

Preparation and *in vitro* characterization of solid dispersion floating tablet by effervescent control release technique with improved floating capabilities

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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 were formulated in many ratio (1:1, 1:2, 1:3 and 1:4). Prepared SDs was optimized for its solubility, % drug content and % dissolution studies. Tablets were formulated by using optimized SDs products and all formulation was evaluated for various parameters. A clear rise in dissolution rate was detected with entirely SD, amid that the optimized 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 was fitted in several kinetics models to explain release mechanism. The F3 formulation shows zero order release. From this study we can concluded that ECRFT containing SDs of DS can be successfully used for achieving better therapeutic objective.

KEY WORDS: Solid dispersion, Diclofenac Sodium, Polyethylene Glycol, Dissolution Enhancement, Floating Tablets.

INTRODUCTION

Diclofenac Sodium (DS) is an effective NSAID with high affinity for both COX-1 and COX-2 Receptors and its 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 (<http://www.drugs.com/diclofenac.html>) 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 (Rao *et al.*, 2012). The release rate can be improved by increasing surface area of existing drug by using several techniques but amongst these methods solid dispersion technique is one of the best techniques for increasing the surface area (Chau *et al.*, 2013). Hence, an effort was made to increase the dissolution characteristics using the solid dispersion technique (Giri *et al.*, 2012, Chau *et al.*, 2013). It has absorption site in upper part of Gastro intestinal tract. Gastric retention of DS was very short that's 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 hours and hence there is a requirement of frequent dosing (3-4 tablets

daily) (Willis *et al.*, 1979) 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's 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 (Shivakumar *et al.*, 2008, Sharma *et al.*, 2012) and then develop effervescent controlled release floating tablet (Baumgartner *et al.*, 2000). 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 (Chanvanpatil *et al.*, 2006) using solid dispersion product of DS in order to regulate the drug release and make available security from First pass metabolism.

MATERIALS AND METHODS

Materials

Diclofenac Sodium (Batch no. A5/206), HPMC K15M, HPMC K4M and crosspovidone (Batch no. YPVP09319040) were obtained from Kwaliti pharmaceutical pvt ltd Amritsar, as gift samples. Sodium bicarbonate (NaHCO₃), citric acid, polyvinyl pyrrolidone (PVP K-30), magnesium stearate, lactose and Isopropyl

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alcohol were purchased from local suppliers. Marketed product, "Voveran SR100 or Voveran 50", (Manufactured by Ranbaxy, India; Batch no. 131003AUor320028), used for comparative studies, was purchased from the local retail pharmacy.

Methods

Preparation of physical mixtures (PM)

PM were ready by the involvement of suitable quantities of the drug and carrier (PEG 6000) in the varied weight proportions of 1:1, 1:2, 1:3 and 1:4 in mortar (Giriet *et al.*, 2012, Chau *et al.*, 2013, Shivakumar *et al.*, 2008, Sharma *et al.*, 2012). The resultant Mixtures were put through a sieve no. 80 collected and stored in hermetic vessel until use.

Preparation of solid dispersion

Melt method was used to prepare solid dispersions (Shivakumar *et al.*, 2008) of Diclofenac Sodium with PEG 6000 comprising several weight ratio (1:1,1:2,1:3,1:4 and 1:5) (table 1). Diclofenac Sodium and PEG 6000 were weighed according to their weighed ratios. PEG 6000 was melted at 600C. In this melted PEG 6000, Diclofenac Sodium was added slowly with continuous stirring and flashed chilled on an ice bath and then stored overnight in desiccators. The formulated solid dispersion was then crushed with the help of mortar and pestle, screens through a strainer no 40 and stored over a fused calcium chloride in desiccators for further use.

Optimization of solid dispersion

In this study three factor namely, concentration of Diclofenac sodium (1% 2% 3% and 4%), concentration of PEG 6000 as a carrier (1% 2% 3% and 4%), were selected as independent variables while Solid dispersion's Saturation Solubility, pH Dependent Solubility and Percent Drug Content were the dependent variables used for optimization of process variables (independent variables) in preparation of solid dispersion.

