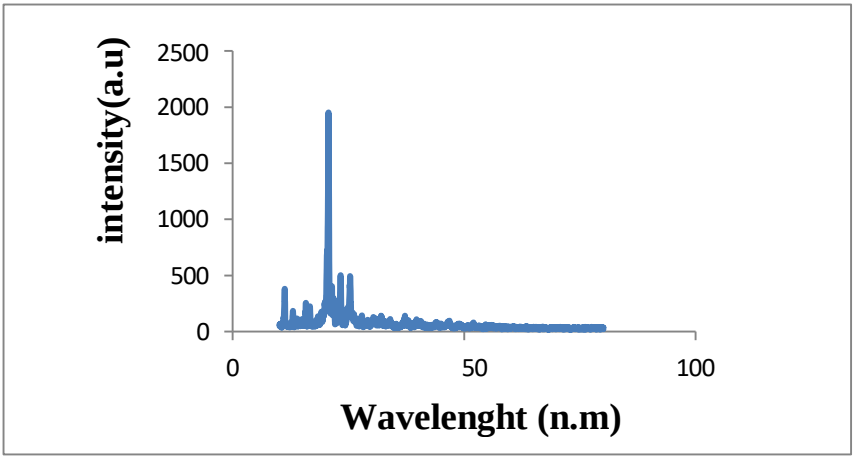

Fig.17. XRD analysis of lafutidine.

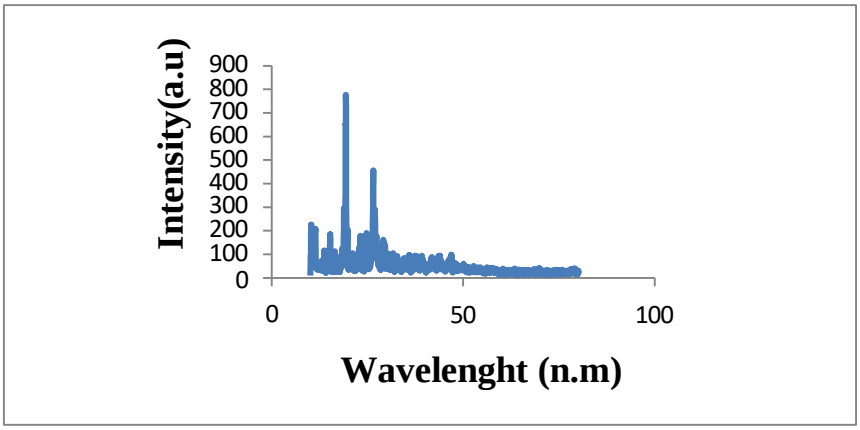

Fig.18. XRD analysis of ciprofloxacin hydrochloride.

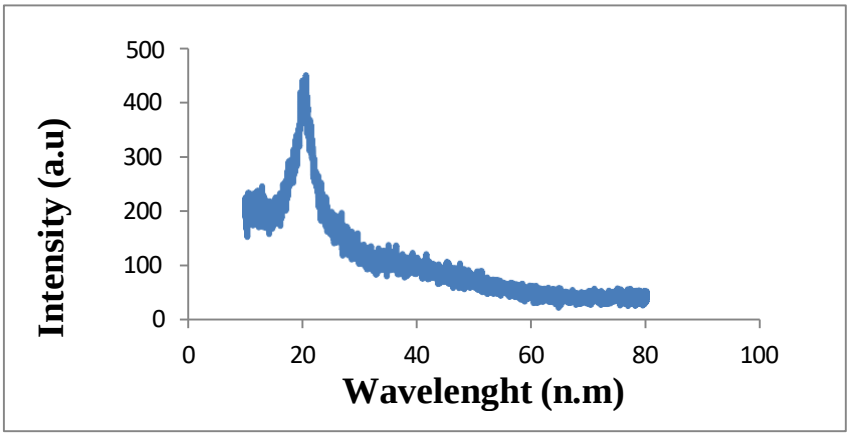

Fig.19. XRD analysis of HPMC.

