



# Formulation and Evaluation of Gastro Retentive Floating Tablets of Diclofenac Sodium Based on Effervescent Technology

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## Abstract

Floating drug delivery systems can prolong gastric retention time by formulating the dosage form with a lower density than that of gastric fluid. This causes the system to float over the gastric contents in the stomach without affecting the gastric emptying rate for a prolonged period of time. The present study was designed with an aim of preparation and *in vitro* evaluation of floating tablet using diclofenac sodium as a model drug. The tablets were prepared by dry granulation method based on effervescent technology where sodium bicarbonate was used as a gas generating agent. A hydrophilic swellable polymer hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) was used to control the release of drug and buoyancy was achieved by sodium bicarbonate and citric acid. Total of five formulations was prepared with varying concentration of HPMC and MCC. The optimized formulation F5 exhibited 33.17 % drug release in 12 hrs, while the floating lag time was 40 seconds. *In-vitro* dissolution study showed that the drug release profile can be sustained by increasing the polymer concentration. The study concluded that HPMC along with gas generating agents can be used to develop gastro-retentive floating tablets with desired controlled and complete release of drug for a prolonged period of time.

## Keywords

Diclofenac sodium, Floating tablets, Gastric Residence Time (GRT), Gastro retentive.

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## INTRODUCTION

Flotation is one of the most practical and promising mechanisms in achieving gastro retention of the drug. Floating drug delivery system (FDDS) or

dynamically controlled system is the low-density system which has sufficient buoyancy to float over the gastric content and remain buoyant in the stomach without affecting the stomachal evacuation

rate for an extended period of time. This results in increased gastric retention time and better control of the fluctuation in plasma drug concentration. [1,2]. The increase in gastric retention time improves the bioavailability of drugs by improving the solubility of less soluble drugs in a high pH environment [3]. Drugs with a narrow absorption window, low aqueous solubility, unstable at alkaline pH and those possessing good absorption from the stomach are good candidates for gastro-retentive systems [4]. Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Diclofenac, Indomethacin, Prednisolone and Cinnarizine are some of the suitable candidates and can be formulated by delivery systems [5].

Diclofenac sodium is an anti-inflammatory drug used for rapid relief of pain and wound edema in posttraumatic and postoperative inflammatory conditions, rheumatoid, osteoarthritis, bursitis, spondylitis, toothache, dysmenorrhoea and renal colic [5,6]. It is rapidly soluble in alkaline pH (5-8) and poorly soluble in water and acidic pH (1-3). Since the biological half-life of the drug is only 1-2 hrs, frequent dosing is required in order to reach therapeutic drug plasma level in several cases. Long term administration of diclofenac leads to gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding. So new drug delivery approaches are under extensive study in order to develop the optimized dosage regimen without compromising the therapeutic efficacy of the drug. The study has suggested gastro-retentive floating system shows more reproducible drug absorption for a prolonged period of time and reduces the risk of local irritation in comparison to the single unit dosage forms [7].

This study aimed to design an innovative carrier based on controlled release gastro-retentive floating tablets of diclofenac using effervescent technology. An attempt has been made to increase the solubility, stability and bioavailability as a whole of diclofenac in the form of gastro-retentive floating tablets. This approach also may help to eliminate the necessity for frequent dosing which in turn increases patient compliance and decreases the occurrence of adverse effects.

## MATERIALS AND METHODS

### Materials:

Diclofenac Sodium was a gift sample from Aurobindo Pharma, Hyderabad, India. Hydroxypropyl methylcellulose (HPMC K100 LV), Microcrystalline cellulose (MCC), Sodium bicarbonate, Citric acid,

Talc, Magnesium stearate and Polyvinyl pyrrolidone (PVP) were procured from Sigma Aldrich Co., USA. All ingredients and reagents used were of analytical grade.

