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Formulation and evaluation of floating matrix tablet of Flurbiprofen

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Abstract
In the present study, Flurbiprofen was used for preparing Floating dosage form that are designed to retain in stomach for a long time and have developed as a Floating drug delivery system by using various polymers like HPMC K100M and PEO to enhance the bioavailability and therapeutic efficacy of Flurbiprofen. The mechanism of action of Flurbiprofen is Non selective COX inhibitor which inhibits the prostaglandin synthesis. Sodium bicarbonate was incorporated as a gas generating agent. The direct compression method is used in present work. The formulation was optimized on basis of acceptable tablet properties like optimum hardness, uniform thickness, consistent weight uniformity and low friability. The prepared formulation shows better and significant result all the evaluated parameter.

Keywords: Flurbiprofen, Floating dosage, HPMC K100, PEO

Introduction
Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable excipients and prepared either by molding or by compression. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrates to promote tablet break-up in the digestive tract; sweeteners or flavors to enhance taste; and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance [1].

Oral bioavailability of a drug depends on aqueous solubility, drug permeability, dissolution rate, first-pass metabolism and susceptibility to efflux mechanisms, aqueous solubility and drug permeability are also important parameters attributed to oral bioavailability [2]. In drug discovery, the number of insoluble drug candidates has increased in recent years, with almost 70% of new drug candidates showing poor water solubility [3]

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration leads to good patients compliance. The retentive characteristics of the dosage form are not significant for the drugs that they are insoluble in intestinal fluids, act locally. To overcome these limitations, Various novel drug delivery systems are being developed to increase effectiveness of the drug in terms of therapeutic action, reduced dosing frequency [4, 5], improved patient compliance, increased bioavailability, minimal degradation of the drug and reduced adverse effects [6].

Thus, to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract includes floating drug dosage systems (FDDS) swelling or expanding systems, mucoadhesive systems, modified-shape systems, high-density system, and other delayed gastric emptying devices. Among these systems, FDDS have been most commonly used [1].

Floating drug delivery systems (FDDS) are invented to retain the drug in the stomach and applicable for drugs with poor solubility and low stability in intestinal fluids. The basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them.

FDDS are hydro-dynamically controlled low-density systems with sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The residual system is emptied from the stomach with the release of the drug. This results in enhanced gastric residence time and good control over plasma drug concentration fluctuations. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [6]. Prolonging the gastric retention of a delivery system is desirable for achieving the greater therapeutic efficacy of the drug substance under certain circumstances. For example, drugs which show better absorption at the proximal part of the gastrointestinal tract and drugs with low solubility and get degraded in alkaline pH found efficient in prolonging gastric retention. In addition, for sustained drug delivery to the stomach and proximal small intestine in treating certain ulcerative conditions, prolong gastric retention of the therapeutic moiety and hence offer numerous advantages including improved bioavailability and therapeutic efficacy with reduction of dosing frequency [7]. Floating drug delivery systems have an advantage to reduce the dose frequency and improves patient compliance. It thus improves the therapy [8].

Different types of floating drugs are effervescent and non-effervescent floating drugs [9].

Effervescent systems include utilize matrices prepared with swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach [9].

The non-effervescent System, after swallowing, swells via imbibition of gastric fluid to an extent that it prevents their exit from the stomach. The formulation methods of such type dosage forms involves the mixing of the drug with a gel, which swells when comes in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer provides buoyancy these dosage forms. The most commonly used excipients in these systems include hydroxypropyl methyl cellulose (HPMC), polyacrylate polymers, polyvinyl acetate, carbopol agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub-types Colloidal gel barrier system, Microporous Compartment system, Alginate beads, Hollow Microspheres/Microballons [10,11,12]

Flurbiprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent (NSAID) with antipyretic and analgesic activity. Oral formulations of flurbiprofen may be used for the symptomatic treatment of rheumatoid arthritis, osteoarthritis and anklylosing spondylitis. Flurbiprofen may also be used topically prior to ocular surgery to prevent or reduce intraoperative miosis. Flurbiprofen is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen. It is primarily indicated as a pre-operative anti-miotic (in an ophthalmic solution) as well as orally for arthritis or dental pain.[13]

The anti-inflammatory effect of flurbiprofen occurs via reversible inhibition of cyclooxygenase (COX), the enzyme responsible for the conversion of arachidonic acid to prostaglandin G_2 (PGG_2) and PGG_2 to prostaglandin H_2 (PGH_2) in the prostaglandin synthesis pathway. This effectively decreases the concentration of prostaglandins involved in inflammation, pain, swelling and fever. Flurbiprofen is a non-selective COX inhibitor and inhibits the activity of both COX-1 and -2. It is also one of the most potent NSAIDs in terms of prostaglandin inhibitory activity [13].