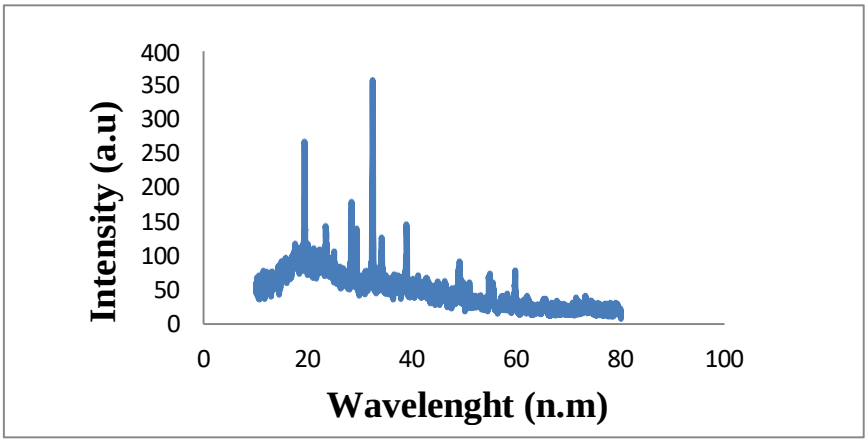

Fig.20. XRD analysis of sodium alginate.

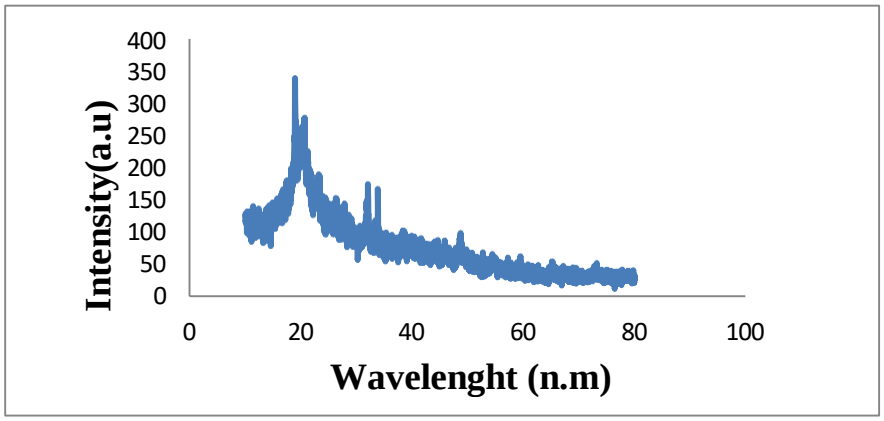

Fig.21. XRD analysis of physical mixture of lafutidine, ciprofloxacin hydrochloride, HPMC and sodium alginate.

Table 6. Composition of formulation.

S. No.	Lafutidine	Ciprofloxacin Hcl	Sodium alginate	HPMC	Magnesium stearate (Mg)	Calcium chloride
F1	100	500	500	500	2%	1%
F2	100	500	750	250	4%	1%
F3	100	500	800	200	2%	1%

F4	100	500	900	100	4%	1%
F5	100	500	800	200	2%	1%

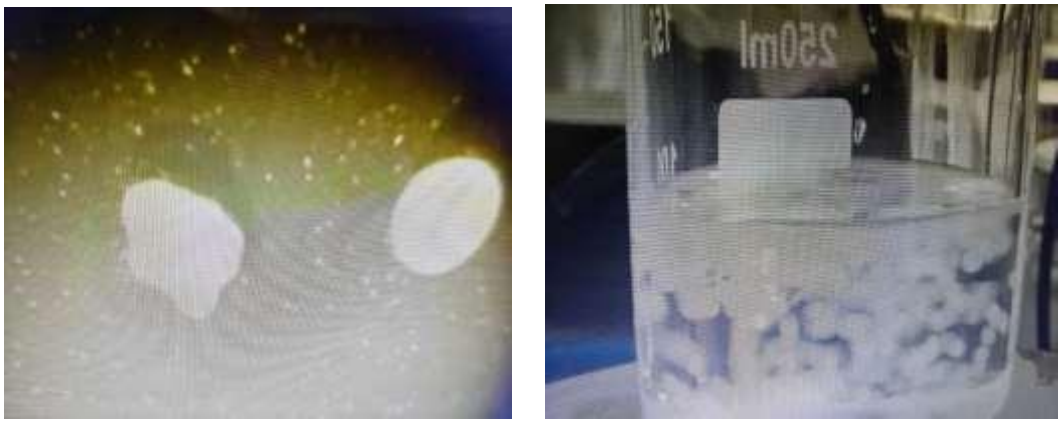

Fig.22. Microcapsule of formulation batches.