### Methods:

#### Preparation of floating tablets of Diclofenac Sodium

Floating tablets containing diclofenac were prepared by direct compression technique. Total of 5 formulations was prepared using varying concentrations (5% - 25%) of hydroxypropyl methylcellulose (HPMC K100 LV) and microcrystalline cellulose (MCC). Ingredients viz. PVP, Sodium bicarbonate, magnesium stearate, talc and citric acid were added in a fixed amount in all formulations. The compositions of all formulations are given in Table 1.

Diclofenac, HPMC, MCC, 10% Sodium bicarbonate were uniformly blended with isopropyl alcohol, passed through a 16-mesh sieve and the formed granules were dried in a tray dryer at 30 °C for 1 hr. After complete drying of the granules, magnesium stearate, talc, citric acid, 5% sodium bicarbonate was added and further mixed for additional 2-3 minutes. The blend was compressed into tablets having an average weight of 250 mg using a tablet punching machine in a die having a diameter of 8 mm, punches with a compression force of 7 tons.

### EVALUATION PARAMETERS

#### Pre-compression parameters

The powder blends of the formulation were evaluated for their bulk and tapped density and from the values obtained, compressibility index and Hausner ratio were calculated. The flow properties of the powder blend were determined from the angle of repose.

#### Post-compression parameters

The prepared diclofenac floating tablets were evaluated for various quality control tests such as weight variation, hardness, thickness, friability and content uniformity.

#### Weight variation

From each batch of the formulations, twenty tablets were selected randomly and weighed individually. The average weight was calculated out and it was then compared with the individual weight. From this percentage deviation was determined and then the result obtained was checked for IP specifications.

#### Hardness and friability

The hardness of tablet was determined by Monsanto tablet hardness tester using randomly picked ten tablets from each batch. Friability test was performed by using Roche friabilator. Twenty tablets were weighed out and were placed into the plastic chamber of the friabilator that revolves at 25 rpm

dropping the tablets at a distance of 6 inches height with each revolution for 4 mins. The tablets were dedusted, reweighed and the percentage friability was calculated after operating for 100 revolutions [8].

#### Tablet Dimensions

The thickness and diameter of tablets were measured by using a calibrated Vernier calliper for which 3 tablets of each formulation were picked randomly and the standard deviation was also calculated [9].

#### Drug Content

The drug content of the prepared diclofenac floating tablets was determined by grinding 10 tablets into a fine powder. The quantities of the powder equivalent to 15 mg of diclofenac were weighed out and transferred it into a 100 ml volumetric flask. It was then filled with ethanol and mixed thoroughly. The solution was made up to volume and filtered (0.45  $\mu$ m pore size). 10 ml of the resulting solution was then diluted to 100 ml with ethanol and the absorbance of the resulting solution was measured at 276 nm using a Thermo Fischer UV-visible spectrophotometer. The linearity equation obtained from the calibration curve was used for estimation of Diclofenac in the tablet formulations [3,10].

#### In vitro buoyancy studies

The prepared diclofenac floating tablets were placed in a 100 ml beaker containing 0.1 N HCl as the dissolution medium. The time required for the tablet to rise to one-third of the surface of the dissolution medium was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained floating on the surface of the dissolution medium was determined as Total Floating Time (TFT) [3, 11].

#### Swelling index

The prepared diclofenac floating tablets were weighed individually (designated as  $W_0$ ) and placed separately in a glass beaker containing 200 ml of 0.1 N HCl maintaining the temperature at  $37^\circ\text{C} \pm 0.5^\circ\text{C}$ . At regular 1-hr time intervals until 5 hrs, the floating tablets were removed from beaker, and the excess surface liquid was removed. The swollen floating tablets were then re-weighed ( $W_t$ ), and % Swelling Index (SI) was calculated using the following formula [12].

