Chapter

Preparation and *in vitro* Characterisation of Solid Dispersion Floating Tablet by Effervescent Control Release Technique with Improved Floating Capabilities

Peeush Singhal, Rajneesh Dutt Kaushik and Vijay Jyoti Kumar

Abstract

In this research, an effort has been done for the development of effervescent controlled release floating tablet (ECRFT) from solid dispersions (SDs) of diclofenac sodium (DS) for upsurge the solubility and dissolution rate. ECRFT of DS was prepared by using SDs of DS and its SDs prepared with PEG as carrier using thermal method (simple fusion). SDs of DS was formulated in many ratios (1:1, 1:2, 1:3 and 1:4). Prepared SDs were optimised for its solubility, % drug content and % dissolution studies. Tablets were formulated by using optimised SDs products and all formulation was evaluated for various parameters. A clear rise in dissolution rate was detected with entirely SD, amid that the optimised SD (SD4) was considered for ECRFT. Among all the tablet formulations, its F3 formulation was better in all the terms of pre-compression and post-compression parameters. It had all the qualities of a good ECRFT, based on this F3 formulation was selected as the best formulation. Data of *in vitro* release were fitted in several kinetics models to explain release mechanism. The F3 formulation shows zero order release. From this study, we can conclude that ECRFT containing SDs of DS can be successfully used for achieving better therapeutic objective.

Keywords: solid dispersion, diclofenac sodium, polyethylene glycol, dissolution enhancement, floating tablets

1. Introduction

Diclofenac sodium (DS) is an effective NSAID with high affinity for both COX-1 and COX-2 receptors and it is one and only maximum frequently recommended drugs in India for the cure of pain, inflammation and joint stiffness caused by arthritis. According to BCS classification system DS belonging from class II means to say having poor solubility and poor dissolution rate [1] hence the focus of this study was on converting BCS class from II to I by increasing its solubility and

dissolution rate of DS Which was taken as model drug [2]. The release rate can be improved by increasing surface area of existing drug by using several techniques but among these methods solid dispersion technique is one of the best techniques for increasing the surface area [3]. Hence, an effort was made to increase the dissolution characteristics using the solid dispersion technique [3, 4]. It has absorption site in upper part of gastro intestinal tract. Gastric retention of DS was very short that is why the bioavailability of drug is 54% which is very low because near about 50% portion of orally given drug misses the absorption window. The pharmacokinetic profile of DS showed that the half-life is about ~1.2–2 h and hence there is a requirement of frequent dosing (3–4 tablets daily) [5] but this requirement of frequent dose is very dangerous for patients because due to this frequent dosing fluctuation in plasma drug level in body and need constant monitoring of patient for adjustment of dose regimen. That is why this reason may consequently support faster absorption of drug in stomach with higher concentrations for bioavailability improvement. Therefore in order to improve drug dissolution and reduced dosing frequency, it was attempted to formulate solid dispersion of DS [6, 7] and then develop effervescent controlled release floating tablet [8]. The emphasis of the current research was to increase the release rate and bioavailability of DS through preparing ECRFT (effervescent control release floating tablets) with dual approach [9] using solid dispersion product of DS in order to regulate the drug release and make available security from first pass metabolism.

2. Methodologies

2.1 Preformulation studies

Prior to the development of dosage forms, it is essential that certain fundamental, physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined and should be considered in the formulation in relation to the proposed dosage form and route of administration.

These studies should focus on those physiochemical properties of the drug that could affect drug performance and development of an efficacious dosage form.

A typical preformulation program should begin with the description of the organoleptic qualities of the drug substance. The colour, odour and taste are of immense value in developing an aesthetically acceptable formulation.

2.1.1 Identification and characterisation of diclofenac sodium

2.1.1.1 Physical appearance

Drug sample has been noted for its organoleptic properties. The drug is white to slightly yellowish crystalline powder, odour: slight and characteristic [1]. Drug was received as gift sample (15 g) from Kwality Pharmaceuticals Ltd., Amritsar.

2.1.1.2 Melting point determination

The melting point of compound is the temperature at which it changes from a solid to liquid [10]. This is a physical property often used to identify compounds.

2.1.1.2.1 Procedure

a. A capillary melting tube was taken.

b. A small amount of compound was placed on a clean surface. The compound was put in to open end of capillary tube.

c. The capillary melting point tube was placed in melting point apparatus (Macro scientific works).The sample was observed continuously, so that the melting point of the sample was not missed. Slow heating was done for most accurate results. The melting range was recorded which beings when the sample first starts to melt and ends when the sample completely melted.

2.1.1.3 Solubility studies

Solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous dispersion [11]. The solubility of diclofenac sodium was studied in various aqueous and non-aqueous solvents. About 10 mg of drug was taken in 10 ml of each solvent at room temperature in screw-capped test tubes and shaken for 30 min in a sonicator. The solubility was checked by U-V spectroscopy in all cases and reported in **Table 1**.

2.1.1.4 U.V. spectrophotometer

The organic molecule in solution when exposed to light in the ultra-violet region of the spectrum, absorbed light of particular wavelength depending on the type of electronic transition associated with absorption [12].

2.1.1.4.1 Diclofenac sodium

The solution (10 μg) of diclofenac sodium was prepared in simulated gastric fluid pH 1.2 and scanned spectrophotometrically (Systronics, Double beam UV-VIS Spectrophotometer: 2201). The scanning range was in between 200 nm to 400 nm. Standard solution of diclofenac sodium was then scanned and graph plotted. The

Parameter	**Evaluation**
API	DICLOFENAC SODIUM
Description	Crystalline
Colour	White
Odour	Odourless
Bulk Density	0.56 gm/ml
True Density	0.64 gm/ml
Carr's Index	14.28%
Hausner's Ratio	1.14
Melting Point	STD: 280°C OBS: 282–283°C
Solubility	Sparingly soluble: Water Freely soluble: methanol Soluble: 0.1 N HCl Insoluble: ether, chloroform and toluene
Partition coefficient	1.25

Table 1.
Preformulation characters of diclofenac sodium.

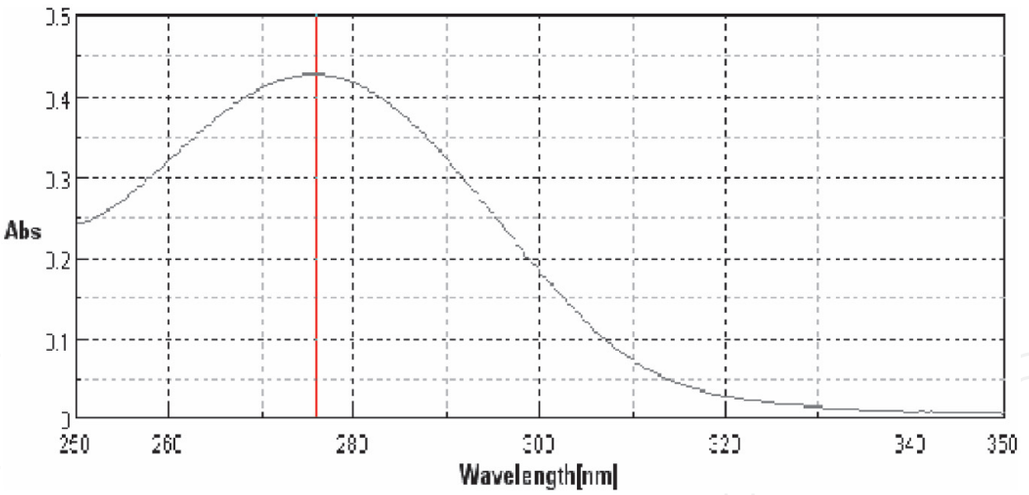

Figure 1.
U.V. scan of diclofenac sodium in simulated gastric fluid (PH 1.2).

determined λmax, 276 nm (**Figure 1**) was similar as reported in the literature (276 nm).

2.1.1.5 I.R. spectrophotometry

About 1 mg of the sample and 100 mg of the potassium bromide (KBr) was taken in a mortar and triturated [13]. A small amount of triturated sample was taken into a pellet maker and compressed at 10 kg/cm^2. The pellet was kept onto the sample holder and scanned from 4000 to 400 cm^{-1}.The I-R spectrum of drug sample was obtained using FTIR-8400 s, shimadzu. Important peaks are reported in **Table 2** and graphically represented in **Figures 2**, **3**. This I-R spectrum was found concordant with the IR of diclofenac sodium reported in the official monograph.

2.1.1.6 Quantitative estimation of drug

For the present study the spectrophotometric method given in the official books was selected for its sensitivity, specificity, simplicity, reproducibility, rapidity and accuracy [14].

2.1.1.7 Preparation of calibration curve of diclofenc sodium in simulated gastric fluid (pH 1.2)

Accurately weighed 50 mg of drug (diclofenac sodium) was dissolved in 100 ml of simulated gastric fluid pH 1.2 to give a solution of 500 μg/ml concentration and

IR spectrum	Standard peaks value	Observed peaks value cm^{-1}	Groups	Stretching/ deformation
DICLOFENC SODIUM	1600–1475	1556.61, 1498.74	C═C(aromatic)	Stretching
	1320–1210	1305.85	C—O stretching	Stretching
	1556	1556.61	Dichlorophenyl ring	Stretching
	1300–1000	1284.63	C—CO—C stretching	Stretching

Table 2.
Characteristic peaks of diclofenac sodium.