Characterization of solid dispersion/ physical mixtures of diclofenac sodium with PEG-6000SDs (Shivakumar *et al.*, 2008, sharma *et al.*, 2012)

Compatibility studies

FTIR spectra of drug, PEG 6000 and Solid dispersion of DS were scanned. Around 1mg of sample was assorted carefully with 100 mg potassium bromide IR powder and compressed under vacuum at a pressure of about 12 psi for 3 minutes. The obtained disc was placed in an appropriate frame in FTIR-8400S Fourier transform, Shimadzu and the IR spectrum was scanned from 4000 cm⁻¹ to 400cm⁻¹ in a scan time of 12 minutes (Barzegar *et al.*, *et al* 2012). The obtained spectra were matched for any spectral variations. Fig. 1 shows the FTIR spectra of the I) drug II) carrier III) Surface Solid Dispersion. There was no major alteration in the spectrum of solid

dispersions, as addition of Diclofenac into the carrier (PEG6000) did not alter the location of its functional groups.

Determination of saturation solubility

Shake Flask technique was used for determining Saturation solubility (Sharma *et al.*, 2012, Barzegar *et al.*, 2012). Adding Excess quantities of all products (DS, SDsPMs) with 25 ml distilled water in conical flasks, which is coded 1, 2 and 3, respectively. After that the entire flask put in orbital shaker at 37°C and at 100rpm for 72 hrs. Absorbance of resultant was determined on UV/Visible Spectrophotometer (UV-TCC-240A, Shimadzu, Kyoto, Japan) at 276 nm.

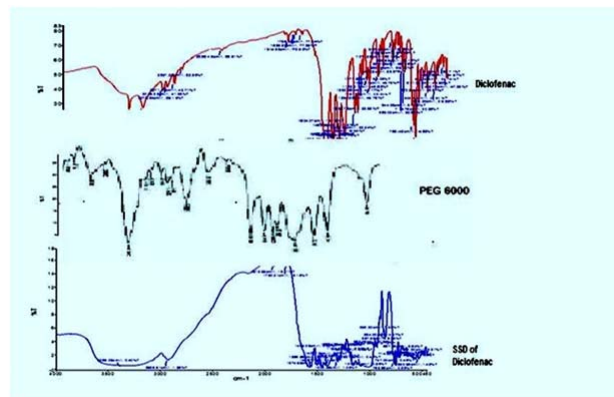


Fig. 1: Comparative FTIR spectra of Diclofenac, PEG 6000, & solid dispersion of Diclofenac with PEG6000.

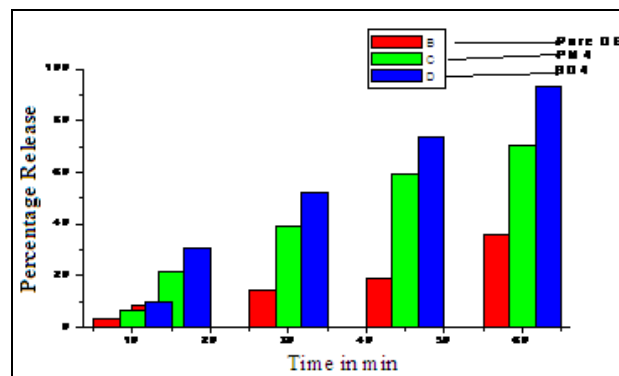


Fig. 2: Dissolution of the pure DS, SD4 and PM4.

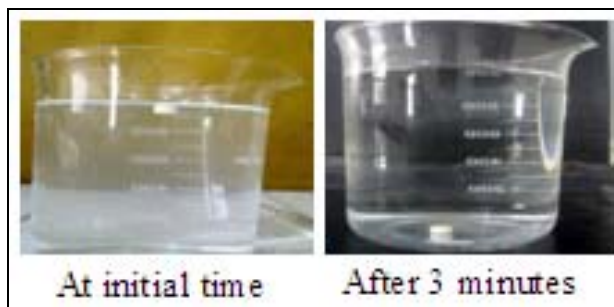


Fig. 3: In vitro lag time measurement of optimized Formulation F3.