$$\text{SI (\%)} = \frac{W_t - W_0}{W_0} \times 100 \quad (1)$$

Where SI is swelling index,

$W_t$  is the weight of tablet at time t,

$W_0$  is the weight of the dry tablet before placing in the glass

#### In-vitro dissolution study

The *in vitro* dissolution study was performed in a United States Pharmacopeia (USP) type II (paddle) apparatus at a rotational speed of 100 rpm. The tablet was placed inside the dissolution vessel containing 900 ml of 0.1N HCl as the dissolution media maintaining the temperature at  $37 \pm 0.5^\circ\text{C}$ . 5 ml of sample were withdrawn at specified time intervals for 12 hrs and replaced with fresh dissolution media. The absorbance of the samples was measured at 276 nm using a UV spectrophotometer. The release studies were performed using 3 tablets, and the mean values obtained were plotted against time [3].

#### In vitro drug release kinetics

The following plots were made to find out the mechanism of drug release from the prepared tablets-

- Zero-order kinetic model - %  $Q_t$  Vs t
- First-order kinetic model -  $\log(100 - \% Q_t)$  Vs t
- Higuchi's model - %  $Q_t$  Vs  $t^{1/2}$
- Korsmeyer-Peppas equation -  $\log \% Q_t$  Vs  $\log t$ .

Different kinetic models such as zero order (percentage cumulative drug release vs time), first order ( $\log$  cumulative percentage of drug vs time), Higuchi model (percentage cumulative drug release vs square root of time) and Korsmeyer-Peppas model ( $\log$  percentage cumulative drug release vs  $\log t$ ) were applied to interpret the drug release kinetics from the formulations. Based on the highest regression values for correlation coefficients for formulations, the best-fit model was decided [3,13].

## RESULTS AND DISCUSSIONS

### Pre-compression parameters

The results of pre-compression study parameters are shown in Table 2. All the pre-compression study parameters were within the Pharmacopoeia limits.

### Post-compression Parameters

The appearances of the prepared diclofenac floating tablets were found to be off-white, smooth, and flat in shape. The results of physical characterizations are shown in Table 3. The thickness of the diclofenac floating tablets was measured by calibrated dial calliper. Tablets diameters were uniform in all the formulations with a value of  $8.1 \pm 0.05$  mm and thickness were in the range of  $4.1 \pm 0.05$  to  $4.2 \pm 0.05$  mm. The standard deviation values showed that all the formulations were within the range and show uniform thickness and diameter.

The average weight of each formulation was recorded. The values were almost uniform and lie within the specifications. The values of tablets ranged from  $249.8 \pm 2.04$  to  $250.3 \pm 1.55$  mg. The

prepared diclofenac floating tablets passed the weight variation test since the % weight variation was within the pharmacopeia limits of  $\pm 5\%$  of the weight. The hardness of all formulations was in the range of  $6.5 \pm 0.5$  to  $7.5 \pm 0.52$  kg/cm<sup>2</sup> which indicates that the hardness of all the formulations was almost uniform and possess good mechanical strength.

The friability values of prepared tablets were less than 1% which indicates that the tablets of all formulations have good compactness and showing enough resistance to the mechanical shock and abrasion.

The content uniformity was performed for all five formulations. The percent drug content of tablets was found to be 98.15%, 98.27%, 97.68%, 99.13% and 100.51% of diclofenac for all the formulations F1, F2, F3, F4 and F5 respectively.

#### ***In vitro* buoyancy studies**

The diclofenac floating tablets were prepared by effervescent technology. All floating effervescent tablets float immediately after placing it into 0.1 N HCl solution maintaining the temperature at  $37 \pm 0.5$  °C and remain buoyant over 24 hrs without disintegration as given in Table 4. The *in vitro* buoyancy of diclofenac floating tablets were induced by sodium bicarbonate and anhydrous citric acid in the ratio of (5:1) without compromising the integrity of the polymer matrix with the possible shortest floating lag time (FLT) and total floating time (TFT) more than 24 hrs. The reaction between Sodium bicarbonate and citric acid in the acidic environment produces carbon dioxide. It was observed that the gel formed due to the hydration of the polymers was responsible for entrapping and protecting the gas generated within the tablet, thereby decreasing the density of the tablet below 1, and the tablet starts floating. The prepared diclofenac floating tablets F5 exhibited short buoyancy lag time of 40 sec comparing to other formulations F1, F2, F3 and F4 but the total buoyancy time remained the same for all the formulations. The decrease in floating lag time of the formulation F5 could be due to increase in the polymer concentration that produces a firm gel that entrapped an increased amount of carbon dioxide to