Materials and Methods

Materials Required

Table 1: Composition of different floating tablet formulations of Flurbiprofen

Ingredients (Mg)	Formulation			
	F1	F2	F3	F4
Flurbiprofen	50	50	50	50
Hpmc K100	50	37	25	12.5
Polyethylene Oxide (Peo)	12.5	25	37	50
Microcrystalline Cellulose(Mcc)	30	30	30	30
Sodium Bicarbonate	40	40	40	40
Magnesium Stearate	8	8	8	8
Talc	7.5	7.5	7.5	7.5
Aerosil 200	5	5	5	5
Total	200	200	200	200

Methodology

Preparation of Calibration curve

Calibration curve of Flurbiprofen was made in 0.1N HCl (pH 1.2) by preparing a serial dilution of Flurbiprofen with different concentrations (2, 4, 6, 8, 10, 12 µg/ml) from stock solution containing 1000µg/ml Flurbiprofen. The prepared samples were analyzed spectrophotometrically at 247 nm by using UV-visible spectrophotometer.

Preparation of Flurbiprofen floating tablets

Floating tablets were prepared by direct compression method using HPMC as a rate controlling polymer and Sodium bicarbonate as a gas generating agent. The powder mixture containing drug, polymers and other excipients were weighed and thoroughly blended in mortar and pestle and then passed through sieve no 40 and directly compressed using 8mm flat punches on a rotary punching machine. The compression force was adjusted to obtain tablets with crushing strength in the range of 5 to 6 kg/cm. Four batches of tablets were prepared by this technique given in Table no. 1.

Pre compression parameters

- **Angle of repose** [14]

The angle of repose of powder blend was determined by the funnel method. The accuratelyweight powder blend were taken in the funnel. The height of the funnel was adjusted in such away the tip of the funnel just touched the apex of the powder blend. The powder blend wasallowed to flow through the funnel freely on to the surface. The diameter of the powder conewas measured and angle of repose was calculated using the following equation 54.

$$\tan \Theta = h/r,$$

Where,
Θ: angle of repose, h: height, r: radius.

- **Bulk Density** [15]

The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and therefore more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder. Apparent bulk density (g/ml) was determined by pouring preserved bulk powder into a graduated cylinder via a large funnel and measuring the volume and weight. Bulk density can then be calculated by the following formula:

Bulk density = W/Vo

Where,
W = wt. of powder, V = initial volume.

- **Tapped Density** [16]

An accurately weighed quantity of crystals from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted, which gave the tapped volume. The tapped density was determined by the following formula.

Tapped density = W/V_f,

Where,
W = wt. of powder, V_f = final volume

- **Compressibility Index(Carr's Consolidation Index)** [17]

The Compressibility index is measure of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index. The compressibility index is calculated using measured values for bulk density (D) and tapped density (D) as follows:

Compressibility index = Dt - D /D * 100

Where,
D = Bulk density, Dt = Tapped density

- **DSC** [18]

DSC are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DS Cinstrument equipped with an intercooler. Indium/Zinc standards are used to calibrate the DSC temperature and enthalpy scale. The Sample preparations are hermitically sealed in an aluminumpan and heated at a constant rate of 10°C/min; over a temperature range of 25° C – 65°C. Inertatmosphere is maintained by purging nitrogen gas at the f low rate of 50ml/min. DSC curves: (A) Flurbiprofen, (B) physical mixture. DSC thermo gram of pure flurbiprofen and mixture will be exhibited to the endothermic response.

- **Drug-excipient compatibility studies by FTIR**[19,20]

Compatibility studies were carried out to know the possible interactions between Flurbiprofen and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility using the Infra Red spectrophotometer [12]. FTIR is a technique used to obtain an infrared spectrum of absorption or emission of a solid, liquid or gas. Flurbiprofen and the admixture of drug with HPMC K100 and PEO were characterized by TIR spectroscopy to test the compatibility.

Post compression parameter

- **Weight uniformity test** [21]

If the drug forms greater part of the tablet, any variation in the tablet weight obviously indicates a variation in the active ingredient this test resembles weight uniformity test. 20 tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average. It is calculated as:

Average weight of tablets = Total weight of tablets/Number of tablets

Average weight of tablets (X) = (X1+X2 +X3+…+ X20) / 20

- **Hardness uniformity studies** [22]

The hardness of prepared formulation was measured by using Pfizer hardness tester. Five floating tablets were used for hardness uniformity studies. The hardness data used to calculate mean and standard deviation.

- **Friability (F)** [23]

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined using the below given formula [23].

Thickness and diameter [24]

Tablet thickness is important for tablet packaging; very thick tablets affect packaging either in blisters or plastic containers. The tablet thickness is determined by the diameter of the die, the amount of fill permitted to enter the die and the force or pressure applied during compression. The thickness of the tablet may be measured manually or by automatic equipment. The thickness and diameter of the tablets was measured by Vernier Calipers. It is expressed in mm.