Determination of pH dependent solubility

Shake flask technique (Barzegar *et al.*, 2012) identical as that for saturation solubility was used for pH Dependent Solubility evaluation.

% drug content

For calculating the % drug content, the SDs similar to 50 mg of Diclofenac Sodium were weighed correctly and triturated with the help of mortar and pastel and dissolved in 50ml of ethanol by using automatic shaker for 30 min. The drug solutions were clarified and drug content was finding out by taking absorbance at 276nm by UV/Visible spectrophotometer (Sharma *et al.*, 2012; Barzegar *et al.*, 2012). From all previous evaluation tests, SD4 formulation was confirmed as optimized formulation (table 3) which was then Selected for *in vitro* dissolution studies.

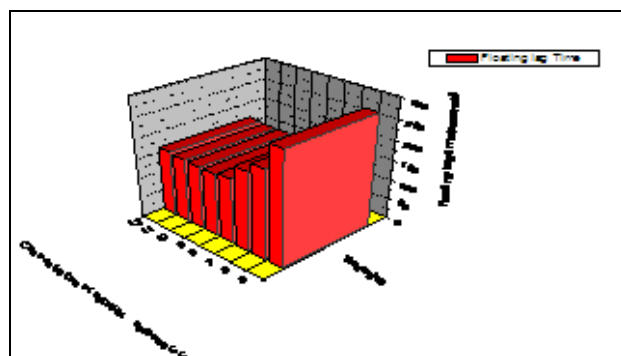


Fig. 4: Comparison of floating lag time prepared from concentration of calcium carbonate.

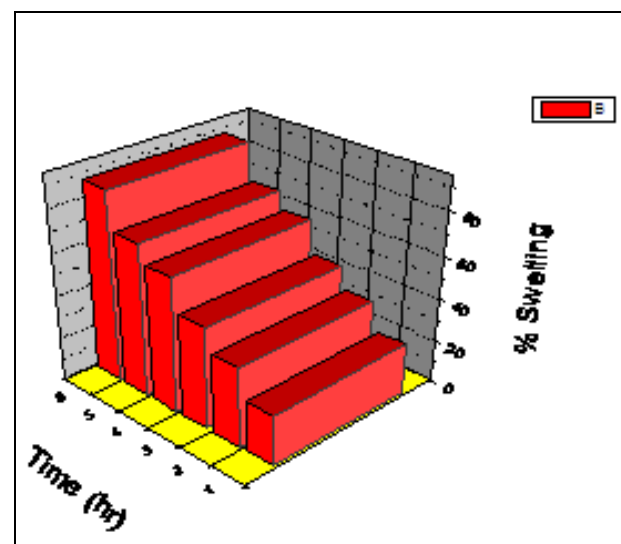


Fig. 5: % Swelling Index (Percentage Water Uptake) of ECRFT

In vitro dissolution studies

In vitro dissolution studies of diclofenac sodium from solid dispersion were performed in 900ml of simulated

gastric fluid at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and 75 rpm by using paddle type apparatus with three repeats (Shivakumar *et al.*, 2008, Sharma *et al.*, 2012, Barzegar *et al.*, 2012). In all experiments, Periodically 5ml of dissolution sample was taken, filtered and substituted with a same volume of fresh medium to keep a constant total volume. Samples were analysed by measuring absorbance on UV/Visible spectrophotometer at 276nm.