Particle size and zeta potential

All the formulation Batches were evaluated for the various physical parameter like particle size and zeta potential. The particle size was determined using Imaging System (Biowizard Software 4.1) The particle size and zeta potential of formulation (F1 to F5) are as shown in table.

Table 7. Particle size and zeta potencial of lafutidine.

S. No.	Particle size	Zeta potential
FI	60.55±0.08	-35.7 mV
F2	73.30±0.04	-45.2 mV
F3	79.00±0.04	-32.4 mV
F4	81.25±0.11	-48.6 mV
F5	77.01±0.19	-46.7 mV

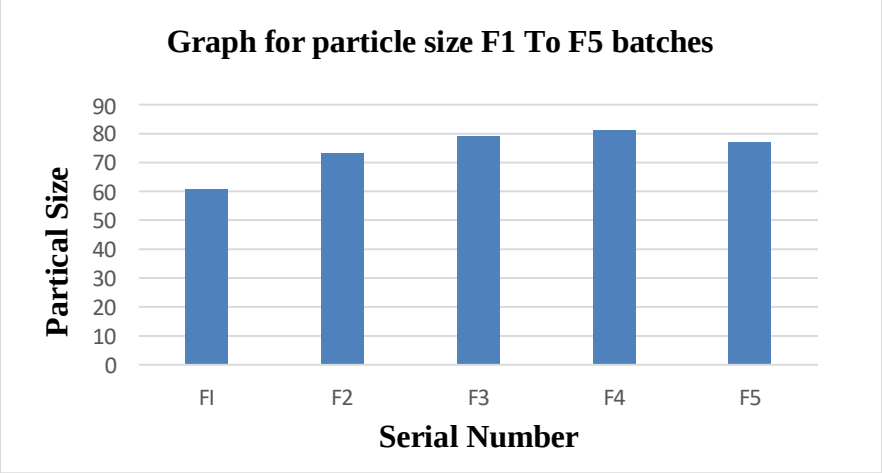

Fig.23. Particle size analysis of batches FI to F5.

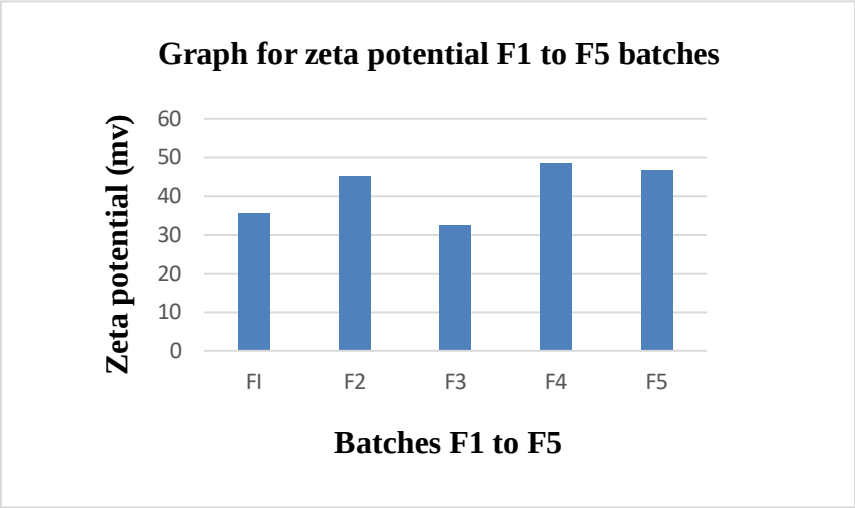

Fig.24. Determining zeta potential of batches F1 to F5.