- **Content uniformity** [25,26]

Twenty tablets were weighed and triturated. The tablet triturate equivalent to 100 mg of the drug wasweighed accurately, dissolved in pH 1.2 buffers and diluted to 100 ml with the same. Furtherdilutions were done suitably to get a concentration of 10 mcg/ml with simulated gastric fluid pH1.2. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer, using buffer solution as a blank [25, 26].

- ***In vitro* buoyancy / floating study** [27]

In vitro buoyancy studies were performed for all the formulations. The randomly selected tablets from each formulation were kept in a 200ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

- **Swelling Index** [28]

The swelling behavior of a dosage unit is measured by studying its weight gain. The swelling index of tablets will be determined by placing the tablets in the basket of dissolution apparatus using dissolution medium pH 6.8 buffer at 37 ± 0.5^{0}C. After 0.5, one, two, three, four, five, six, seven and eight hours, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment performed in triplicate for each time point. Swelling index is calculated by using the following formula. Tablets were randomly selected and one tablet was introduced in each tube disintegration apparatus and placed in 1litre beaker containing water at 37± 2^{0}C and the time of disintegration was recorded. The study was done at room temperature without disc being added.

- ***In vitro* dissolution studies** [29]

The release rate of flurbiprofen from floating tablets will be determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test performed using 900 ml of pH 1.2 HCL buffer for 2 hrs followed by pH 6.8 Phosphate buffer for 8hrs. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with of pH 1.2 HCL buffer for 2 hrs followed by pH 6.8 Phosphate buffer for 8hrs. Absorbance of these solutions was measured at 222 nm using a UV/Visible spectrophotometer.

Results and Discussion

Calibration curve

Calibration curve of Flurbiprofen in 0.1N HCl (pH 1.2) was constructed and represented in Fig 1.

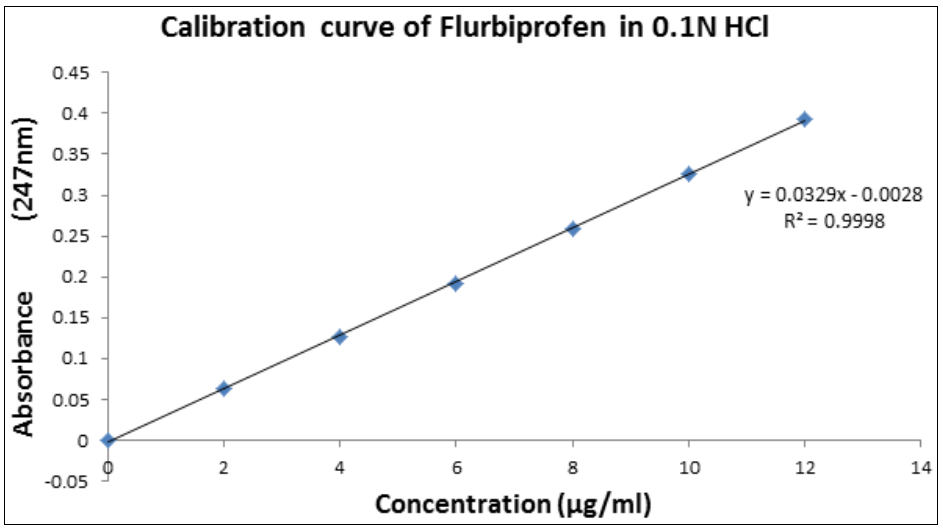

Fig 1: Calibration Curve of Flurbiprofen in 0.1N HCl (pH 1.2)

Pre-compression parameter

The powder blends of all formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index and DSC as shown in Table.2. The results showed that:

- The angle of repose for all the formulations blend was found to be in the range of 27.09 to 28.28.This indicates excellent to good flow property.
- Compressibility index was found to be in the range of 10.775 to 11.213. This indicates good flow property.

Table 2: Pre-compression parameters of powder blend

Formulation code	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)
F1	27.41	0.833	0.924	11.058
F2	28.28	0.833	0.915	10.775
F3	28.15	0.832	0.922	11.084
F4	27.09	0.830	0.912	11.213

Differential Scanning Calorimetry

DSC thermogram of Flurbiprofen, HPMC K100, PEO and mixture was done. The DSC thermogram of HPMC K100 is depicted in figure 2, thermogram of Flurbiprofen and HPMC K100 is depicted in figure 3, thermogram of Flurbiprofen and PEO is depicted in figure 4, thermogram of Flurbiprofen is depicted in figure 5. The thermogram indicates a sharp endothermic peak at 78.17 ^{0}C, 103.00 ^{0}C, 70.15 ^{0}C, 121.12 ^{0}C respectively.