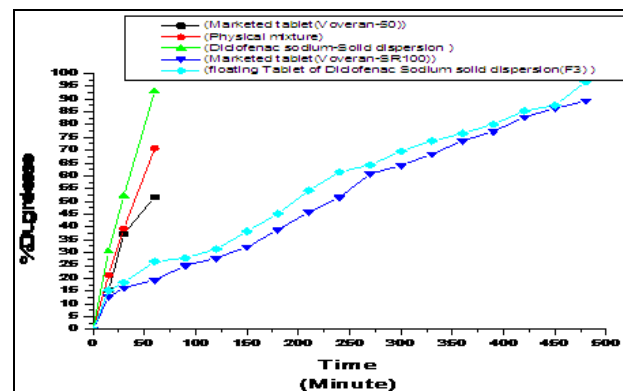


Fig. 6: Comparative *in vitro* release study of marketed tablets, physical mixture, solid dispersion and ECRFT of Diclofenac solid dispersion

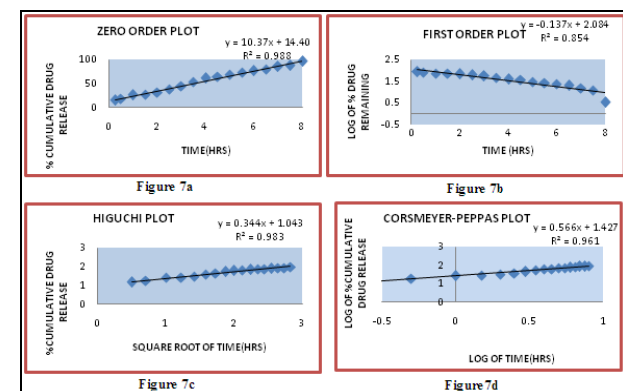


Fig. 7: Pharmacokinetics graphs of optimized formulation (a) Zero order release kinetics (b) First order release kinetics (c) Higuchi kinetics (d) Korsmeyer-Peppas kinetics



Fig. 8: Images of complete biodegradation of F3 Formulation (ECRFT) after 3 hours

Preparation of ECRFT

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

manufacturing of ECRFT of Diclofenac Sodium. Tablets were formulated by (10) consuming HPMC K4M, HPMC K15M as a release retardant, Carbopol as a swelling agents and NaHCO_3 as gas generating agent. Citric acid was also merged in the formulation to deliver sufficiently gastric environment for NaHCO_3 to react and maintain buoyancy. The component of various formulations is given in table 2. All ingredients (except gas generating agents and magnesium stearate) were screen through strainer no. 60 and mixed in a polybag for 10 minutes and granulated using PVP K30 (in isopropyl alcohol). The wet mass was sieved through strainer number 14 and dried in oven at 50°C for 1.5 hours. Dried granules were assorted with magnesium stearate as lubricant, talc as glidant and compacted using rotary tablet press (Model no: K-10402NP, Ahmedabad, India) using flat punch in order to Attain ECRFT containing 50mg of Diclofenac Sodium. Before compression, granules were evaluated for their different necessary properties.

Evaluation of granules properties

Flow properties determination

A flow property of granules is generally assessed by determining angle of repose, which is a function of the surface roughness. If the surface of particle is irregular or rough, it means angle of repose is high. The angle of repose was measured by allowing an accurately weighed mass of granules to flow freely through funnel (Chanvanpatil *et al.*, 2006, Davis *et al.*, 1986). The granules pile diameter and height was determined and angle of repose was Determined using the behind equation.

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

Where, h and r are the height and radius of the Granules pile, respectively.

density

Both bulk density (BD) and tapped bulk density (TBD) were evaluated. A weighted amount of granules from every one batch which is earlier casually assorted to disruption any agglomerates formed was added into a graduated measuring cylinder. Once the preliminary volume was noted, the cylinder was permitted to tap mechanically using tapping device until constant volume noted (Chanvanpatil *et al.*, 2006). BD and TBD were evaluated using the following formulas.

BD = Weight of the Powder/Volume of the packing.

TBD = Weight of the powder /Tapped volume of the packing.