Table 8. Percent encapsulation efficiency and percent drug loading efficiency of batches F1-F5 were shown in table

S. No.	% Drug loading	% Entrapment efficiency
F1	34.21±0.03	82.2%
F2	38.12±0.058	85.2%
F3	38.47±0.046	90.2%
F4	39.41±0.014	87.6%
F5	40.77±0.015	84.3%

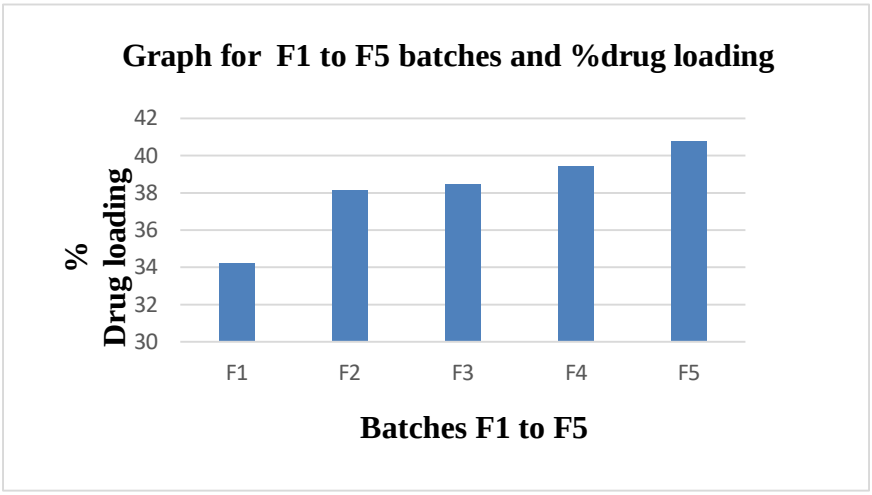

Fig.25. Graph for both % drug loading and % entrapment efficiency.

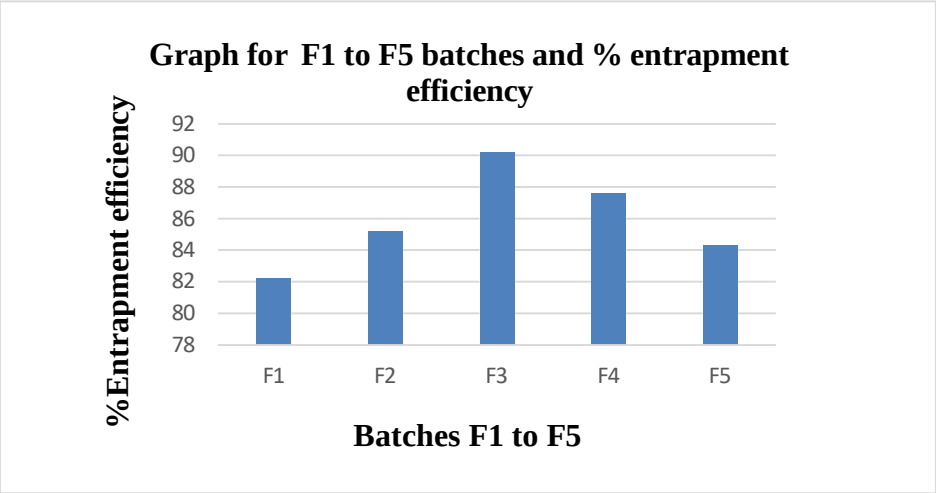

Fig.26. Encapsulation efficiency of batches F1 to F5.

Table 9. Evaluation of % swelling index from Fi to F5.