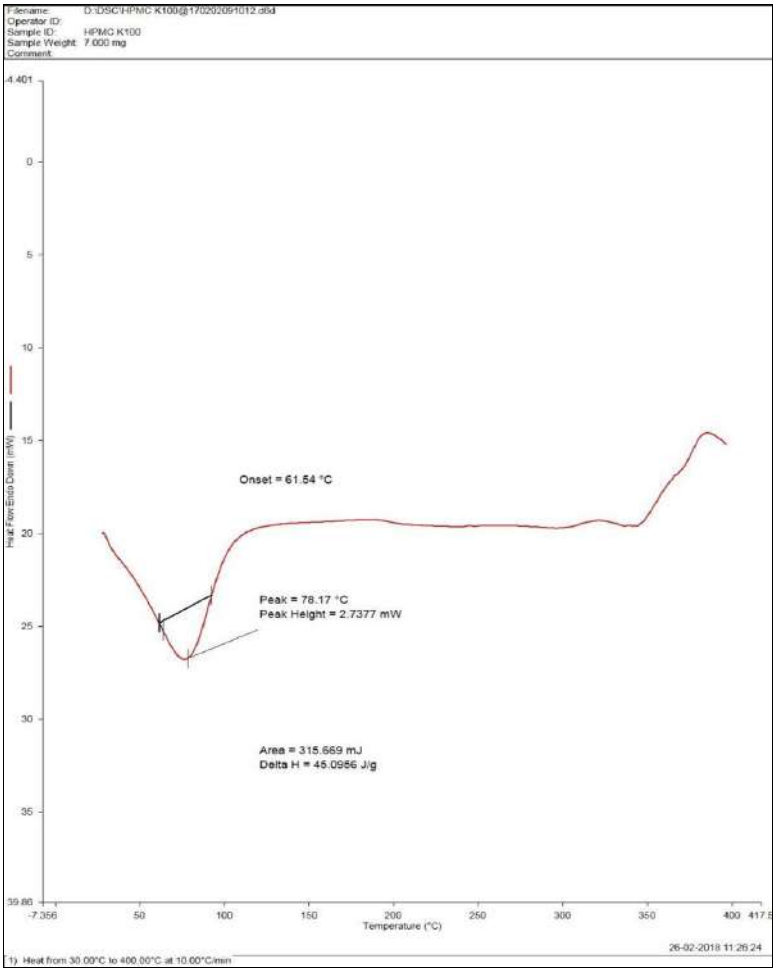

Fig 2: DSC of HPMC K100

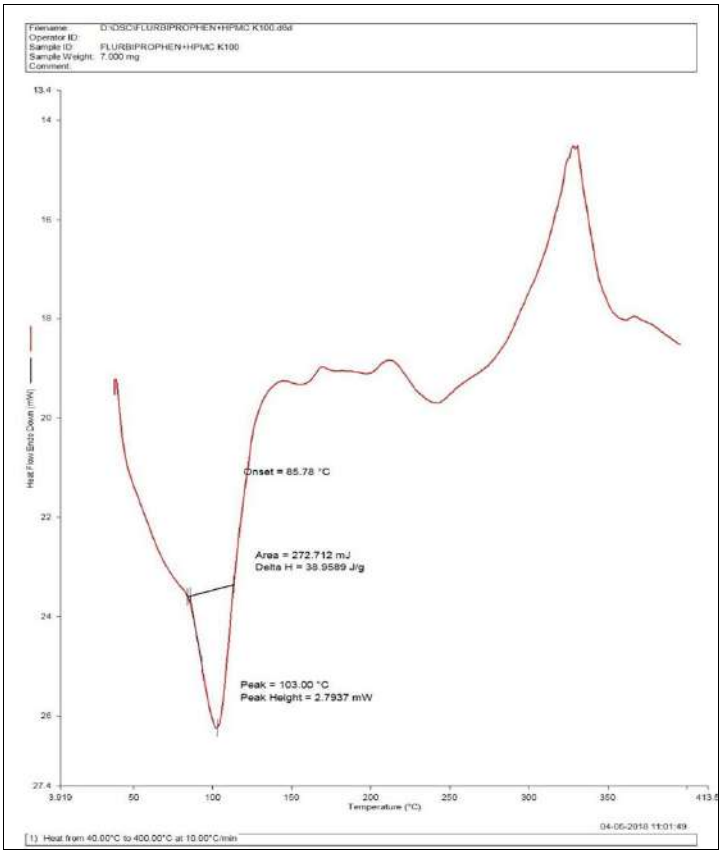

Fig 3: DSC of Flurbiprofen+HPMC K100

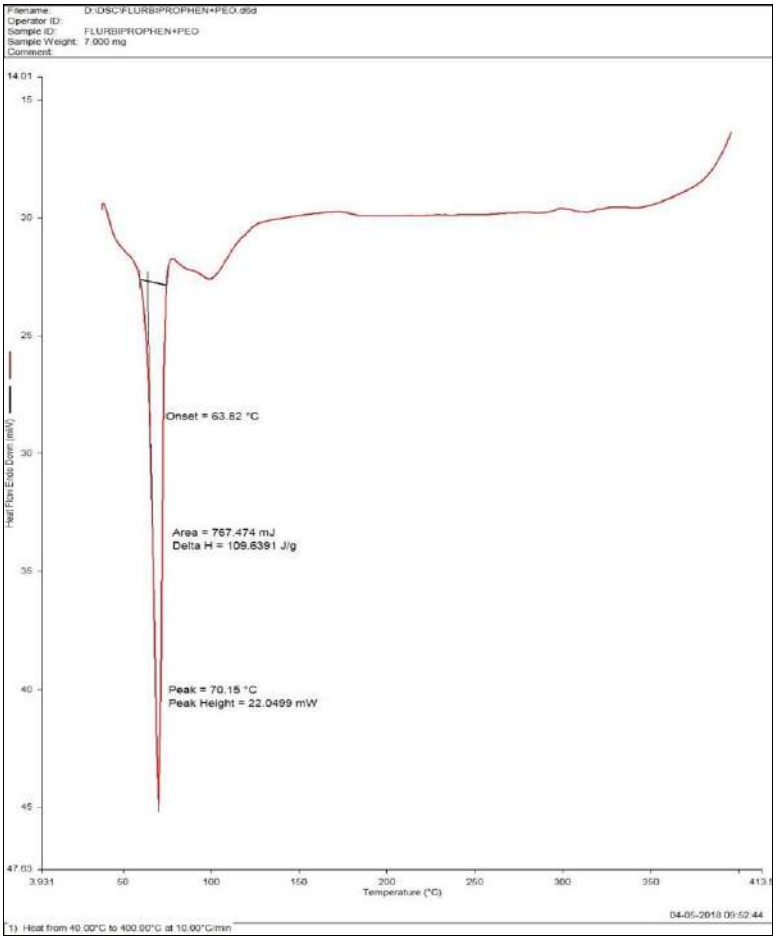

Fig 4: DSC of Flurbiprofen+PEO

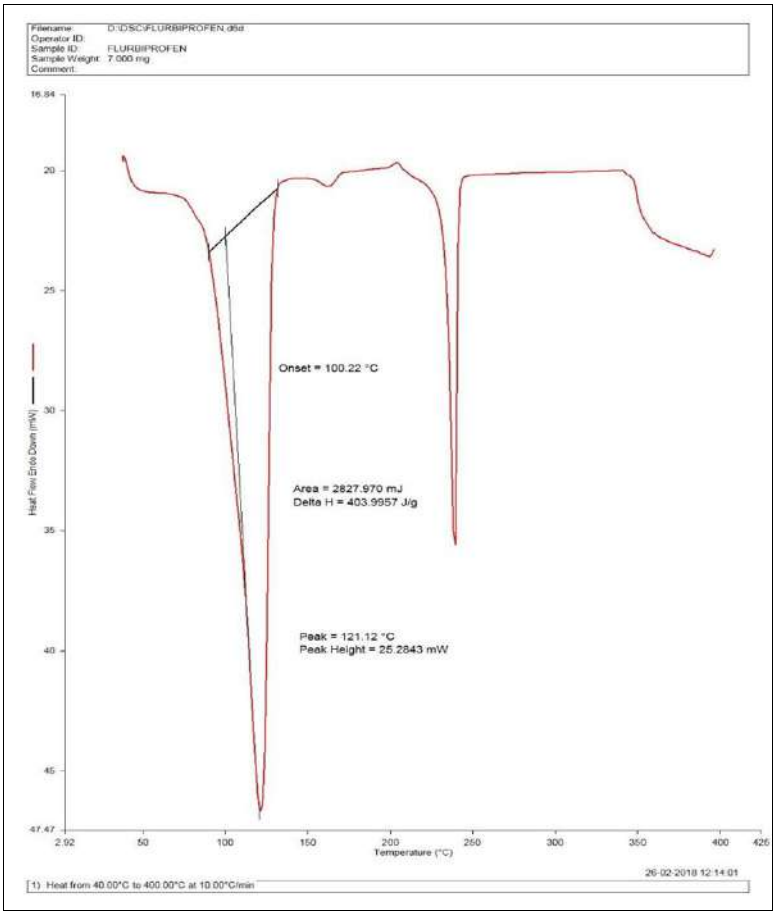

Fig 5: DSC of Flurbiprofen

Fourier-transform infrared spectroscopy (FTIR)

The FTIR spectrum of the drug and the polymer are shown in Fig 6,7 and 8 and respective structural assignment are described in Table 3,4 and 5. Different stretch and bend vibrations showed their respective peaks. From the FTIR spectra of the physical mixture, it is found that all the characteristic groups present are same as that of pure drug. Therefore it can be concluded that no interaction has been taken place between the drug and the polymers.