give rapid buoyancy as well as providing the tablet buoyant for longer period of time [14,15]. *In vitro* buoyancy study of formulation F5 at the initial time, after 40 secs and after 24 hrs is given in Figure 1.

#### **Swelling index**

The percentage of swelling obtained from the water uptake studies of all the formulations is shown in Figure 2. It was observed that the swelling indices were increased with increase in polymer concentration. Formulation F5 containing a high percentage of polymer shows the maximum swelling i.e. 107.28% at 5 hrs compared to that of the formulations F1, F2, F3 and F4 containing lower polymer concentration than F5. The swelling was strong enough to maintain the matrix integrity without disintegrating the tablets as well as to avoid burst effect and retarded the release of drug for a prolonged period of time. Generally swelling is essential to ensure the floating of the tablets. Therefore, an appropriate balance between swelling and water uptake is necessary [15,16].

#### ***In vitro* drug release studies**

*In-vitro* dissolution studies of all the formulations of diclofenac were carried out in 0.1 N HCl and percentage drug release was calculated. The drug release profiles of various prepared formulation are shown in Figure 3. By increasing the amount of HPMC K100 LV the drug release was decreased proportionately in the following order  $F5 < F4 < F3 < F2 < F1$ . *In vitro* drug release studies show that the drug release is higher in the case of F1 i.e. 40.53% and least in case of F5 i.e. 33.17% respectively in 12 hrs [17,18].

#### **Drug release kinetics**

The comparison between different kinetic models found that Higuchi square root model showed a higher degree of correlation coefficient ( $R^2$ ) for all the prepared tablet formulations than other models as given in Table 5. Hence, the drug release profile of the prepared tablet formulations follows diffusion mechanism. Also, the model Korsmeyer-Peppas indicates the type of diffusion, which was evaluated by the value of n between 0.45 and 0.89 implies non-fickian diffusion [19,20].

**TABLE 1: FORMULATION COMPOSITION OF ALL DICLOFENAC SODIUM FLOATING TABLETS**

Ingredients (mg)	F1	F2	F3	F4	F5
Diclofenac Sodium	100	100	100	100	100
HPMC	40	50	60	70	80
PVP	9.25	9.25	9.25	9.25	9.25
Sodium bicarbonate	37.5	37.5	37.5	37.5	37.5
Mg. Stearate	1.25	1.25	1.25	1.25	1.25
Talc	2.5	2.5	2.5	2.5	2.5
MCC	52	42	32	22	12
Citric acid	7.5	7.5	7.5	7.5	7.5

**TABLE 2: PRE-COMPRESSION PARAMETERS**

Formulation No.	Angle of repose ( $\theta$ )	Carr's Index	Hausner ratio
F1	25.01	12.93	1.175
F2	25.83	13.48	1.16
F3	25.10	13.11	1.165
F4	26.09	14.18	1.15
F5	25.43	14.18	1.15

**TABLE 3: POST COMPRESSION PARAMETERS**

Formulation No.	Thickness (mm)	Diameter (mm)	Weight variation	Friability (% wt loss)	Hardness (Kg/cm <sup>2</sup> )
F1	4.1±0.05	8.1±0.05	249.4±1.2	<1	6.5±0.5
F2	4.1±0.05	8.1±0.05	249.9±2.75	<1	6.5±0.52
F3	4.2±0.05	8.1±0.05	250.3±1.55	<1	7±0.54
F4	4.1±0.05	8.1±0.05	249.8±2.04	<1	7±0.38
F5	4.2±0.05	8.1±0.05	250.3±1.55	<1	7.5±0.52