Time in hour	F1	F2	F3	F4	F5
0	0	0	0	0	0
2	92	85	96	83	98
4	92.8	86.1	96.7	84	98.1
6	94	87	98.3	85.3	98.6
8	96	88.4	98.9	86	99
10	96.2	89	98.9	86.4	99

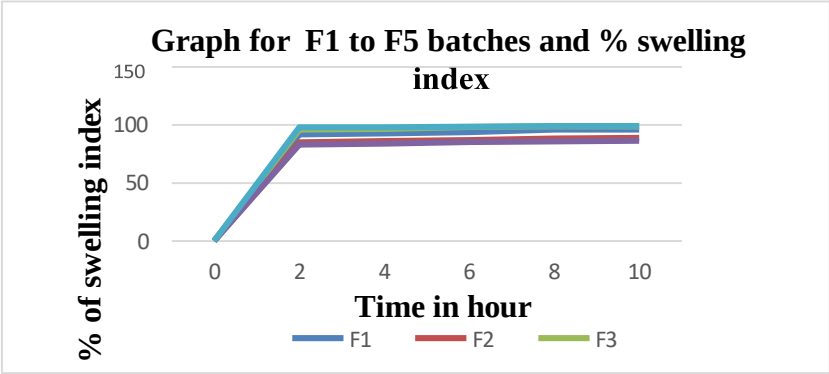

Fig.27. Graph for swelling index.

Table 10. *In-vitro* drug release data for microcapsules.

Time/hr.	F1	F2	F3	F4	F5
0	0%	0%	0%	0%	0%
2	15.35%	18.35%	25.35%	16.45%	18.95%
4	20.56%	28.56%	45.56%	35.45%	45.78%
6	25.08%	35.08%	56.45%	45.35%	56.75%
8	45.15%	55.15%	60.56%	56.45%	68.48%
10	60.92%	68.92%	75.92%	85.85%	90.98%
12	75.25%	80.25%	91.25%	92.25%	95.97%

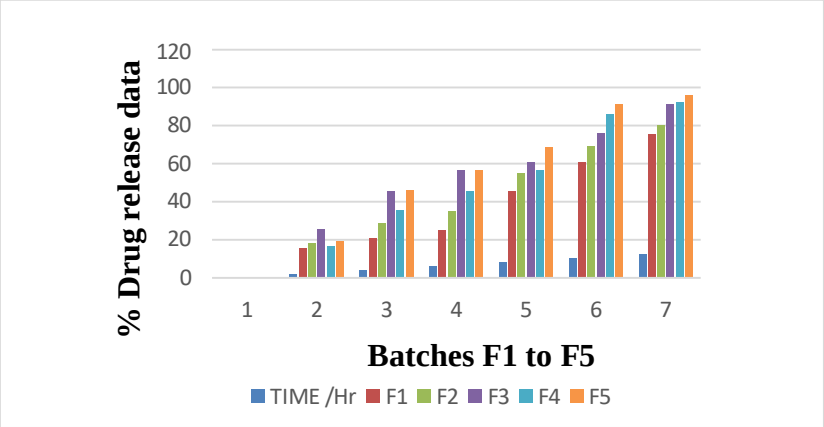

Fig.28. *In-vitro* % drug release data for microcapsules.

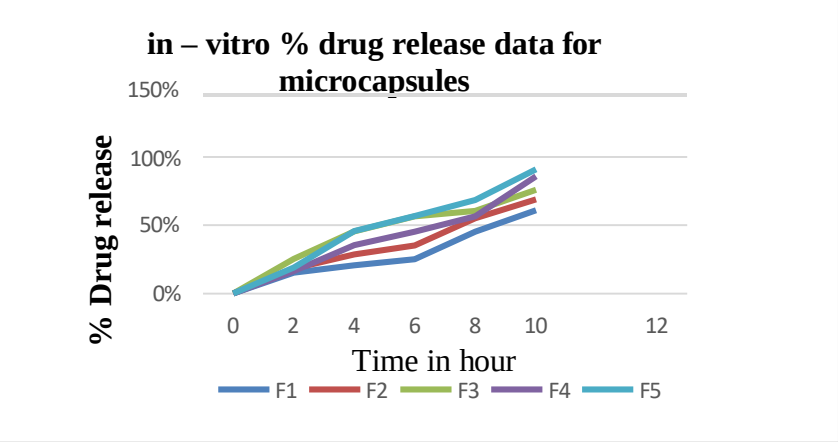

Fig.29. *In-vitro* % drug release data for microcapsules.