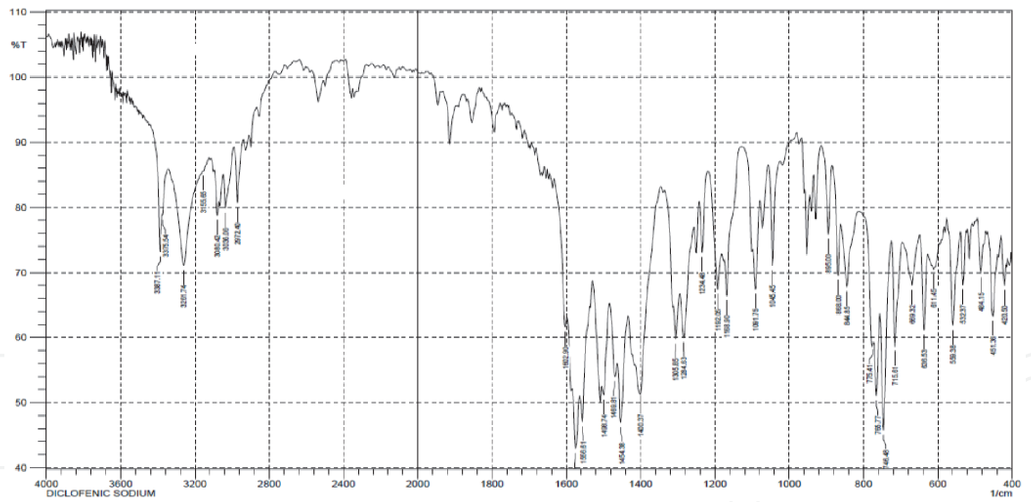

Figure 2.
FTIR spectroscopy of pure diclofenac sodium.

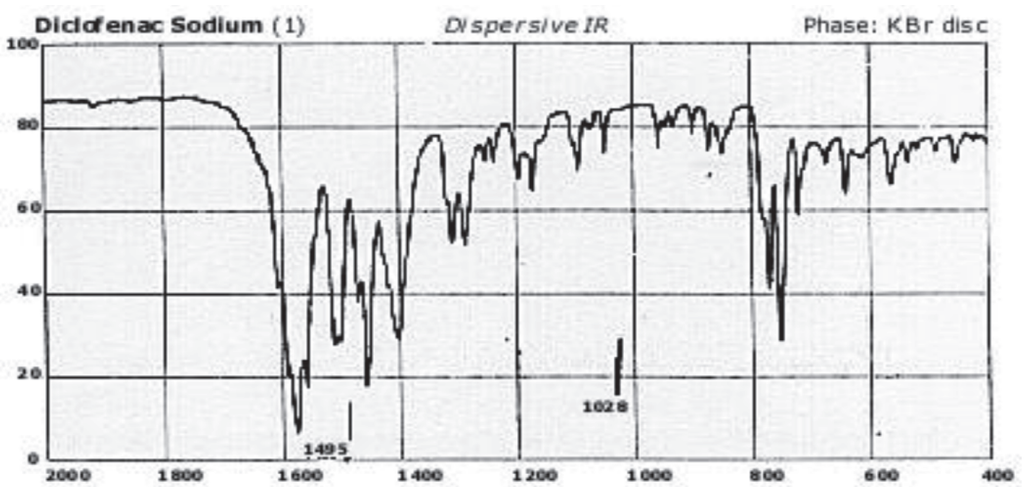

Figure 3.
I-R spectra of pure diclofenac sodium from I.P. 1996.

this was served as a standard solution [15, 16]. From this solution 10 ml was taken and diluted to 100 ml using simulated gastric fluid pH 1.2 to get a solution of 50 μg/ml concentration and this solution was served as the standard solution. In to a series of 10 ml volumetric flasks, aliquots of standard solution (i.e. 0.4, 0.8, 1.2, 1.6, 2.0, 3.0, 4.0, 5.0, 6.0 ml) were added and made up the volume up to 10 ml using simulated gastric fluid pH 1.2. The absorbance of these solutions was measured against reagent blank at 276 nm (**Table 3**). A standard curve between concentration and absorbance was plotted (**Figure 4**). A straight line passing through origin is obtained.

2.1.1.8 Partition coefficient

The partition coefficient directly influences the permeability of drug through various membranes [17–19]. The study has been designed to determine partition coefficient of drug in 1-octanol and pH 1.2 solutions. The partition coefficient between 1-octanol and Simulated gastric fluid (pH 1.2) was determined by shake flask method. About 10 mg of drug was dissolved in one of the phases, and is shaken with the other partitioning solvent for 30 min, allowed to stand for 5 min and then majority of the lower aqueous phase was run off. The drug concentration in both the

S. No	Concentration (μg/ml)	Abs(λmax-276 nm) (mean ± SD)
1	0	0.000 ± 0.00
2	2	0.068 ± 0.002
3	4	0.128 ± 0.005
4	6	0.190 ± 0.0015
5	8	0.246 ± 0.0021
6	10	0.315 ± 0.0022
7	12	0.329 ± 0.004
8	14	0.401 ± 0.001
9	16	0.445 ± 0.0032
10	18	0.522 ± 0.0051
11	20	0.589 ± 0.0059

Table 3.
Data for calibration curve of diclofenc sodium in simulated gastric fluid pH 1.2 at 276 nm (n = 3).

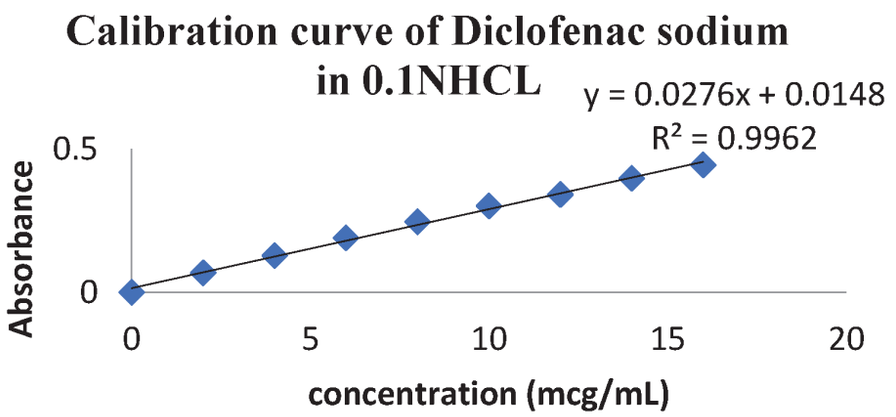

Figure 4.
Calibration curve of diclofenac sodium in pH 1.2 at 276 nm.

aqueous and 1-octanol phases was determined spectrophotometrically at 276 nm and calculated the partition coefficient. The partition coefficient was found to be 1.25.

Partition Coefficient = Conc.of drug in oil phase/Conc.of drug in aqueous phase (1)

2.1.2 Result and discussion

Samples of diclofenac sodium obtained as a gift sample from kwality pharmaceuticals pvt. Ltd., Amritsar was identified and characterised as per the identification test given in official monograph. Physical appearance and melting point of the drug sample under investigation was found to be same as that of the official reports. The results are given in **Table 4**. The solubility of diclofenac sodium was determined in aqueous and non-aqueous solvents. Diclofenac sodium was found to be soluble in 0.1NHCl and ethanol; sparingly soluble in water, practically insoluble in ether, chloroform and toluene. Partition coefficient of the drug was found to be 1.25.The results are given in **Table 1**.

S. No	Melting ranges	Melting point (mean ± SD)
1	288–290°C	289.12 ± 0.21

Table 4.
Melting point result of diclofenac sodium.

The drug was identified by IR spectroscopy and the characteristic peaks obtained (**Figure 2**) compared with standard spectra (**Figure 3**) of pure drug reported in official monograph (IP1996). The IR spectra of drug sample are in agreement with the standard IR spectra of pure diclofenac sodium given in official monograph [1]. Important peaks are reported in **Table 2**.

In the present study, a reported U-V spectrophometric method was used for the estimation of diclofenac sodium. The calibration curve of diclofenac sodium was prepared in simulated gastric fluid pH 1.2. The data was regressed to obtain straight line. The correlation coefficient was found to be 0.996 in simulated gastric fluid pH 1.2 indicating good linearity. The calibration curve was found to obey Beer-Lamberts Law in the concentration range studied (0–20 μg/ml).

3. Materials

Diclofenac Sodium (Batch no. A5/206), hydroxyl propyl methyl cellulose (HPMC) K100M (Batch no. HP121406 MC) and crosspovidone (Batch no. YPVPP09319040) were obtained from kwality pharmaceutical pvt ltd Amritsar, as gift samples. Sodium bicarbonate (NaHCO3), citric acid, polyvinyl pyrrolidone (PVP K-30), magnesium stearate, lactose and Isopropyl alcohol were purchased from local suppliers. Marketed product, "Voveran SR100 or Voveran 50", (Manufactured by Ranbaxy, India; Batch no.131003 AU or 320,028), used for comparative studies, was purchased from the local retail pharmacy.

4. Methods

4.1 Preparation of physical mixtures (PM)

Physical mixtures were prepared by mixing the appropriate amounts of the drug and carrier (PEG 6000) in the different weight ratios of 1:1, 1:2, 1:3 and 1:4 in mortar [3, 4, 6, 7]. The resulting mixtures were sieved through sieve no. 80, collected and stored in closed container away from light and humidity until use.

4.2 Preparation of solid dispersion

Melt method was used to prepare solid dispersions of diclofenac sodium with PEG 6000 containing different weight ratio (1:1, 1:2, 1:3, 1:4, and 1:5) (**Table 5**). Diclofenac sodium and PEG 6000 were weighed according to their weighed ratios. PEG 6000 was melted at 60°C. In this melted PEG 6000, diclofenac sodium was added. It was mixed well and flashed cooled on an ice bath and then stored overnight in desiccators. The prepared solid dispersion was then grounded by using a mortar and pestle, sieved through a mesh no. 40 and stored over a fused calcium chloride in a desiccators' for further use.

S. no.	Ratio (diclofenac sodium:PEG6000)	Batch code
1	1:1	SD1
2	1:2	SD2
3	1:3	SD3
4	1:4	SD4
5	1:5	SD5

Table 5.
Composition of solid dispersion and there assign batch code.