% Compressibility index/ carr's index

The flow property was also finding out by determining the compressibility index. It is an vital Parameter that can be calculated from the BD and TBD. On the basis of theory we can say that the less compressible materials are more flow able. According to official books a material

having values of less than 20 to 30% is under category of free flowing material. With the help of BD and TBD, compressibility index of samples (granules) was evaluated by using the following formula (Chanvanpatil *et al.*, 2006, Davis *et al.*, 1986).

$$\text{Compressibility Index} = \frac{\text{Tap density} - \text{Bulk density}}{\text{Tap density}} \times 100$$

Evaluation of ECRFT

General Characteristic

The prepared tablets were evaluated for its general features.

Thickness and diameter

verniercaliper was used for measuring Thickness and diameter of tablets. Randomly select three tablets from all batches as a sample and middling values were determined.

Weight uniformity test

It is desirable that each single tablet in a batch is uniform in weight because non-uniformity in weight can lead to variation in dosing that's why all formulated batches of tablets (20 tablets) are weighted individually and collectively. From the combined weight of 20 tablets middling weight per tablet were calculated. The weight of individual tablets was then compared with average weight to determine whether they were inside limits or not.

Friability test

It is normally indications loss in weight of tablets in the containers due to subtraction of fine particle from there surface. For the determination of Friability of tablets Roche friability test apparatus was used. Pre-weighed 20 tablets were placed in the friabilitor, which was rotated for 100 revolutions. After that tablets are weighted once again. The difference in two weights represents friability. The weight loss should not be more than one percent. The % friability was determined by using following formula.

$$\% F = \frac{\text{loss in weight}}{\text{initial weight}} \times 100$$

Hardness test

Hardness of tablets is telling about its tensile power and is determined in term of load /pressure essential to break it when place on its edge. In this study Monsanto hardness testers was used for testing hardness of formulated tablets.

Percent drug content

Casualy selected 10 tablets from every batch were weighed and crumpled. A quantity of the tablet powder same to 50mg of Diclofenac Sodium was dissolved in 100ml of simulated gastric fluid, filtered, diluted appropriately and analysed for % drug content at 276nm using UV/Visible spectrophotometer.

Table 1: Composition of solid dispersion & there Assign batch code.

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 2: Composition of different formulations of Diclofenac sodium ECRFT

Ingredient (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
SD4 (Solid Dispersion of Diclofenac sodium)	250	250	250	250	250	250
HPMC K4M	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 3: Optimization of solid dispersion batch*

Formulation Code	Saturation Solubility in 0.1 NHCL (mg/ml)	pH Dependent Solubility in Distilled Water (mg/ml)	Drug Content (%)
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
PM (1:5)	0.5937±0.0057	11.275±0.112	90.89±1.32
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
SD5 (1:5)	1.9153±0.0171	14.288±0.158	96.77±1.65

Mean ± S.D., n=3,

Table 4: Pre Compression Parameters of Granules

Parameter	F1	F2	F3	F4	F5	F6
Angle of Repose	22.53 ⁰	22.17 ⁰	23.42 ⁰	21.57 ⁰	22.87 ⁰	23.34 ⁰
Bulk Density	0.953±0.026	0.948±0.031	0.975±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

In vitro buoyancy determination studies

In vitro buoyancy studies were done for entire preparations as per the technique reported in literature (Rosa *et al.*, 1994). The casually choose tablets from all preparation were retained in a 100ml beaker comprising simulated gastric fluid, pH 1.2 as per Official monograph. The time engaged for the tablet to upswing to the surface and time was taken as floating lag time (FLT). The period

of time the dosage form continually stayed on the surface of medium was measured as the total floating time (TFT) (Chanvanpatil *et al.*, 2006, Li *et al.*, 2003, Machida *et al.*, 1989, Moes *et al.*, 1993).