**TABLE 4: IN VITRO BUOYANCY TEST**

Formulation No.	Floating Lag Time (FLT)	Total Floating Time (TFT)
F1	68 secs	> 24 hrs
F2	68 secs	>24 hrs
F3	67 secs	> 24 hrs
F4	67 secs	> 24 hrs
F5	40 secs	> 24 hrs

**TABLE 5: RELEASE KINETIC DATA OF FORMULATIONS**

Kinetic Models	Zero order	First order	Korsemeyer Peppas	Higuchi
F1	R <sup>2</sup> =0.9516 K <sub>0</sub> = 3.1067	R <sup>2</sup> = 0.9728 K <sub>1</sub> = -0.0173	R <sup>2</sup> = 0.9874 n = 0.565	R <sup>2</sup> = 0.9937 K <sub>H</sub> = 11.427
F2	R <sup>2</sup> =0.9478 K <sub>0</sub> = 2.9743	R <sup>2</sup> = 0.9695 K <sub>1</sub> = -0.0162	R <sup>2</sup> = 0.9881 n = 0.6001	R <sup>2</sup> = 0.9954 K <sub>H</sub> = 10.972
F3	R <sup>2</sup> =0.9557 K <sub>0</sub> = 2.9404	R <sup>2</sup> = 0.9748 K <sub>1</sub> = -0.0158	R <sup>2</sup> = 0.9897 n = 0.6492	R <sup>2</sup> = 0.997 K <sub>H</sub> = 10.81
F4	R <sup>2</sup> =0.959 K <sub>0</sub> = 2.8754	R <sup>2</sup> = 0.9761 K <sub>1</sub> = -0.0153	R <sup>2</sup> = 0.983 n = 0.68762	R <sup>2</sup> = 0.9951 K <sub>H</sub> = 10.543
F5	R <sup>2</sup> =0.9762 K <sub>0</sub> = 2.7479	R <sup>2</sup> = 0.9875 K <sub>1</sub> = -0.0144	R <sup>2</sup> = 0.9797 n = 0.7432	R <sup>2</sup> = 0.987 K <sub>H</sub> = 9.9455

\*R<sup>2</sup> = correlation coefficient, K<sub>0</sub> = Zero order rate constant, K<sub>1</sub> = First order rate constant, K<sub>H</sub> = Higuchi dissolution constant, n = release exponent

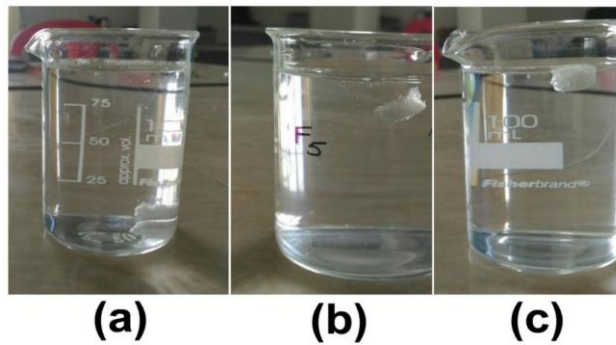


Figure 1: *in vitro* buoyancy study of F5 (a) at the initial time (b) at 40 secs (c) after 24 hrs