4.3 Characterisation of solid dispersion/ physical mixtures of diclofenac sodium with PEG-6000SDs

4.3.1 FTIR spectroscopy

FTIR spectra of drug, PEG 6000 and solid dispersion of DS were obtained. About 1 mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 min. The resultant disc was mounted in a suitable holder in perkin elmer USA spectrum 65 IR spectrophotometer and the IR spectrum was recorded from 4000 to 400 cm^{-1} in a scan time of 12 min [20]. The resultant spectra were compared for any spectral changes. **Figure 5** shows the FTIR spectra of the (i) drug, (ii) carrier and (iii) Surface solid dispersion. There was no significant change in the spectrum of solid dispersions, as incorporation of diclofenac into the carrier (PEG6000) did not modify the position of its functional groups.

4.3.2 Determination of saturation solubility

Saturation solubility was determined by using shake flask method [20]. Excess quantities of pure DS, prepared SDs and PMs were added in 25 ml distilled water in

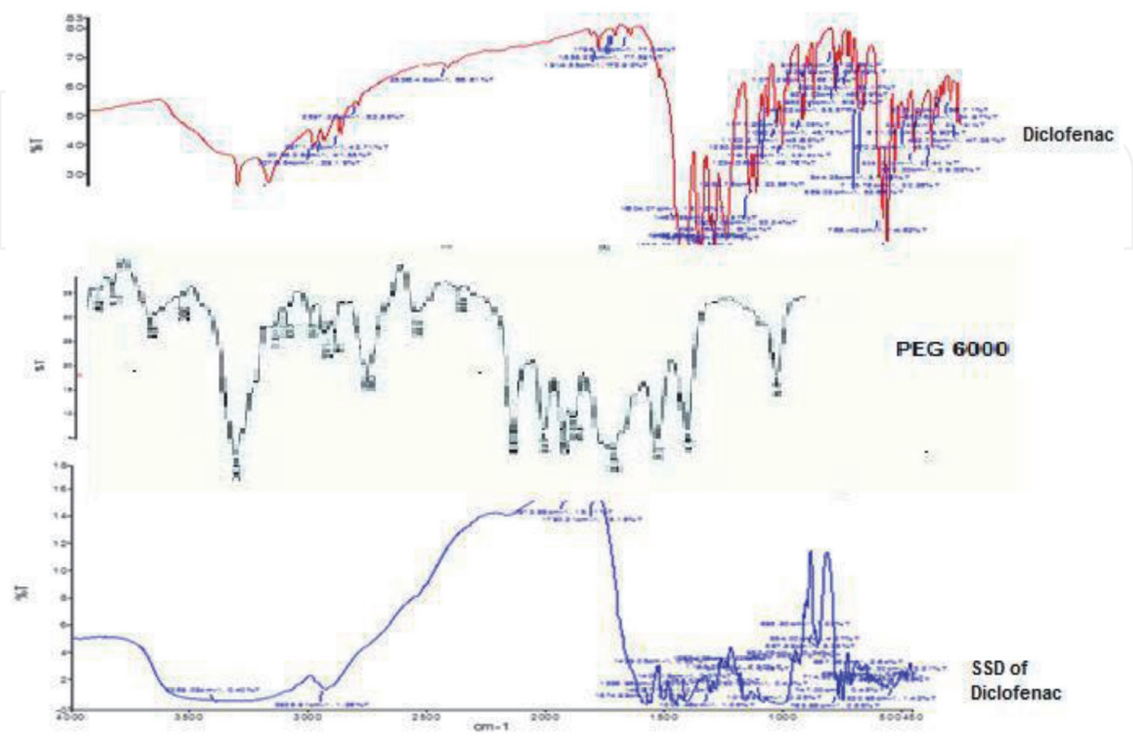

Figure 5.
Comparative FTIR spectra of diclofenac, PEG6000, & solid dispersion of diclofenac with PEG6000.

conical flasks which were then put in orbital shaker at 37°C and at 100 rpm for 72 h. Absorbance of resulting solution was measured on UV/Visible spectrophotometer (UV-1800 Shimadzu, Japan) at 276 nm.

4.3.3 Determination of pH dependent solubility

Shake flask method same as that for saturation solubility [20] was used with 0.1 N HCl.

4.3.4 Percent drug content

SDs equivalent to 50 mg of diclofenac sodium were weighed accurately and dissolved in 50 ml of ethanol by using mechanical shaker for 30 min. The solutions were filtered using whatman filter paper and drug content was determined by measuring absorbance at 276 nm by UV/visible spectrophotometer [6, 20]. From above evaluation tests, optimised formulation was confirmed (SD4 in **Table 6**) which was then subjected to *in vitro* dissolution studies.

4.3.5 In vitro *dissolution studies*

In vitro dissolution studies of prepared SDs were carried out in 900 ml of 0.1 N HCl as a medium using USP type 2 test apparatus with three replicates. The paddle rotation speed was 75 rpm and a temperature of 37°C ± 0.5 was maintained. In all experiments, 5 ml of dissolution sample was withdrawn at 5 min interval, filtered using a 0.45-mm Whatman filter, and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were analysed on UV/Visible spectrophotometer at 276 nm**.**

4.4 Results and discussions

IR study was carried out to check the compatibility between the selected Polymers, with the drug. When the spectra were compared it was found that there was no shifting of functional peaks and no overlapping of characteristic peaks and also there was no appearance of new peaks. **Figure 5** shows the IR spectra of various samples. No significant change in the IR spectra of diclofenac sodium complexes was obtained, except for the broadening of the peaks. The broadening of peaks may be probably due to the restriction of bending and stretching vibrations of the

Formulation code	Saturation solubility in 0.1 N HCl (mg/ml)	pH dependent solubility in 0.1 N HCl (mg/ml)	Percent drug content (in 50 mg)
Pure DS	0.3886 ± 0.0044	6.020 ± 0.038	—
PM1 (1:1)	0.4481 ± 0.0045	8.328 ± 0.069	82.75 ± 1.54
PM2 (1:2)	0.4603 ± 0.0073	9.765 ± 0.0073	86.68 ± 1.27
PM3 (1:3)	0.5168 ± 0.0034	10.278 ± 0.086	88.01 ± 0.94
PM4 (1:4)	**0.5947 ± 0.0046**	**11.265 ± 0.101**	**90.92 ± 1.44**
SD1 (1:1)	1.1802 ± 0.0136	11.984 ± 0.064	93.87 ± 1.89
SD2 (1:2)	1.2612 ± 0.0097	12.735 ± 0.028	94.50 ± 2.11
SD3 (1:3)	1.4894 ± 0.0036	13.324 ± 0.071	95.16 ± 1.34
SD4 (1:4)	**1.9261 ± 0.0154**	**14.291 ± 0.144**	**96.72 ± 1.53**

Table 6.
Saturation solubility, pH dependent solubility and percent drug content studies of pure DS, SDs and PMs.

molecule. Various SDs of DS were prepared using PEG-6000, as carriers by thermal method (Simple fusion) technique to increase the solubility as well as dissolution of poorly aqueous soluble drug DS. The prepared SDs and PMs of DS were evaluated for saturation solubility, pH dependent solubility; percent drug content and *in vitro* dissolution studies. The saturation solubility and pH dependent solubility of pure DS, various prepared SDs and PMs of DS in 0.1 N HCl were measured and the results are given in **Table 6**. All PMs showed higher saturation solubility as compared with pure DS. Again, SDs of DS showed higher saturation solubility than their respective PMs of DS and carrier. This might be attributable to an improvement of wetting of drug particles and localised solubilisation by the hydrophilic polymeric carriers.

Based on the saturation solubility, pH dependent solubility in 0.1 N HCl and drug content among the 8 formulations, PM4 and SD4 were selected to carry out *in vitro* dissolution study and were compared with that of pure DS. The *in vitro* dissolution study of the pure DS, SD4 and PM4 using PEG-6000 as carrier was carried out in 0.1 N HCl at 37°C ± 1°C for 60 min and it was examined by plotting % drug dissolved against a function of time (**Figure 6**). SD4 and PM4 showed improved dissolution of DS over that of pure DS. Pure DS alone yields the slowest dissolution with only 35.65% drug and the dissolution of PM4 (70.76%) was found to be significantly faster when compared with pure DS. SD4 showed the fastest dissolution (92.99%) than PM4 and pure DS. This observation (**Table 7**) indicated that the increased dissolution of DS from SD4 due to presence of drug in amorphous state as compared PM4 and pure DS. As the proportion of PEG-6000 increased, dissolution rates have also been increased. The improvement of dissolution may be due to its hydrophilic nature of the carrier. Thus it can be concluded that the solubility of the poorly soluble drug, DS can be improved markedly by using solid dispersion technique and the carrier, PEG-6000 has increased the dissolution of the drug.

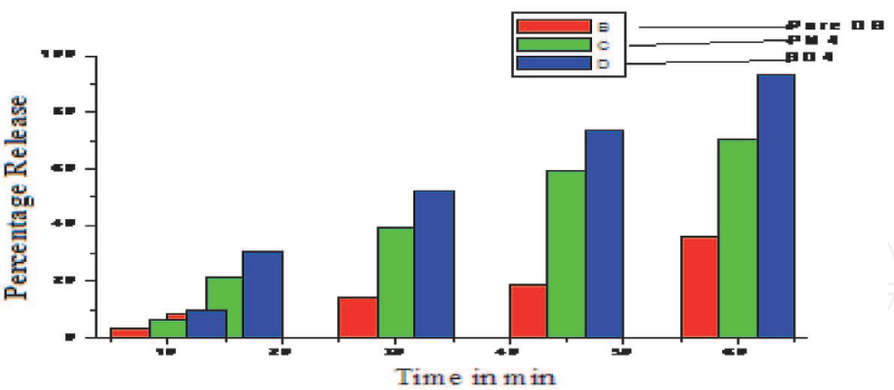

Figure 6.
Dissolution of the pure DS, SD4 and PM4.

	Percentage of diclofenac sodium dissolved from				
***Time in min*/formulation code**	**10**	**15**	**30**	**45**	**60**
Pure DS	3.37	8.50	14.35	18.85	35.65
PM4	6.67	21.23	39.44	59.41	70.76
SD4	**9.73**	**30.51**	**52.25**	**74.00**	**92.99**

Table 7.
Dissolution of the pure DS, SD4 and PM4.