Determination of percentage water uptake (%WU)

The Percentage Water Uptake of ECRFT was evaluated by placing the Pre weighted tablet in the dissolution test

apparatus, in 900 ml of distilled water at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and 50 rpm. Periodically the tablet were removed from dissolution medium and weighted again after draining free from water by blotting paper, these were evaluated for weight gain. % WU was determined by the equation: $\text{WU \%} = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$

Dissolution Studies Using Paddle type Apparatus with acid resistant Sinker device: Dissolution release rate of DS from ECRFT was determined by using Paddle type Apparatus with acid resistant Sinker device. The *in vitro* dissolution study was performed for 500 minutes in 900 ml of simulated gastric fluid as a dissolution media, at $37 \pm 0.5^{\circ}\text{C}$ and 50 rpm. From time to time 5ml samples were taken and filtered and samples were substituted by its equal volume of fresh dissolution media. The absorbance of DS was measured UV/Visible spectrophotometrically at 276nm. From this absorbance the amount of DS released from tablets was easily calculated.

Kinetic modeling of drug release

The outcome of in-vitro dissolution studies of tablet were fitted with several 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 clarify drug release mechanism due to swelling (upon hydration) along with regular destruction of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer and Peppas semi-empirical model to determine the mechanism of drug release.

Stability studies

The main objective of Accelerated testing is to make available sign of how the quality of preparation fluctuates with time under the impact of various environmental factors. To assess the formulation stability, accelerated testing was performing on the basis of ICH guidelines. The Optimized preparation F3 was evaluated for accelerated testing for a period of 90 days at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / 75% RH $\pm 5\%$ for their various parameter.

Biodegradability studies of ECRFT

The biodegradability studies were carried out using USP rotating basket apparatus. A Optimized ECRFT (50mg) 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 $37 \pm 0.5^{\circ}\text{C}$.

RESULTS

Compatibility studies

IR study was done for compatibility detection between Carriers with the drug. Fig. 1: Comparative FTIR spectra

of Diclofenac, PEG6000, & solid dispersion of Diclofenac with PEG6000.

Optimization of solid dispersion batch

The Various SD of DS was prepared using PEG-6000, as carriers by thermal method (Simple fusion method) to upsurge the solubility as well as dissolution of poorly aqueous soluble drug (DS). The formulated SDs and PMs of DS were tested for various solubility and % drug content (Shivakumar *et al.*, 2008, Sharma *et al.*, 2012, Barzegar *et al.*, 2012). Both solubility, and % Drug Content of Pure DS, several manufactured SDs and PMs of DS and PGE 6000 in simulated gastric fluid were measured (table 2)

Release studies of solid dispersion batch

On the basis of solubility and drug content studies of 8 preparations, PM4 and SD4 formulation were nominated for *in vitro* dissolution study and were compared with that of pure DS. The *in vitro* dissolution study of the pure DS, SD4 and PM4 was performed in simulated gastric fluid at $37.0 \pm 1^{\circ}\text{C}$ for 1hrs and it was determined by plotting % drug dissolved against a function of time (fig. 2). SD4 and PM4 exhibited better dissolution of DS over that of pure DS. Pure DS only produces the minimum dissolution with only 35.65% drug and the dissolution of PM4 (70.76%) was found to be considerably quicker when compared with pure DS. SD4 displayed the maximum dissolution (92.99%) than PM4 and pure DS.

Preliminary trial batch

The ECRFT of SDs of DS were prepared in 6 dissimilar sets F1 to F6 by consuming hydrophilic polymers (HPMC K4M, HPMC K15M) and hydrophobic polymer (Carbopol 934P) along with effervescing agents, NaHCO_3 and citric acid (table 3). Wet granulation method was used for the Preparation of tablet (Baumgartner *et al.*, 2000).

Evaluation of granules of different batches

The various pre formulation parameters such as angle of repose, bulk density, tapped density, and Carr's index estimated were found to be inside the official recommended limits and the result was tabulated in table 4.