4. Discussion

Lafutidine floating microcapsules were successfully prepared by ionotropic gelation method using sodium alginate, HPMC K4M and ethyl cellulose as polymers, sodium bicarbonate as gas generating agent and calcium chloride as cross linking agent. FTIR spectra of the physical mixture revealed that the drug and the polymers used were compatible. The Flow properties of all formulations were within the acceptable range. The particle size of floating microspheres were found to increase with increase in polymer concentration i.e. the formulations with HPMC K4M gave particles in the range of 85-312 µm and that of ethyl cellulose exhibited particles in the range of 167-329 µm. The surface study of floating microcapsules revealed that the microcapsules were spherical in shape with slightly rough surface having small distinct pores on the surface which may be responsible for drug release. The percentage yield obtained in all the batches was good and in the range of 75% to 83.7%. The drug release decreased with the increase in polymer concentrations in floating microcapsules. Formulations F1, F2, F3, F4, F5, F6, F7 and F8 followed Peppas model with non fickian drug release mechanism. The studies revealed that the optimized microcapsules remained intact floating in stomach for more than 10 h.

5. Conclusion

The gastroretentive drug delivery systems are retained in the stomach and assist in improving the oral sustained delivery of drugs. These systems help in continuously releasing the drug before it reaches to the absorption window, thus ensuring optimal bioavailability. Anti-peptic ulcer drugs are an important class of drugs that are used in the treatment of certain stomach and esophagus problem for reducing the amount of acid in stomach. Absorption of this class of drug is dependent on the site of drug release in the gastrointestinal tract. Bioavailability of such drugs decreases when from the deeper part of the gastrointestinal tract and have a limited solubility at alkaline pH. The concept of floating microcapsule can

be utilized to minimize the degradation of drug in the colon by avoiding direct contact with mucosa and improved availability of the drug in the stomach and upper GIT for absorption. The present research work may lead to the development of microcapsule capable of retaining in the stomach and releasing drug there for prolonged period of time. Formulation showed good results with respect to the various evaluation parameters, so it was selected as the optimized formulation. The particle size increased with increase in polymer concentration. The drug entrapment efficiency was increased with increase in concentration of polymers. The *in-vitro* drug release decreased with respect to increase in concentration of polymers. The optimized formulation showed good floating for 8 h in stomach of rat. The formulation was stable at the end of 60 days with stability study.

Declaration of competing interest

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

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors. The authors are helpful to the National Institute of Technology (NIT), Rourkela, Odisha, India for providing all required facilities.

References

1. Muthusamy K, Govindarazan G, Ravi TK. Preparation and evaluation of Lansoprazole floating micropellets. Indian J.Pharm.sci.2005; 67(1):75-79.
2. 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.
3. Patel PA, Fleisher LA. Aspirin, clopidrogel and the surgeon. Adv Surg. 2014;48:211-22.
4. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther. 2013;15 Suppl 3:S3.
5. Gigante A, Tagarro I. Non-steroidal anti-inflammatory drugs and gastroprotection with proton pump inhibitors: a focus on ketoprofen/omeprazole. Clin Drug Investig. 2012;32(4):221-33.
6. Alipour, S., H. Montaseri, and M. Tafaghodi, Preparation and characterization of biodegradable paclitaxel loaded alginate microparticles for pulmonary delivery. Colloids and Surfaces B: Biointerfaces, 2010. 81(2): p. 521-529.
7. Beneke, C., A. Viljoen, and J. Hamman, Polymeric plant-derived excipients in drug delivery. Molecules, 2009. 14(7): p. 2602-2620.
8. Davidovich-Pinhas, M., O. Harari, and H. Bianco-Peled, Evaluating the mucoadhesive properties of drug delivery systems based on hydrated thiolated alginate. Journal of Controlled Release, 2009. 136(1): p. 38- 44.
9. Benavides, S., R. Villalobos-Carvajal, and J. Reyes, Physical, mechanical and antibacterial properties of alginate film: Effect of the crosslinking degree and oregano essential oil concentration. Journal of Food Engineering, 2012. 110(2): p. 232-239.
10. Saha, T., Z.U. Masum, and S. Ashrafi, Preparation and In-Vitro Evaluation of Sodium Alginate Based Gastroretentive Floating Tablet of Domperidone. Galore International Journal of Health Sciences & Research, 2018. 3(1): p. 1-4.
11. Jain N. K, (2004). Progress in controlled and drugs delivery system **(**1st Edition), CBS Publisher, Delhi:77-95.
12. Kumar K Ranjiti, DVRN Bhikshapathi, B Sandhyarani, Preparation and *In Vitro* Evaluation of Lafutidine floating microspheres, Research Journal of Pharmaceutical, Biological and Chemical Sciences, ISSN: 0975-8585
13. 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.