4.5 Preparation of floating gastro retentive tablets

Various ratios of solid dispersions of diclofenac sodium with PEG-6000 were evaluated for percent drug content and out of them the best ratio was selected for preparation of floating tablet of diclofenac sodium. Tablets were prepared by conventional wet granulation method using HPMC K4M, HPMC K15M as a release retardant, carbopol as a swelling agents and $NaHCO_3$ as gas generating agent. Citric acid was also incorporated in the formulation to provide sufficiently acidic medium for $NaHCO_3$ to react and maintain buoyancy. The composition of various formulations is given in **Table 8**. All ingredients (except gas generating agents and magnesium stearate) were passed through sieve no. 60 and mixed in a polybag for 10 min and granulated using PVP K30 (in isopropyl alcohol). The wet mass was passed through sieve number 14 and dried in hot air oven at 50°C for 1.5 h. Dried granules were mixed with magnesium stearate as lubricant, talc as glidant and compressed using 16-station rotary tablet press (Rimek Minipress-I, India) using 13 mm flat punch in order to obtain controlled release floating gastro retentive tablets containing 50 mg of diclofenac sodium. Prior to compression, granules were evaluated for their flow and compressibility characteristic**.**

4.6 Characterisation of granules

4.6.1 Drug-polymer interaction studies

To study the interaction between drug and polymer, interaction study were performed, drug polymer study were carried out according to the following procedure. Drug and polymer were mixed in 1:1 ratio and put into the glass vials. The glass vials were sealed and placed in the stability chamber at 40°C and 75% RH for 21 days. The sample was analysed for colour change, liquification and bad odours after 7, 15 and 21 days. The IR spectra were taken after 21 days and analysed for any shift in major peaks. No shift was observed in the IR spectrum and no additional peak observed indicating no interaction between drug and polymer.

Ingredient (mg)	**Formulation code**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
SD4 (solid dispersion of diclofenac sodium)	250	250	250	250	250	250
HPMC K4	70	—	93	—	105	—
HPMC K15M	—	70	—	93	—	105
Carbopol 934P	70	70	47	47	105	105
Sodium bicarbonate	45	45	45	45	65	65
Citric acid	30	30	30	30	40	40
Avicel PH 102	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5
PVP K-30 5% PVP IN IPA						
Total weight	520	520	520	520	620	620

Table 8.
Composition of different formulations of diclofenac sodium floating tablets.

4.6.2 I-R spectrum of pure drug

About 1 mg of the sample and 100 mg of the potassium bromide (KBr) was taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and compressed at 10 kg/cm$^{2.}$ The pellet was kept onto the sample holder and scanned from 4000 to 400 cm^{-1}.The I-R spectrum of drug sample was obtained using FTIR-8400 s, Shimadzu (**Figure 2**).

4.6.3 I-R spectra for diclofenac sodium with HPMC K4M + HPMC K15M and carbopol 934P

Sample mixture of diclofenac sodium with HPMC K4M + HPMC K15M and carbopol 934P were prepared in KBr discs (1 mg sample in 100 mg KBr). A small amount of triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2. The scanning range was 4000–400 cm^{-1}, and the resolution was 4 cm^{-1} (**Figures 7** and **8**).

4.7 Evaluation of granules properties

4.7.1 Angle of repose

The angle of repose of was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface [9, 21]. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1}(h/r) \tag{2}$$

where, h and r are the height and radius of the powder pile, respectively.

4.7.2 Bulk density

Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any

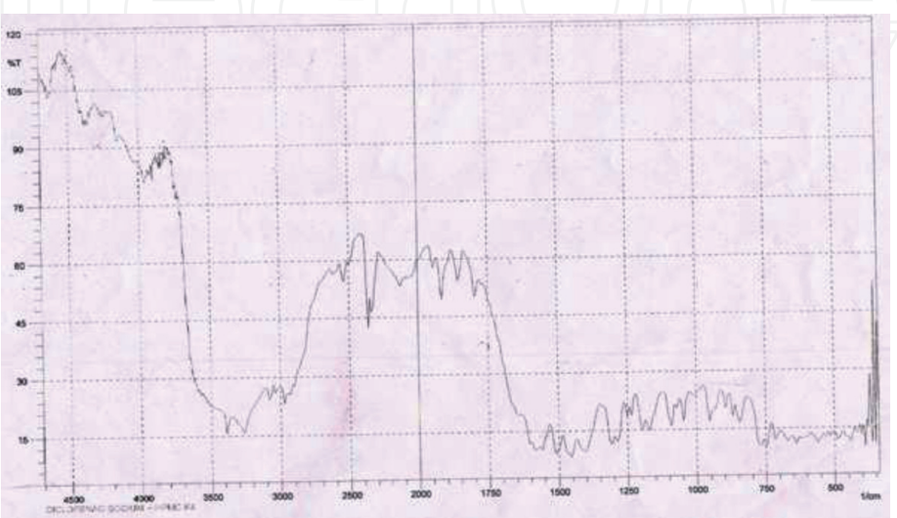

Figure 7.
FTIR of diclofenac sodium + HPMC K4M + HPMC K15M.

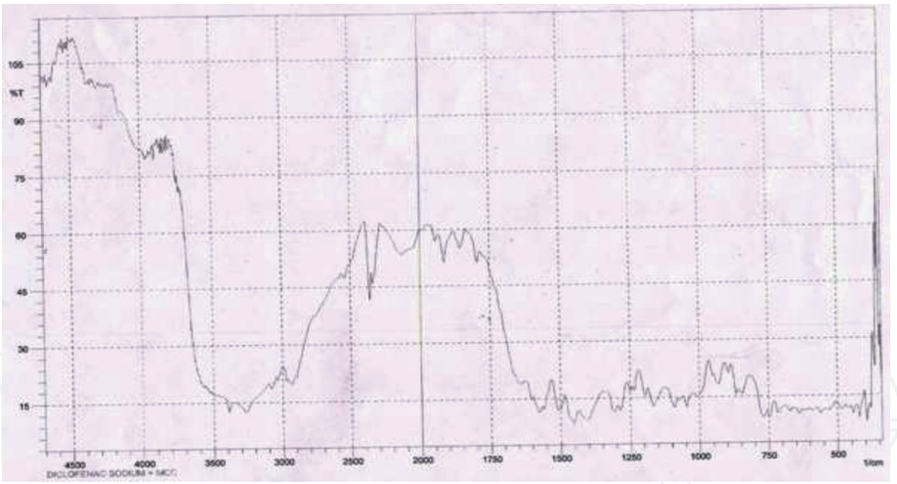

Figure 8.
FTIR of diclofenac sodium + carbopol 934P.

agglomerates formed, was introduced into a 10 ml measuring cylinder [9]. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted.

BD and TBD were calculated using the following formulas**.**

$$\text{BD} = \text{Weight of the Powder/Volume of the packing.} \quad (3)$$

$$\text{TBD} = \text{Weight of the powder/Tapped volume of the packing.} \quad (4)$$

4.7.3 Compressibility index/carr's index

The flow property was also determined by measuring the compressibility index. It is an important measure that can be obtained from the BD and TBD. According to the theory, the less compressible materials are more flowable. A material having values of less than 20–30% is defined as the free flowing material [9, 21]. Based on the BD and TBD, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\text{Compressibility Index} = \frac{\text{Tap density–Bulk density}}{\text{Tap density}} \times 100 \quad (5)$$

4.8 Evaluation of floating tablets

4.8.1 In vitro *buoyancy determination studies*

In vitro buoyancy studies were performed for all the formulations as per the method described by Rosa *et al* [22]. The randomly selected tablets from each formulation were kept in a 100 ml 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) [9, 23–25].

4.8.2 General characteristic

The formulated tablets were assessed for its general appearance.

4.8.2.1 Thickness and diameter

Thickness and diameter of tablets was determined using vernier calliper. Three tablets from each batch were used, and average values were calculated.

4.8.2.2 Weight variation

Formulated floating tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not.

4.8.2.3 Friability test

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre-weighed tablets were placed in the apparatus, which was given 100 revolutions, after which the tablets were reweighed. The percentage friability was calculated.

$$\%F = \{1 - (\text{loss in weight}/\text{initial weight})\} \times 100 \quad (6)$$

4.8.2.4 Hardness test

Hardness of the tablet was determined using the monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

4.8.2.5 Percent drug content

Ten tablets were weighed and powdered. An amount of the powder equivalent to 50 mg of diclofenac sodium was dissolved in 100 ml of 0.1 N HCl, filtered, diluted suitably and analysed for drug content at 276 nm using UV/Visible spectrophotometer.

4.8.2.6 Determination of percent swelling index (percentage water uptake)

The swelling properties of floating tablet containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of distilled water at 37°C ± 0.5°C paddle rotated at 50 rpm. The tablets were removed periodically from dissolution medium. After draining free from water by blotting paper, these were measured for weight gain. Swelling characteristics were expressed in terms of percentage water uptake (%WU) according to the equation shows relationship between swelling index and time.

$$WU\% = \frac{\text{Weight of swollen tablet–Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100 \quad (7)$$

4.8.2.7 Dissolution studies using USP type II apparatus with wire sinker

Dissolution test was carried out using USP type II apparatus with wire sinker. The drug release study was carried out for 12 hr. in 900 ml of 0.1 N HCl dissolution

media, maintained at 37°C ± 0.5°C and agitated at 50 rpm. Periodically 5 ml samples were withdrawn and filtered through whatman filter paper and samples were replaced by its equivalent volume of dissolution media. The absorbance of DS was measured UV/Visible spectrophotometrically at 276 nm. The percentage cumulative drug release was calculated and amount of CP released from tablets was determined. The floating tablet is wound with the helical wire sinker.