Evaluate general characteristic of ECRFT

Formulation F3 was appraised for various physical parameters like tablet thickness, diameter, hardness, friability, weight variation, %swelling index, in-vitro drug release studies. Which is satisfied the acceptance criteria of official books (Pharmacopoeias) and the result was tabulated in table 5.

In vitro buoyancy studies

In vitro Buoyancy of entire formulated ECRFT preparations was evaluated using 100 ml beaker, which was filled with simulated gastric fluid. Result was tabulated in table 6.

Table 5: General characteristic of various ECRFT formulations

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

Mean± S.D., n=3, Optimized value

Table 6: *In vitro* Buoyancy determination

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

Table 7: Release Kinetic Equation Values of the Optimized Formulations

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

Table 8: Stabilities studies of Optimized ECRFT Batch*

Parameter	Optimized Formulation (F3)				
	At 0 day	At 15 days	At 30 days	At 60 days	At 90 days
Physical appearance	+	+	+	+	+
Hardness (Kg/cm ²)	5.4	5.4	5.4	5.2	5.0
Friability (%)	0.17	0.17	0.19	0.20	0.22
Uniformity of Weight (mg)	+	+	+	+	+
Drug content (%)	100.01±0.04	100.01±0.12	99.50 ±0.58	98.89±0.12	98.54±0.12
Thickness (mm)	+	+	+	+	+
Buoyancy Lag Time (sec)	+	+	+	+	+
Floating Time (Hrs)	+	+	+	+	+
<i>In vitro</i> release in 8 Hours ±SD	96.769±1.19	94.34±1.52	93.05±0.81	92.89±0.69	92.45±1.21

*Mean± S. D., n=3, + No change

Effect of NaHCO₃ concentration on lag time of ECRFT

The percentage of NaHCO₃ was found to be critical factor that influenced buoyancy of tablets. Sodium bicarbonate released CO₂ gas that was trapped into the polymeric matrix of HPMC that made the tablets float. Various concentrations of sodium bicarbonate ranging from 5% to 12% of tablet weight were used.

Swelling studies

From the swelling studies of formulation it was concluded that swelling index was improved with time because weight gain by tablet was improved equivalently with rate of hydration (Patel *et al.*, 2006). The direct relationship was clearly observed in result (fig. 5).

***In vitro* dissolution studies**

ECRFT (F3) formulation was selected for *in vitro* dissolution studies using paddle type device with sinker

device in 900ml of simulated gastric fluid. The findings are shown in fig. 6.

Kinetic Modeling of drug release

The various release kinetic models (fig. 7) were used to determine the mechanism of drug release from ECRFT and the result is tabulated in table 7.

Stability studies

Optimized 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 analyzed for Physical appearance, Hardness (Kg/cm²), Friability (%), Uniformity of Weight (mg), Drug content (%), Thickness (mm), Buoyancy Lag Time (sec), Floating Time (Hrs) 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 table 8.

Biodegradability studies of ECRFT

Biodegradability studies revealed that the ECRFT (F3) was found to disintegrate and dissolve in intestinal pH within 3 hours (fig. 8).

DISCUSSIONS

When the spectra were analyzed it was found that there was no fluctuation in functional peaks and no coinciding of specific peaks and there was no new peaks appear. Fig. 1 shows the IR spectra of various samples. No major alteration in the IR spectra of Diclofenac Sodium complexes was obtained, excluding enlargement of the peaks. The broadening of peaks may be probably due to the restriction of bending and stretching vibrations of the molecule (Sharma *et al.*, 2012).

From the results of Optimization studies of solid dispersion (Table 2) we concluded that All PMs showed higher solubility and % Drug Content as compared with pure DS. Another time, SDs of DS exhibited higher both solubility and Percent Drug Content than their respective PMs of DS and carrier. This might be attributable to an enhancement of wetting of drug particles and localized solubilisation by the hydrophilic polymeric carriers. Due to the statistically non-significant difference in Saturation Solubility, pH Dependent Solubility and % Drug Content observed between the Diclofenac sodium: PEG6000 ratio 1:4 and 1:5 respectively, then smaller ratio (1:4) was chosen for floating tablet formulation. Formula that showed 1.9261 ± 0.0154 mg/ml Saturation Solubility, 14.291 ± 0.144 mg/ml pH Dependent Solubility and 96.72% Drug Content and consisting of 4% w/v PEG6000 and 1% w/v diclofenac sodium at 1:4 Drug/ PEG6000 ratio was selected for further investigations and this concord with the earlier reported work (Barzegar *et al.*, 2012).