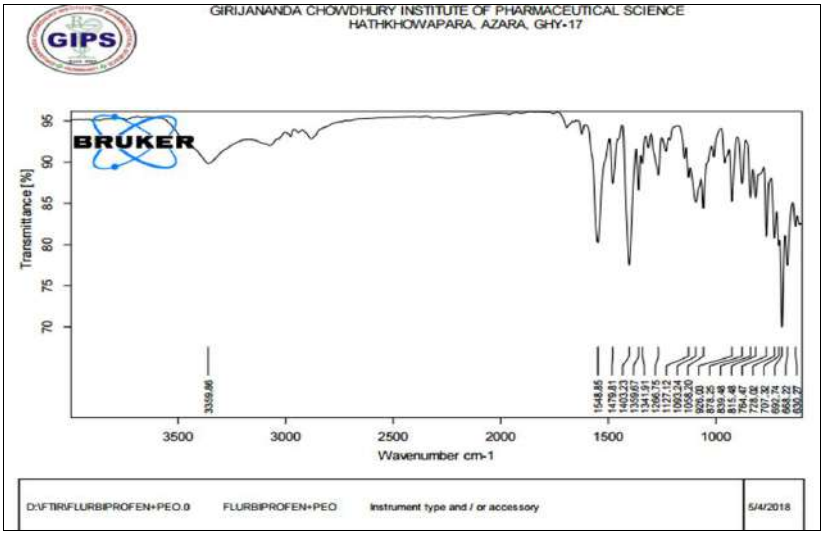

Fig 6: FTIR of Flurbiprofen+PEO

Table 3: Structural assignment of Flurbiprofen+PEO

Wave no(cm^{-1})	Functional group
3359.86	O-H Stretching
1548.85	C=C Bending
1403.23	C-H Bending
692.74	C-Cl Bending

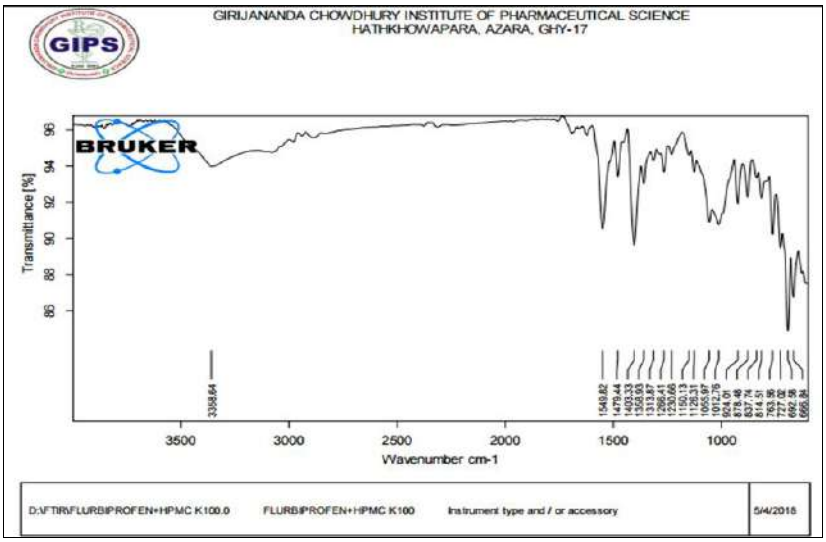

Fig 7: FTIR of Flurbiprofen+HPMC K100

Table 4: Structural assignment of Flurbiprofen+HPMC K100

Wave no(cm^{-1})	Functional group
3358.64	O-H Stretching
1549.82	C=C Bending
1403.33	C-H Bending
692.58	C-Cl Bending

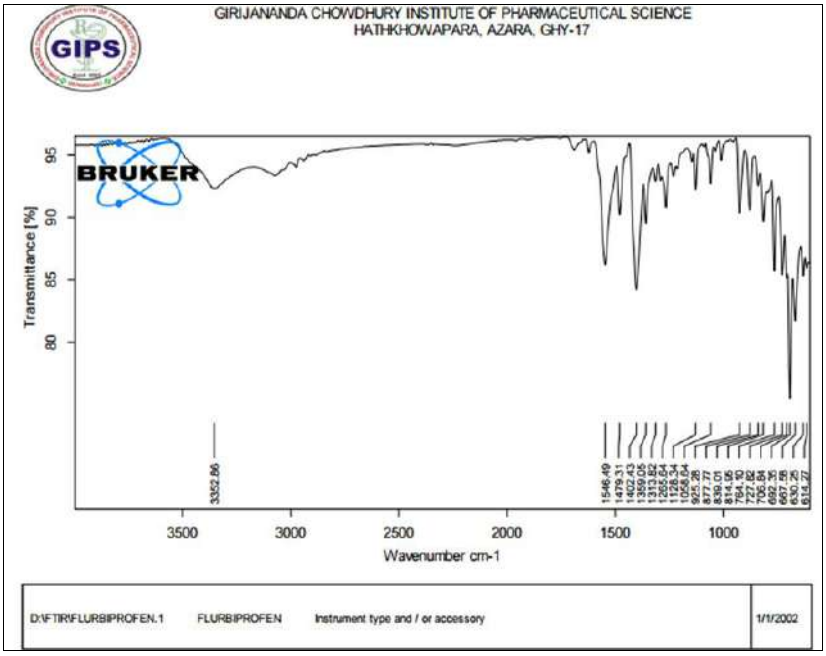

Fig 8: FTIR of Flurbiprofen

Table 5: Structural assignment of Flurbiprofen

Wave no(cm^{-1})	Functional group
3352.86	O-H Stretching
1546.49	C=C Bending
1402.43	C-H Bending
692.35	C-Cl Bending