4.8.2.8 Kinetic of drug release

The result of *in vitro* dissolution studies of tablet were fitted with various kinetics models, like zero order (% cumulative drug release vs. time), first order (log % drug remaining vs. time), Higuchi's model (% cumulative drug release vs. square root of time) but these models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer and Peppas semi-empirical model to ascertain the mechanism of drug release.

$$\mathbf{log}\ (Mt/M\infty) = \log k + n \log t \tag{8}$$

Where, M∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablets; and n is the diffusional exponent; indicative of the mechanism of drug release. **Table 9** shows an analysis of diffusional release mechanism obtained by various value of n. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

4.8.2.9 Biodegradability studies of floating tablet

The biodegradability studies were carried out using USP rotating basket apparatus. A tablet (50 mg) were introduced into the baskets which were rotated at 50 rpm in 900 ml of different pH buffer solution (5.0, 6.8, 8.0) maintained at 37°C ± 0.5°C.

4.8.2.10 Stability studies

To assess the drug and formulation stability, stability studies were done according to ICH guidelines. The promising formulation F4 was tested for accelerated testing for a period of 2 months at 40°C ± 2°C/ 75% RH ±5% for their drug content and other parameters.

S. No	n value	Mechanism
1	$n \leq 0.5$	Quasi-fickian diffusion
2	0.5	Fickian diffusion
3	$0.5 \geq n \leq 1.0$	Anomalous (non-fickian) diffusion
4	$n \geq 1.0$	Non-fickian super case 11
5	1	Non-fickian case 11

Table 9.
Release mechanism with variation of n values.

5. Result and discussion

The effervescent floating tablets of SDs of DS were formulated in 6 different batches F1 to F6 by using hydrophilic polymers HPMC K4M, HPMC K15M and hydrophobic polymer carbopol 934P along with effervescing agents, sodium bicarbonate and citric acid (**Table 8**). All the formulations were prepared by wet granulation method. In order to get the longer duration of floating time the high viscosity polymer selected, HPMC K4M was chosen and it was found that, increased viscosity of a polymer prolongs the drug delivery from the dosage form. IR study was carried out to check the compatibility between the selected polymers with the diclofenac sodium drug. This study was performed to assure that there is complete physical entrapment of the drug into the polymer matrix without any mutual interaction. IR spectra were taken for samples like pure drug, and drug-polymer physical mixture at a wavelength of between 4000 and 400 cm^{-1}. All the spectra were compared for shifting of major functional peaks and also for the loss of functional peaks for identification of incompatibility, if any. When the spectra were compared it was found that there was no shifting of functional peaks and no overlapping of characteristic peaks and also there was no appearance of new peaks. **Figures 2**, 7 and **8** shows the IR spectra of various samples. No significant change in the IR spectra of diclofenac sodium complexes was obtained, except for the broadening of the peaks. The broadening of peaks may be probably due to the restriction of bending and stretching vibrations of the molecule [6]. The preformulation studies such as angle of repose, bulk density, tapped density, and carr's index evaluated were found to be within prescribed limits and indicated good free flowing property (**Table 10**).

In vitro Buoyancy of all the prepared tablets formulations were determined using 100 ml beaker containing 0.1NHCl medium shown in (**Table 11**) and the results can be concluded that the batch F3 containing HPMCK4M and carbopol 934P in higher concentration showed good buoyancy lag time is 4.3 min and total floating time is 15 hrs. TFT depends upon the amount of HPMC as the polymer content increased the floating time was increased due to the formation of thick gel which entrapped the gas formed due to $NaHCO_3$ firmly. Among these formulations, the *in vitro* buoyancy was increased in the following order: F3 > F1 > F4 > F2 > F5 > F6. The **Table 9** revealed that FLT minimum for F3 formulation, while its TFT was maximum i.e. 24 h; hence, F3 was selected for further evaluations and *in vitro* drug dissolution studies.

Formulation F3 was evaluated for physical characters like tablet thickness, diameter, hardness, friability, weight variation, percent swelling index, *in vitro* drug release studies. The thickness, diameter and hardness of the formulations satisfied the acceptance criteria. The friability and weight variation was found to be within the limits specified in pharmacopoeia. The drug content was found

Parameter	F1	F2	F3	F4	F5	F6
Angle of repose	22.53°	22.17°	23.42°	21.57°	22.87°	23.34°
Bulk density	0.953 ± 0.026	0.948 ± 0.031	0.975 ± 0.0.098	0.881 ± 0.102	0.836 ± 0.057	0.899 ± 0.083
Tapped density	1.05 ± 0.011	1.041 ± 0.019	1.031 ± 0.026	0.978 ± 0.020	0.981 ± 0.017	0.969 ± 0.038
Carr's index	7.64 ± 0.94	6.66 ± 0.71	5.69 ± 0.56	8.99 ± 0.62	8.68 ± 0.83	7.97 ± 0.49

Table 10.
Pre-compression parameters of granules.

Parameter	F1	F2	F3	F4	F5	F6
Floating lag time (FLT) (s)	160	182	158	163	221	223
Total Floating time (TFT) (h)	22	21	24	20	24	21

Table 11.
In vitro *buoyancy determination.*

spectrophotometrically indicating good content uniformity in the prepared formulation results were shown in **Table 12**.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased because weight gain by tablet was increased proportionally with rate of hydration. The direct relationship was observed in **Table 13**.

The floating formulation F3 was subjected for the dissolution studies using USP type II apparatus with wire sinker in 900 ml of 0.1 N HCl medium. The results are given in **Table 14**. The formulation showed a constant rate of release in a sustained manner similar to zero order kinetics with good buoyancy property. Diclofenac sodium effervescent floating controlled release tablet formulation using solid dispersion (F3) showed far better release than marketed products.

5.1 Effect of sodium bicarbonate concentration on lag time of tablets

The concentration of sodium bicarbonate was found to be critical factor that influenced buoyancy of tablets (**Table 15**). Sodium bicarbonate released CO_2 gas that was trapped into the polymeric matrix of HPMC that made the tablets float. Various concentrations of sodium bicarbonate ranging from 5–12% of tablet weight were used. From the results, it was concluded that with the increasing

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	4.3 ± 0.016	4.8 ± 0.4	0.24 ± 0.08	542.4 ± 1.9	99.86 ± 0.15
F2	4.4 ± 0.013	5.1 ± 0.3	0.51 ± 0.03	555.8 ± 1.5	99.45 ± 0.08
F3	**4.5 ± 0.015**	**5.4 ± 0.6**	0.17 ± **0.04**	**554.3 ± 1.1**	**100.01 ± 0.04**
F4	4.5 ± 0.013	4.9 ± 0.4	0.46 ± 0.03	545.1 ± 1.8	99.96 ± 0.18
F5	5.5 ± 0.014	4.4 ± 0.1	0.35 ± 0.05	649.1 ± 1.7	98.90 ± 1.05
F6	5.7 ± 0.011	5.8 ± 0.3	0.41 ± 0.04	647.3 ± 0.4	99.02 ± 0.01

Table 12.
General characteristic of floating tablets.

% Swelling index (percentage water uptake)	
Time (h)	**Formulation F3**
1	24
2	37
3	48
4	63
5	71
6	88

Table 13.
% Swelling index (percentage water uptake) of floating tablets.

Time (mins)	Marketed tablet (Voveran-50) (% drug release)	Physical mixture	Diclofenac sodium-solid dispersion (% drug release)	Marketed tablet (Voveran-SR100) (%drug release)	Floating tablet of diclofenac sodium solid dispersion (3) (%drug release)
0	0	0.00	0.00	0.000	0.000
15	15.25 ± 0.64	21.23 ± 0.61	30.51 ± 0.54	12.706 ± 0.67	15.266 ± 0.41
30	37.37 ± 0.53	39.44 ± 0.64	52.25 ± 0.49	16.258 ± 1.27	18.365 ± 0.38
60	51.77 ± 0.86	70.76 ± 0.58	92.99 ± 0.78	19.353 ± 0.98	26.548 ± 0.51
90				24.930 ± 0.79	27.897 ± 0.50
120				27.966 ± 0.93	31.377 ± 0.43
150				32.220 ± 0.76	38.323 ± 0.45
180				38.922 ± 1.22	45.233 ± 0.29
210				45.875 ± 0.96	54.320 ± 0.27
240				51.519 ± 1.23	61.522 ± 0.30
270				60.865 ± 1.31	64.267 ± 0.31
300				64.037 ± .55	69.613 ± 0.35
330				68.561 ± 1.53	73.670 ± 0.51
360				73.686 ± 0.77	76.568 ± 0.42
390				77.371 ± 1.16	80.179 ± 0.44
420				82.957 ± 0.98	85.363 ± 0.47
450				86.414 ± 0.74	87.573 ± 0.58
480				89.213 ± 1.78	96.769 ± 1.19

Table 14.
Comparative in vitro *release study of marketed tablets, physical mixture, solid dispersion and floating tablets of diclofenac solid dispersion.*

S. No.	Concentration of sodium bicarbonate (%)	Floating lag time (s)
1	5	280
2	6	220
3	7	198
4	8	164
5	9	158
6	10	159
7	11	160
8	12	165

Table 15.
Comparison of floating lag time prepared from concentration of sodium bicarbonate.

concentration of sodium bicarbonate, the lag time decreased. A concentration of 8.5–9% w/w sodium bicarbonate was found to be optimal that resulted in tablets having lag time < 3 min and floating time of over 12 h. Similar conclusions were also drawn by other researchers working on floating delivery systems. In both the reported works, optimum concentration of sodium bicarbonate was found to be around 10% w/w of the tablet weight [26, 27] which is slightly higher than our optimal concentration.

5.2 Effect of HPMC grade on lag time of tablets

It was interesting to note that the grade and quantity of HPMC used in the formulations has impact on floating lag time of the tablet. With the increasing molecular weight/quantity of HPMC, the viscosities of the gel matrix around the tablet also increased which in turn in- creased the floating lag time. The lag time for HPMC K15M tablets was slightly higher compared to HPMC K4M tablet. This may be attributed to the increased density of tablet with increasing molecular weight of HPMC (**Table 16**).