Release studies of solid dispersion batch (fig. 2) specified that the improved dissolution of DS from SD4 due to existence of drug in amorphous state as compared PM4 and pure DS. As the percentage of PEG-6000 increased, dissolution rates have also been increased. Hydrophilic nature of carrier was one of the main causes for increasing the dissolution rates (Shivakumar *et al.*, 2008, Sharma *et al.*, 2012, Barzegar *et al.*, 2012). Accordingly it can be says that the solubility of the poorly soluble drug, DS can be enhanced strictly by using solid dispersion method.

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 rise

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, that's why In order to get the immediate buoyance / prolongs the drug release from the ECRFT the low viscosity polymer (HPMC K4M) selected in comparison of HPMC K15M.

From *in vitro* Buoyancy studies, I can determined that the formulation F3 having HPMCK4M and Carbopol 934P in excess proportion displayed decent floating lag time was 158 sec (fig 3) and total floating time is 15hrs. This result was similar near about previous reported work (Dhumal *et al.*, 2006) where the average lag time was below 3min. TFT based on the concentration of HPMC as the polymer concentration increased the floating time was also improved due to the creation of dense gel, which entrapped the gas formed due to NaHCO_3 firmly. All formulation showed the *in vitro* floating in the subsequent sequence: $F3 > F1 > F5 > F2 > F4 > F6$. From table 9 we can conclude that formulation F3 was showed maximum TFT and Minimum FLT hence, formulation F3 was chosen for further evaluations. Fig. 3: *In vitro* lag time measurement of Formulation F3.

From the studies, it was determined that with the increasing percentage of NaHCO_3 , the lag time reduced (fig. 4). A concentration of 9% w/w sodium bicarbonate was found to be optimal that resulted in tablets having lag time <3 min and floating time of over 12h. Similar conclusions were also drawn by other researchers working on floating delivery systems. In both the reported works, best percentage of NaHCO_3 was determined to be around 10% w/w of the tablet weight (Dhumal *et al.*, 2006) which is slightly higher than our optimal concentration.

From the swelling studies of formulation it was concluded that swelling index was improved with time because weight gain by tablet was improved equivalently with rate of hydration (Patel *et al.*, 2006). The direct relationship was clearly observed in result (fig. 5).

The release pattern of preparation F3 was constant release rate in sustained mode like zero order kinetics with decent floating property. Diclofenac Sodium effervescent floating controlled release tablet (F3) formulation using solid dispersion was compared with marketed tablet (Voveran SR), which showed near about similar release profile.

The *in-vitro* drug release of optimized formulation (F3) exhibited the maximum regression coefficient values for Zero order model, thus representing absolute correlation between the two variables for the Zero order model. Optimized formulations followed Zero order equation

proving that the release was by diffusion mechanism. The Korsmeyer and Peppas equation was used for Determining values of release exponent (n) and the 'n' value was determined to be 0.5665 indicating Anomalous (non-fickian) diffusion.

Stability studies shows that all parameters are within the acceptable limits which indicated that formulation were stable over the period of 90 days.

In Biodegradability studies 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, suddenly become rough with an irregular surface and thereafter was degraded. Accordingly the ECRFT of diclofenac ascertained to be appropriate gastro retentive dosage form, because they have an inflexible structure that showed no degradation in gastric pH but exhibit complete biodegradation in phosphate buffer pH 8.0.

CONCLUSION

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 optimized 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 optimized formulation F3 was found to be favorable 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.

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