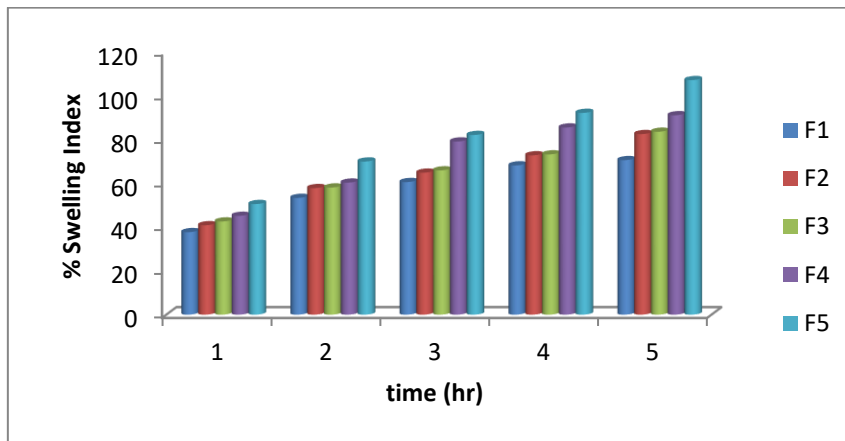


Figure 2: Swelling Indices of Diclofenac Floating Tablets (F1to F5)

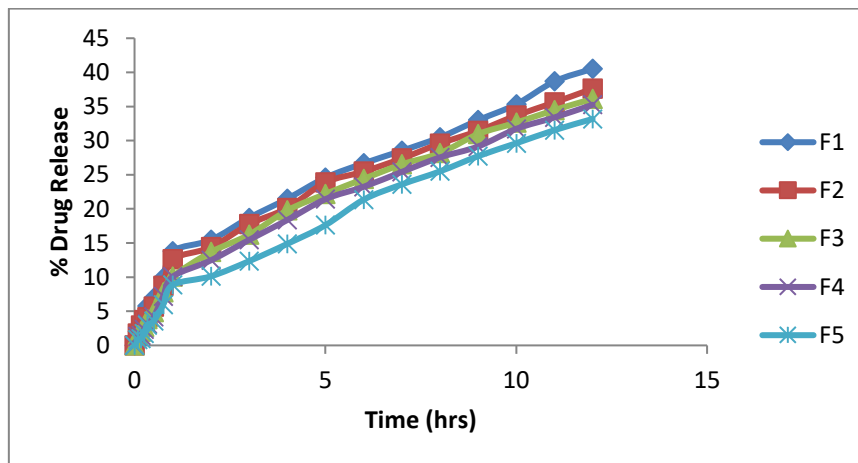


Figure 3: *In vitro* release profile of diclofenac from formulations F1, F2, F3, F4 and F5 respectively

## CONCLUSION

Gastro retentive floating tablets of diclofenac sodium were successfully prepared by effervescent technology using sodium bicarbonate and citric acid as a gas-generating agent and hydroxypropyl methyl cellulose (HPMC k100 LV) as a polymeric matrix. Diclofenac floating tablets prepared were found to be good without chipping, capping and sticking. Tablets prepared with 15% w/w sodium bicarbonate

at  $6.5 \pm 0.5$  –  $7.5 \pm 0.52$  (Kg/cm<sup>2</sup>) hardness showed satisfactory results with respect to floating lag time, total floating duration, swelling ability, and sustained drug release profile. It was found that floating lag time diclofenac floating tablets F5 exhibited short buoyancy lag time of 40 sec compared to other formulations F1, F2, F3 and F4 but the total buoyancy time was over 24hrs for all the formulations. Floating tablets prepared with the increasing concentration

of polymer was found to provide sustained throughout the period of 12 hrs. Moreover, formulation F5 containing a high percentage of polymer shows the maximum swelling compared to other formulations. *In vitro* release studies confirmed that the F5 formulation showed the drug release of 33.17% in 12 hrs. The formulations were found to follow Higuchi order kinetics and the mechanism of drug release was diffusion which was of non-fickian type. Based upon the results obtained F5 was found to be most suitable for hydrodynamically balanced drug delivery system among all other formulations. The slow release of diclofenac along the gastrointestinal tract could result in more reproducible drug absorption and reduce the risk of local irritation, compared with single-unit dosage forms.

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#### CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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