5.3 Kinetic of drug release

The various release kinetic models (**Figures 9–12**) were applied to determine the mechanism of drug release from gastro retentive floating tablets and the data is tabulated in **Table 17**. The *in vitro* drug release of optimised formulation (F3) showed the highest regression coefficient values for zero order model, thus indicating absolute correlation between the two variables for the zero order model. Optimised formulations followed Zero order equation proving that the release is by diffusion mechanism. The values of release exponent (n) were calculated from korsmeyer and peppas equation and the 'n' value was determined to be 0.5665 indicating **Anomalous (non-fickian) diffusion.**

So it can be conclude that the optimised formulation follows the zero order plot to a major extend along with other plots to some extent.

S. No.	Quantity of HPMC (mg)	Floating lag time (s)
1	70 (HPMC K4M)	160
2	93 (HPMC K4M)	158
3	105 (HPMC K4M)	163
4	70 (HPMC K15M)	182
5	93 (HPMC K15M)	221
6	105 (HPMC K15M)	223

Table 16.
Comparison of floating lag time prepared from different grade or quantity of HPMC.

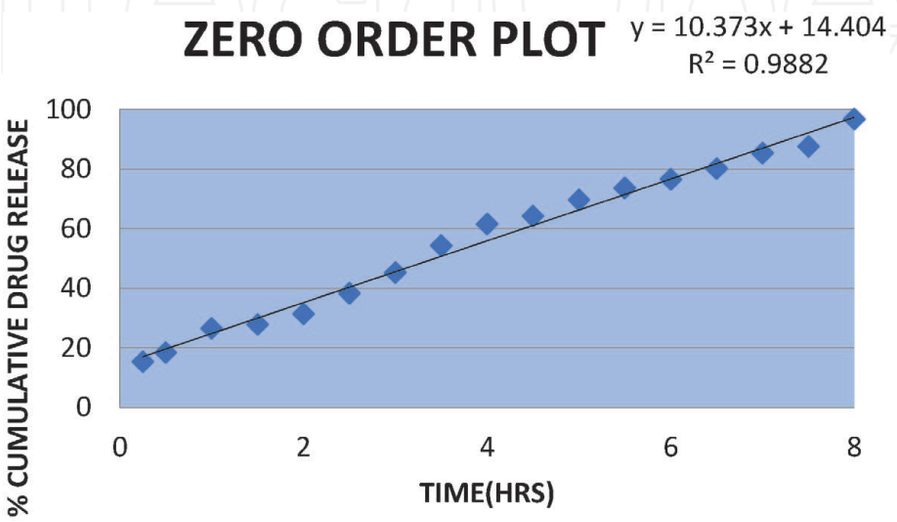

Figure 9.
Zero order release kinetics of optimised formulation.

Figure 10.
First order release kinetics of optimised formulation.

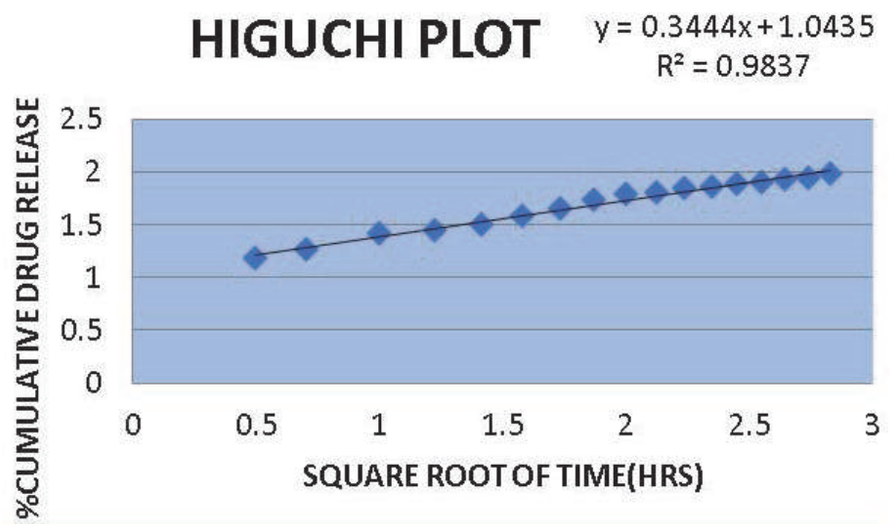

Figure 11.
Higuchi kinetics of optimised formulation.

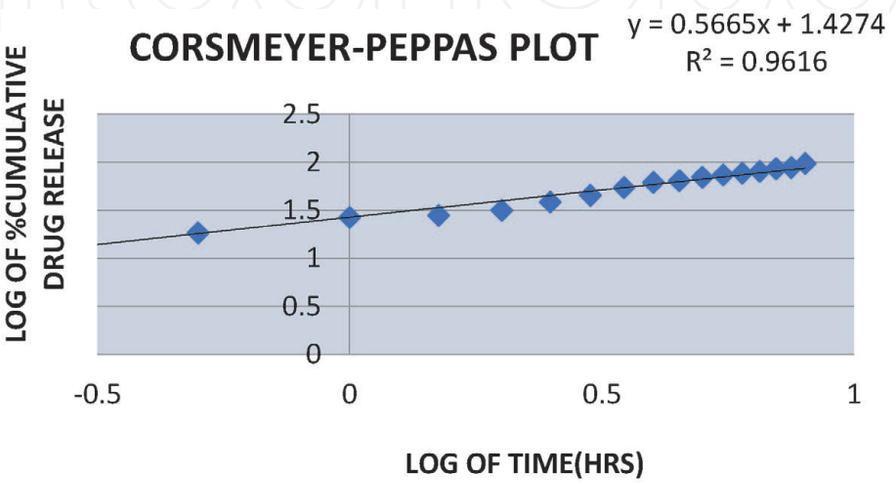

Figure 12.
Korsmeyer-Peppas kinetics of optimised formulation.

S.No	Formulation	Zero order		First order		Higuchi		Korsmeyer-peppas	
1	F3	K	R^2	K	R^2	K	R^2	N	R^2
		10.373	0.9882	−0.1373	0.8541	0.3444	0.9837	0.5665	0.9616

Table 17.
Release kinetic equation values of the optimised formulations.

5.4 Biodegradability studies of floating tablet

Biodegradability studies revealed that the gastro retentive floating tablet of diclofenac (F3) was found to disintegrate and dissolve in intestinal pH within 3 h (**Figure 13**).

Formulation F3 seemed to completely biodegrade in intestinal fluid, and it is the pH of media, which is responsible for slow dissolution of the tablet in intestinal fluid. This indicates that after gastric emptying the regular shaped tablet, gradually become rough with an irregular surface and thereafter was degraded. Thus the gastro retentive floating tablets of diclofenac proved to be suitable gastro retentive dosage form, as they have a rigid structure that resist biodegradation in gastric pH but exhibit complete biodegradation in phosphate buffer pH 8.0.

5.5 Stability studies

Pharmaceutical dosage forms are complex systems composed not only of drug substances but also of various excipients. These excipients, which are non-therapeutic, are intended to contribute desirable, practical properties to the dosage form. These dosage forms may undergo both chemical and physical degradation [28]. Thus, the success of the effective formulation can be evaluated only through the stability studies. This study pursues two particular aims:

- Determination of the optimum formulation and shelf life during developmental stages.

- Derivation of the stability of a product, which guarantees the safety and efficacy of the product up to end of the shelf life at a defined storage condition and pack profile.

So, stability of a pharmaceutical product may be defined as the capability of a particular formulation in a specific container, to remain in its physical, chemical, microbiological, therapeutic and toxicological specifications. Ability of a

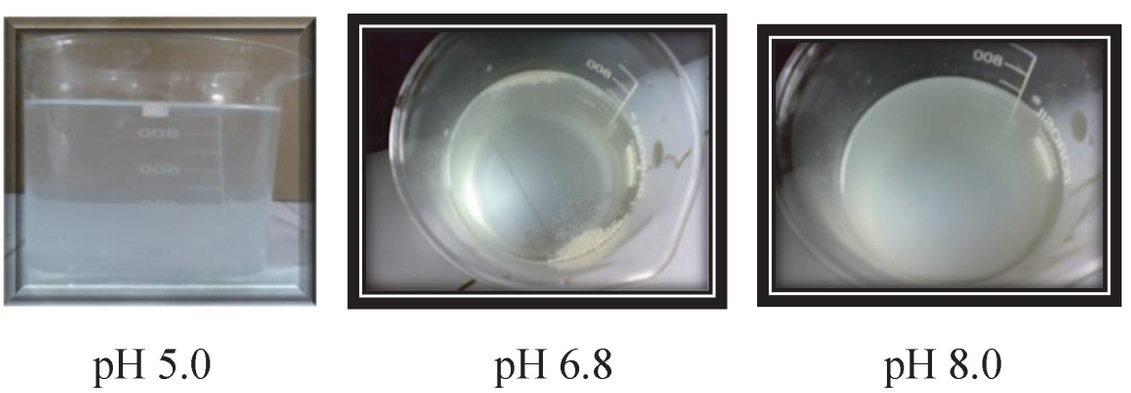

Figure 13.
Images of complete biodegradation of F3 floating tablet after 3 h.

formulation to retain properties in specified limits throughout its shelf-life is referred as stability [28].

The stability of finished pharmaceutical products depends on several factors. On the one hand, it depends on environmental factors such as ambient temperature, humidity and light. On the other hand, it depends on product related factors such as chemical and physical properties of active substance and pharmaceutical excipients, the dosage form and its composition, the manufacturing process, the nature of container closure system and properties of packaging materials.

A study of stability of a pharmaceutical product is essential for safety of the patients, legal requirements concerned with the identity, strength, purity and quality of the drug and to prevent the economic repercussions of marketing an unsuitable product [29, 30].