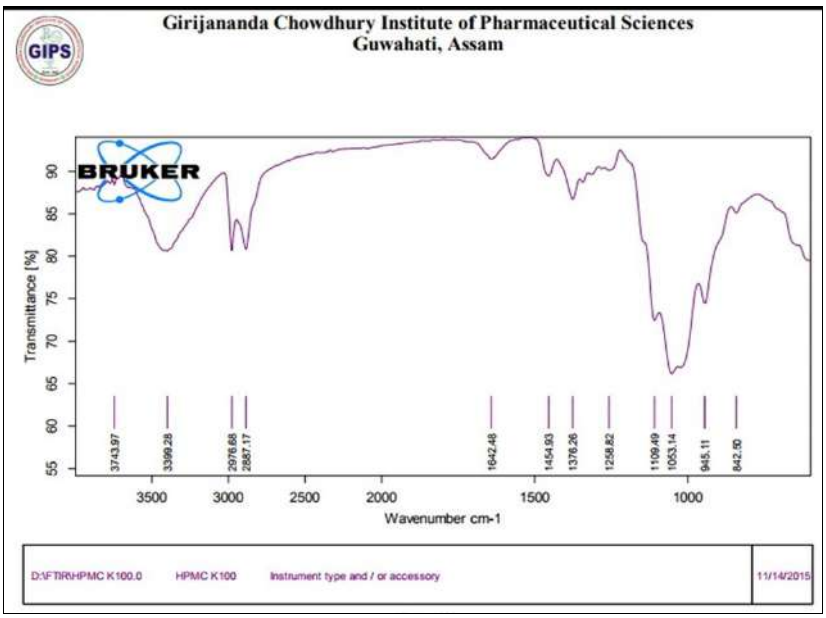

Fig 9: FTIR of HPMC K100

Table 6: Structural assignment of HPMC K100

Wave no(cm^{-1})	Functional group
2917.04	C-H Stretching
1464.29	N-H Bending
1113.39	C=O Bending
719.93	C-Cl Bending

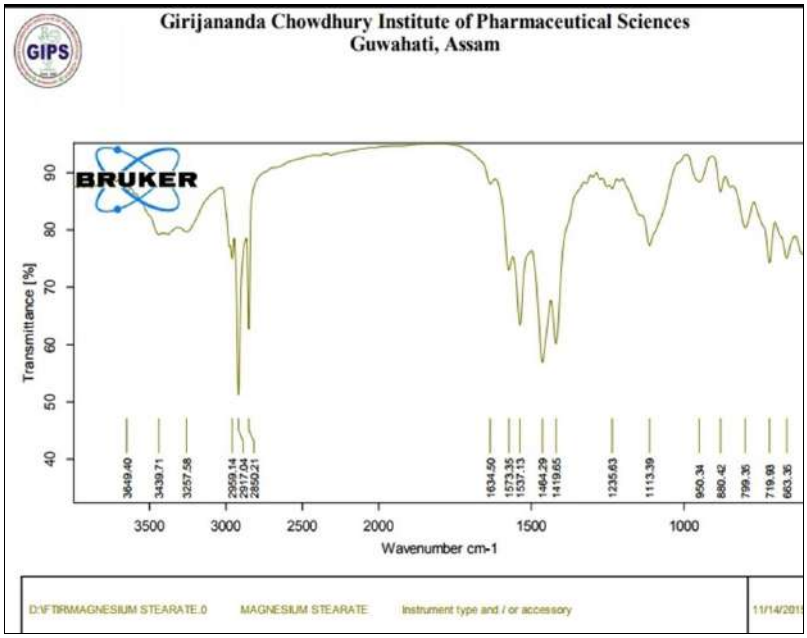

Fig 10: FTIR of Magnesium stearate

Post-compression parameter

Weight variation

All the formulation tablet F1 to F4 passed the weight variation test as the percent weight variation was within the pharmacopeia limit of 5% of average weight (Table 3).

Hardness

The hardness of the floating tablet measured by the Monsanto tester of formulation F1 to F4 were controlled between 4.6 to 5.8 kg/cm^2 .The standard hardness of the tablet is 5 kg/cm^2 (Table 3).

Friability

The friability of the floating tablet measured by the Roche Friabilator of formulation F1 to F4 and were controlled between 0.19 to 0.48 %. The standard friability of the tablet is below 0.8% according to IP and 1% according to USP (Table 3).