14. Kotha R, Bolmol U.B, Reddy ER, Reddy K.R, Anusha P (2013), Formulation and evaluation of floating microspheres of Ranolazine for the treatment of chronic angina.*IJPS*,6(3):2137-2144.
15. Mostafavi A,Emami J, Vashosaz J,Rezazadeh M,(2013)Development of a prolonged release gastroretentive tablet formulation of Ciprofloxacin hydrochloride: Pharmacokinetic characterization in healthy volunteer. *Int. J. Pharm*. 409:128-136
16. El-kamel AH, Sokar MS, Al Gamal SS, Nagaar VF (2001). Preparation and evaluation of Ketoprofen floating oral delivery system. IJPS,220:13-21.
17. Garg R, Gupta GD. Gastroretentive Floating Microspheres of Silymarin: Preparation and In Vitro Evaluation.Tropical J of Pharma Res 2010;9:59-66.
18. Hafeez A, Maurya A, Singh J. Rana L (2013).In vitro evalution of floating microspheres of ketoprofen.*JSIR*,2(3),714-722
19. Alexander Streubel, (2006) Drug Delivery to the upper small intestine window using Gastroretentive technologies, current option in pharmacology,501 – 508.
20. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, (2007). Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation. *Eur J Pharm Biopharm*,67: 196-201.
21. Chien Y. W, Novel Drug Delivery system, (2nd Edition), Marcel Dekker (1992),139-196.
22. Caldwell LJ, Gardner RC, Cargill RC (1988). Drug delivery device which can be retained in the stomach for a controlled period of times, US patent 4735804, April 5, 245-262.
23. Deepa MK, Karthikeyanb M, (2009). Cefpodoxime proxetil floating microspheres: Formulation and in vitro evaluation. *Iran J Pharm Sci*, 5:69-72.
24. Dave BS, Amin AF, Patel MM 9,(2004). Gastro-retentive drug delivery system of ranitidine hydrochloride: Formulation and in vitro evaluation. *AAPS PharmSciTech* 5,34.
25. El-Gibaly I, (2002) .Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: Comparison with non-floating chitosan microspheres. *Int J Pharm* ,249:7-21.
26. Kawashima Y, Niwa H, Takeuchi H, Hino T, Itoh Y, (1992). Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J Pharm Sci*,81: 135-40.
27. Tania B, Lopez Mendez, Edorta Santos, Jose Luis Pendraz,Gorka Orive ,Rosa Maria Hernandez (2021).cell microencapsulation technologies for sustained drug delivery :Latest advances in efficacy and biosafety. *J of controlled release* 335:619-636
28. Mali K, Dias RJ,GhorpadeVS,HvaldarVD. Sodium Aliginate Microsphere containing Multicomponent Inclusion Complex of Domperidone.Lat.Am.J.Pharm2010;29:1199-1207
29. Patel RC, Keraliye RA, Patel NM. Commonsensical Predermine. Dissolution Time of furosemide achieve by preparing Inclusion complex. Int J Pharm and pharm.sci.2010;(3):142-146
30. Vedha B.N, Reddy A. Floating drug delivery of Nivirapine as a gastroretentive system. J Young Pharm.2010;2(4):350-355.
31. Tripathi GK, Singh S, Nath G. Formulation and evaluation of pH-sensitive oil entrapped polymeric blend amoxicillin beads for the eradication *helicobacter pylori*. IJPR. 2012; 11(2): 447 455.
32. Sahasathian T, PraphairaksitN, Muangsin N. Mucoadhesive and Floating Chitosan Coated Alginate Beads for Controlled Release of Amoxicillin. Arch Pharm Res. 2010; 33: 889-899