5.5.1 Experimental

Optimised formulations were stored in screw capped small glass bottles at room temperature and in stability chamber at 40 ± 1°C and 75% relative humidity. Samples were analysed for physical appearance, Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), Buoyancy lag time (s), Floating time (h) and *in vitro* release after a period of 15, 30, 45, 60, 75, 90 days. Initial drug content was taken as 100% for each formulation. Observations are recorded in **Tables 18** and **19**.

5.5.1.1 Physical characteristics

Various physical parameters were evaluated such as appearance, Buoyancy lag time (s), floating time. Observations are recorded in **Table 18**.

S. No.	Physical parameters	0 days	15th days	30th days	60th days	90th days
1	Appearance	+	+	+	+	+
2	Floating time	+	+	+	+	+
3	Buoyancy lag time (s)	+	+	+	+	+

+, no change.

Table 18.
Effect of ageing on physical parameters.

Parameter	Optimised formulation (F3) (n = 3)			
	At 0 day	At 15 days	At 30 days	At 60 days
Hardness (kg/cm^2)	5.4 ± 0.08	5.4 ± 0.1	5.4 ± 0.09	5.2 ± 0.07
Friability (%)	0.17 ± 0.02	0.17 ± 0.01	0.19 ± 0.02	0.20 ± 0.01
Uniformity of weight (mg)	554.3 ± 1.1	554.3 ± 1.1	554.3 ± 1.1	554.3 ± 1.1
Drug content (%)	100.01 ± 0.04	100.01 ± 0.04	99.50 ± 0.58	98.89 ± 0.12
Thickness (mm)	4.55 ± 0.12	4.55 ± 0.09	4.55 ± 0.10	4.55 ± 0.11

Table 19.
Effect of ageing on physico-chemical parameters of optimised formulation.

5.5.1.2 Physcio-chemical parameters

Various parameters were evaluated such as Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), and *in vitro* release after a period of 15, 30, 45, 60, 75, 90 days. Observations are recorded in **Table 19**.

5.5.1.3 Drug content was assayed by U.V. spectrophotometry

Gastro retentive floating tablet of diclofenac sodium (50 mg) was dissolved in 100 ml of 0.1 N HCl (pH 1.2) by stirring for 6 h using magnetic stirrer. The resulting solution was then filtered using 0.45 m millipore filter, 1 ml of this solution was taken and added to 100 ml of 0.1 N HCl (pH 1.2). It was then analysed spectrophotometrically at the predetermined λ max (276 nm) to determine concentration of the drug. The determinations were made in triplicate.

5.5.1.4 In vitro *dissolution studies*

In vitro dissolution studies were carried out using simulated gastric fluid (pH 1.2).

5.5.2 Result and discussion

5.5.2.1 Physical parameters of the optimised tablets formulation

The Physical parameters after 15th, 30th, 60th, 90th days are as mentioned in **Table 18**. All the Physical parameter are within the acceptable limits which indicated that gastro retentive floating tablet of diclofenac sodium showed no significant change in the physical appearance at room temperature and in stability chamber at 40°C ± 2°C and 75 ± 5% relative humidity indicating that the formulations were physically stable at these temperatures.

5.5.2.2 Physico-chemical parameters of the optimised formulation

Various parameters were evaluated such as Hardness (kg/cm^2), Friability (%), Uniformity of weight (mg), Drug content (%), Thickness (mm), and *in vitro* release

S. No.	Sampling interval (days)	% Residual drug content Mean ± S.D. (n = 3)	
		At room temp.	At 40 ± 2°C/75 ± 5% RH
1	0	100.01 ± 0.03	100.01 ± 0.03
2	15	99.82 ± 0.12	99.66 ± 0.09
3	30	99.56 ± 0.09	99.25 ± 0.18
4	45	98.75 ± 0.14	98.40 ± 0.15
5	60	98.56 ± 0.05	97.72 ± 0.9
6	75	98.07 ± 0.09	97.51 ± 0.10
7	90	97.69 ± 0.07	96.66 ± 0.06

Table 20.
Effect of ageing on residual drug content at room temperature &40 ± 2 °C/ 75 ± 5%RH.

after a period of 15, 30, 45, 60, 75, 90 days. Observations are recorded in **Table 6**. All the physico-chemical parameters are within the acceptable limits which indicated that formulation were stable over the period of 90 days.

5.5.2.3 Residual drug content of stability batch

Initial drug content of formulations was 100.01 ± 0.04.the drug contents at the end of 15th, 30th, 60th, 90th days were found to be as given in **Table 20**. The drug content was within the permissible limits. The percent residual drug content was determined and the log percent residual content was plotted against time t (**Figures 14–17**), which reflected almost linear relationship.

5.5.2.4 In vitro *dissolution studies*

The dissolution results obtained were as given in the **Table 21**.

The dissolution behaviour of samples withdrawn at different interval was similar and the difference in dissolution pattern of samples kept at two different conditions of storage was negligible.

The log % residual drug content vs. time graph was also plotted in order to evaluate shelf-life and half-life of formulations.

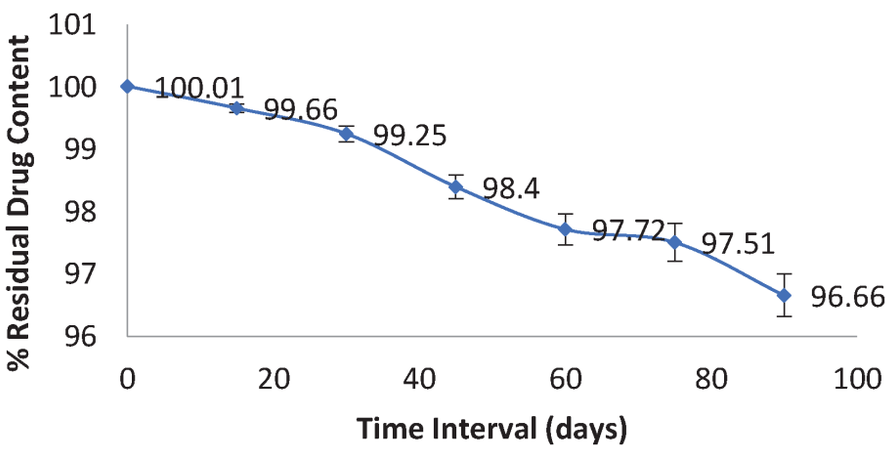

Figure 14.
Effect of ageing on residual drug content at 40 ± 2°C/75 ± 5%RH.

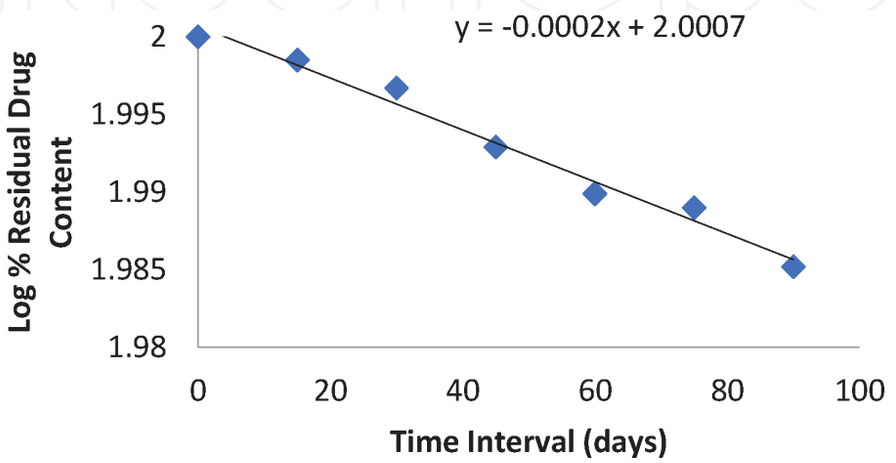

Figure 15.
Plot of log % residual drug content Vs time at 40 ± 2°C/75 ± 5%RH.

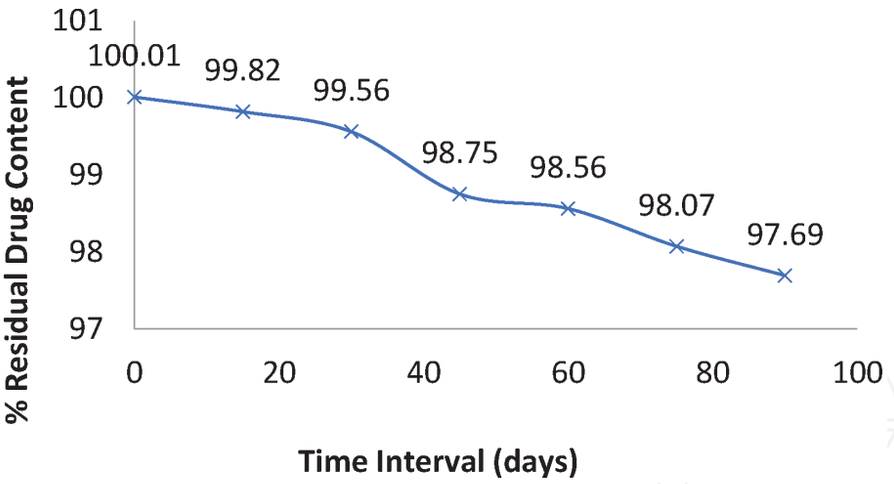

Figure 16.
Effect of ageing on residual drug content at room temperature.

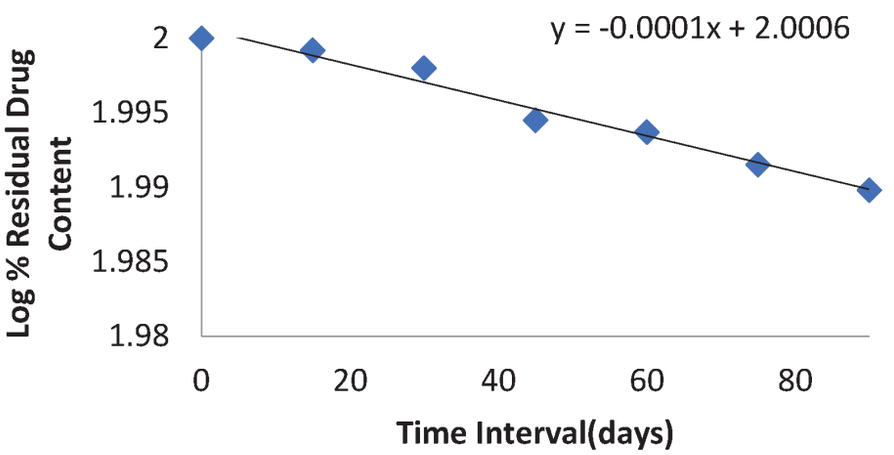

Figure 17.
Plot of log % residual drug content vs. time at room temp.