Thickness

The thickness of floating tablets measured by Screw Gauze of formulation F1 to F4 were ranged between 2.81 to 3.24 mm (Table 3).

Drug content uniformity

The percent drug content of formulation F1 to F4 was found to be 91 to 97 % which was within the acceptable limit, the standard drug content uniformity 100±10% (Table 8).

Table 7: Evaluation of floating tablets

Formulation	Average weight (mg)	Hardness (Kg/cm^2)	Friability % loss	Thickness (mm)	Drug content %
F1	200.02	5	0.19	2.81	97
F2	201.06	4.6	0.39	3.16	91
F3	200.08	5.5	0.32	2.98	94
F4	202	5.8	0.48	3.24	92

In-vitro buoyancy studies

On immersion of tablets of different formulations from F1 to F4 in 0.1N HCl solution at 37±5°C, the tablets floated, and remained buoyant without disintegration, the results of the buoyancy lag time (BLT) and total floating time (TFT) were shown in Table 4. Buoyancy lag time (BLT) and total floating time (TFT) of different formulation were noted. With reference to buoyancy studies results it can be concluded that as the amount of HPMC polymers increase, the formulation showed good buoyancy lag time (BLT) and total floating time (TFT). The formulation of F1 to F4 buoyancy lags time (sec) between 120 to 162 sec and total floating time (hr) 8 to 10 hr (Table 8).

Swelling index study

The Swelling Index for different formulations was shown in table 4. Formulation F3 shows max swelling index comparing to other formulation after 12 hrs while formulation F1 shows less swelling index as compared to other formulation (Tablet 8).

Table 8: Evaluation of floating tablets

Formulation	Buoyancy lag time (sec)	Total floating time (hr)	Swelling index (%)
F1	120	>8	55.40
F2	148	>9	60.38
F3	162	>10	64.54
F4	151	>9.5	62.24

Fig 11: Floating time of Flurbiprofen tablet

In-vitro dissolution study

In vitro drug release studies exhibited a decrease drug release with an increase in polymer concentration which may be due to increase in viscosity of the gel as well as the gel layer with longer diffusion path. Formulations containing high viscosity grade HPMC showed slower drug release compared to formulations containing low viscosity polymers. There was no considerable effect of gas generating agents on the release of the drug. Drug release profile of batches of Flurbiprofen floating tablet F1-F4 was found 49.49%, 65.39%, 71.34%, and 83.89% respectively. F3 formulation of Flurbiprofen floating tablet shows highest release of drug among the all batches (Table 9 & Figure 11).

Table 9: *In vitro* dissolution study of floating tablet Flurbiprofen

Time (hr)	F1	F2	F3	F4
1	4.18	6.39	8.16	12.72
2	7.22	7.64	10.23	15.39
3	9.09	12.25	13.87	19.23
4	10.78	15.06	18.76	26.21
5	12.21	21.48	25.39	34.39
6	14.94	27.63	30.65	41.52
7	18.60	31.90	35.21	48.48
8	22.89	37.78	44.39	57.48
9	30.53	43.19	49.53	63.34
10	37.35	49.46	57.48	71.46
11	43.88	57.57	66.48	78.32
12	49.49	65.39	71.34	83.89

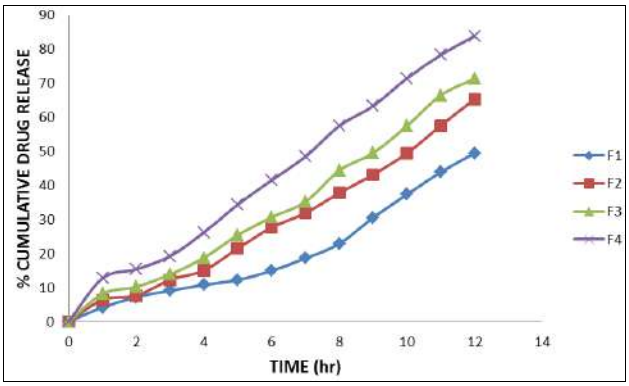

Fig 12: % Cumulative drug release of Flurbiprofen floating tablet

Conclusion

The floating matrix tablets of Flurbiprofen were formulated using direct compression method using varying quantities of the ingredients. The gel forming polymer HPMC and gas generating agent such as sodium bicarbonate are essential to achieve optimum buoyancy. The formulated tablets were tested for the parameters such as weight variation, hardness, thickness, friability and drug content and were found to be within the limits. The floating lag time and the floating duration of the tablets are the most important parameters. Hence, diffusion controlled Flurbiprofen gastro retentive tablets were formulated and evaluated and formulation F1 was concluded as the best formulation for the manufacture of Flurbiprofen gastro retentive tablets which is expected to increase bioavailability of the drug. Floating drug delivery tablets of Flurbiprofen were developed to enhance gastric residence time and there by eradication of inflammation by exerting anti-inflammatory therapeutic action. The optimized formula F1 showed better sustained drug release and which also had good floating properties.

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Conflict of interest: None

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