Time interval (days)	% Cumulative drug release in 8 h ± SD (n = 3)	
	Room temperature	40 ± 2°C/75 ± 5% RH
0	96.769 ± 1.19	96.769 ± 1.19
15	95.78 ± 0.84	94.34 ± 1.52
30	94.81 ± 1.64	93.05 ± 0.81
60	94.45 ± 0.56	92.89 ± 0.69
90	93.97 ± 0.93	92.45 ± 1.21

Table 21.
Effect of ageing on % cumulative drug release at room temperature & 40 ± 2°C/75 ± 5%RH.

Shelf-life was evaluated by the equation:

$$T_{10\%} = 0.104/K \quad (9)$$

Degradation rate constant K was calculated from the slope of straight line between log of % residual drug and time interval. The time required for degradation of 10% drug was calculated as $T_{10\%}$.

S. No.	Storage condition	K (day^{-1})	$T_{10\%}$ (days)	$t_{1/2}$ (days)
1	40 ± 2 °C/75 ± 5%RH	3.822×10^{-4}	272.039	1812.72
2	Room temperature	2.303×10^{-4}	451.58	3009.11

Table 22.
Shelf life of optimised formulation.

Half-life was evaluated by the equation:

$$T_{1/2} = 0.693/K \quad (10)$$

Gastro retentive floating tablet of diclofenac sodium stored at 40 ± 2°C/75 ± 5% RH showed K value as 3.822×10^{-4} and $t_{10\%}$ value as 272.039 days, while those stored at room temperature showed K value as 2.303×10^{-4} and $t_{10\%}$ value as 451.58 days (**Table 22**).

The $T_{10\%}$ obtained in case of formulation stored at 40°C ± 2°C/75 ± 5%RH was found to be lower in comparison with the formulation stored at room temperature which indicated that the formulations tend to degrade faster at higher temperatures and humidity.

The results of stability studies suggest that for adequate shelf life of optimised gastro retentive floating tablet of diclofenac sodium, it should be stored in cool and dry place.

6. Conclusions

In the above research work, ECRFT has been developed by using dual approach; one is solid dispersion (for solubility enhancement) and other is effervescent floating technique (for achieving extended retention in upper G.I.T.), which was prepared from previously optimised solid dispersion of diclofenac sodium. Formulated tablets showed outstanding physicochemical properties, biodegradation studies, stabilities studies, and prolong gastric retention with control release. When compared with marketed tablets of immediate release (Voveran-50) and control release (Voveran-100SR), the optimised formulation F3 was found to be favourable for improving bioavailability of drug, enhancing its therapeutics efficacy and improving patient compliance due to less frequent dosing requirement. Hence, it can be concluded that the prepared formulation can be used positively as a particular oral controlled release-floating tablet for once a day administration.

Acknowledgements

The authors would like to express their hearty gratitude to Kwality Pharmaceutical Pvt Ltd, Amritsar for supplying diclofenac sodium raw material and excipients. We are also thankful to Dr. Abhishek Bansal, Department of Pharmaceutical sciences, Gurukul Kangri University, Haridwar for the help provided during research.

Conflict of interest

There is no conflict of interest.

Acronyms and abbreviations

SEM	scanning electron microscopy
PM	physical mixtures
DT	disintegration time
ECRFT	effervescent controlled release floating tablet
SDs	solid dispersions
DS	diclofenac sodium
BD	bulk density
TBD	tapped bulk density
TFT	total floating time
%WU	percentage water uptake
FLT	floating lag time

Author details

Peeush Singhal[1]*, Rajneesh Dutt Kaushik[1] and Vijay Jyoti Kumar[2]

1 Department of Pharmaceutical Sciences (FMSH), Gurukul Kangri Vishwavidyalaya, Haridwar, India

2 Department of Pharmaceutical Sciences, H.N.B. Garhwal Central University, Srinagar, Uttarakhand, India

*Address all correspondence to: peeushpharma@gmail.com

References

[1] Available from: http://www.drugs.com/diclofenac.html

[2] Rao GK, Mandapalli PK, Manthri R, Reddy VP. Development and in vivo evaluation of gastro retentive delivery systems for cefuroxime axetil. Saudi Pharmaceutical Journal. 2013;**21**(1): 53-59. DOI: 10.1016/j.jsps.2012.01.003

[3] Chau Le-Ngoc VO, Chulhun P, Beom-Jin L. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs review article. European Journal of Pharmaceutics and Biopharmaceutics. 2013;**85**(3) Part B:799-813

[4] Giri TK, Kumar K, Alexander A, Ajazuddin, Badwaik H, Tripathi DK. A novel and alternative approach to controlled release drug delivery system based on solid dispersion technique review article. Bulletin of Faculty Pharmacy, Cairo University. 2012;**50**(2): 147-159

[5] Willis JV, Kendall MJ, Flinn RM, Thornill DP, Welling PG. The pharmacokinetics of diclofenac sodium following intravenous and oral administration. European Journal of Clinical Pharmacology. 1979;**16**(6): 405-410

[6] Sharma N, Jain N, Sudhakar CK, Jain S. Formulation and evaluation of gastro retentive floating tablets containing cefpodoxim proxetil solid dispersions. International Journal of Current Pharmaceutical Research. 2012; **4**(4):82-87

[7] Shivakumar HN, Desai BG, Deshmukh G. Design and optimization of diclofenac sodium controlled release solid dispersions by response surface methodology. Indian Journal of Pharmaceutical Sciences. 2008;**70**(1):22-30

[8] Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. International Journal of Pharmaceutics. 2000;**195**:125-135

[9] Chanvanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Novel sustained release, swellable and bio adhesive gastro retentive drug delivery system for ofloxacin. International Journal of Pharmaceutics. 2006;**316**:86-92

[10] United State Pharmacopoeia 31. The National Formulary. Asian Edition. 26 (I). North Bethesda, Maryland, United States: The Board of Trustees; 2008. pp. 297-298

[11] Seedher N, Bhatia S. Solubility enhancement of cox-2 inhibitors using various solvent systems. AAPS PharmSciTech. 2003;**4**(3):33

[12] Instruction manual pharmaspec. UV-1700 Series. User's System Guide. Kyoto Japan: Shimadzu Corporation;

[13] Pavia LK. Introduction to Spectroscopy. 3rd ed. United States: Thomson Brooks/Cole; 2001. p. 358

[14] ICH Harmonized Tripartite Guideline, Text on Validation of Analytical Procedure (Q2A). London, UK: EMEA; 1994

[15] Beckett AH, Stenlake JB. Practical Pharmaceutical Chemistry. 4th ed. Vol. 2. London, UK; 2007. pp. 282-288

[16] Garatt DC. The Quantitative Analysis of Drugs. 3rd ed. CBS publishers and Distributors; 2005. p. 876

[17] British Pharmacopoeia. The British pharmacopoeia commission offices, London. 2008;**1&2**:685-686

[18] Indian Pharmacopoeia. The Controlled Publication, New Delhi. Vol. 2. 2007. pp. 402-403

[19] Sharma BK. Instrumental Methods of Chemical Analysis. 23rd ed. Goel Publishing House; 2004. pp. 292-302

[20] Barzegar-Jalali M, Alaei-Beirami M, Javadzadeh Y, Mohammadi G, Hamidi A, Andalib S, et al. Comparison of physicochemical characteristics and drug release of diclofenac sodium-eudragit® RS100 nanoparticles and solid dispersions. Powder Technology. 2012;**219**:211-216

[21] Davis SS, Stockwel AF, Taylor MJ, Hardy JG, Whalley DR, Wilson CG. The effect of density on the gastric emptying of single and multiple unit dosage forms. Pharmaceutical Research. 1986;**3**: 208-213

[22] Rosa M, Zia H, Rhodes T. Design and testing in vitro of a bioadhesive and floating drug delivery system for oral application. International Journal of Pharmaceutics. 1994;**105**:65-70

[23] Li S, Lin S, Daggy BP, Mirchandani HL, Chien YW. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. International Journal of Pharmaceutics. 2003;**253**:13-22

[24] Machida Y, Inouy K, Tokumura T, Iwata M, Nagai T. Preparation and evaluation of intragastric buoyant preparations. Drug Design and Delivery. 1989;**4**:155-161

[25] Moes AJ. Gastro retentive dosage forms. Critical Reviews in Therapeutic Drug Carrier Systems. 1993;**10**:143-159

[26] Dhumal RS, Rajmane ST, Dhumal ST, Pawar AP. Design and evaluation of bi-layered floating tablets of cefuroxime axetil for bimodal release. Journal of Scientific and Industrial Research. 2006;**65**:812-816

[27] Patel VF, Patel NM. Intragastricoating drug delivery system of cefuroxime axetil: In vitro evaluation. AAPS PharmSciTech. 2006;**7**:E1-E7

[28] Yoshika S, Stell VJ. Stability of Drugs and Dosage Forms. 2nd ed. New Delhi: Springer Private Ltd; 2006. pp. 151-186

[29] Garret NM. Stability studies of floating drug delivery dosage form. Journal of Pharmaceutical Sciences. 1965;**54**:1557

[30] Gennaro AR. Remington: Pharmaceutical Sciences and Practice of Pharmacy. 20th ed. Vol. 1. Philadelphia: Lippincott Williams & Wilkins; 1990. p. 986