



RESEARCH ARTICLE

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Formulation and Development of Gastroretentive Drug Delivery System of Efavirenz

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ABSTRACT

Efavirenz, a non-nucleotide reverse transcriptase inhibitor is an important drug for treating patients with Human Immunodeficiency Virus infections. It belongs to BCS class II have low solubility and poor intrinsic dissolution rate. It is highly basic (pKa 10.2) which makes it suitable candidate for floating dosage form for continuous delivery in stomach. The study was aimed to improve the solubility by solid dispersion technique. Saturation solubility study and drug content were evaluated for solid dispersion preparation. Saturation solubility shows 8 fold increases in 0.1 N HCL compared to plain drug and drug content was found to be between 95%-102%. Further effervescent floating gastroretentive drug delivery system was prepared by 3² full factorial design with independent variables i.e., concentration of HPMC K100 as matrix forming agent and citric acid as gas generating agent. Lag time, floating time, percent drug release were studied as responses. The optimized batch exhibited floating lag time of 40 sec and the *in vitro* release studies showed 89.5% drug release in 9 h and tablet remained floating for greater than 8 h. The study thus demonstrated that solubility is increased by solid dispersion technique and floating delivery systems may increase solubility and bioavailability of Efavirenz.

Keywords: Efavirenz, GRDDS, Solid dispersion (SD), Solvent evaporation method, Solubility enhancement, Percent drug release.

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INTRODUCTION

Controlled drug delivery systems are recognized as important pharmaceutical systems that have made major inroads in dosage form design. Drugs which have short half-lives are absorbed in gastrointestinal tract (GIT) without any difficulty and also eliminated from the systemic circulation. [1] To obtain desired therapeutic effect, repeated dosing of the drugs is

essential. Oral controlled release formulations enable this limitation to be overcome by slow release of the drug in the GIT and maintain sufficient plasma drug concentration for required time span. [2] Gastric retention devices are intended to prolong the gastric residence time of oral controlled release dosage forms. This results in increased residence time and hence absorption of drugs that act locally. Drugs that have

specific absorption windows in GIT and drugs less soluble in the intestinal fluid are also suitable candidates for gastro retention. [3] Many strategies are available to prolong gastric residence time which includes bioadhesive systems, swelling and expanding systems and floating systems. Among all methods floating drug delivery system enables easy and practical technique to obtain gastroretention. [4] Floating dosage form has density less than that of gastric fluids and consequently remains a float in the stomach contents to lengthen the gastric retention time. [5-9]

HIV is a retrovirus of the lentivirus family, which in particular destroys CD4+ T cells that are important for proper functioning of the immune system. [9-10] The highly active antiretroviral treatment (HAART) has saved 2.8 million lives worldwide. Efavirenz (EFV) is an authorised first line HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) approved by The World Health Organisation (WHO) for the treatment of HIV. EFV is (S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one. It attaches to and blocks the HIV enzyme called reverse transcriptase. It's a crystalline powder, non-hygroscopic, sour in taste and insoluble in water, protein-binding of >99 % and poor oral bioavailability (40-50%). It belongs to BCS (Biopharmaceutical classification system) class II drug having low aqueous solubility (4µg/ml), poor intrinsic rate of dissolution (0.037 mg/cm²/min). It is highly basic with pKa = 10.2 and lipophilic with log P value of 5.4 [10] which makes it suitable candidate for the preparation of floating dosage form for continuous delivery of EFV in the stomach.

The aim of current work was to improve the solubility of EFV by solid dispersion technique and development, evaluation of stable GRDDS (Gastro retentive drug delivery system) formulation. Solid dispersion is among the successful and reliable techniques in which active pharmaceutical ingredients is dispersed in an inert polymeric carrier in solid state and it is prepared by using different method such as the melting, solvent evaporation and melting-solvent evaporation method. [11-12] Solid dispersions of EFV with HPMC E5 were prepared in different ratios to improve its solubility and dissolution rate. EFV solid dispersion (SD) was further incorporated into floating tablet to overcome the problems of oral absorption of drug. [12] Effect of mixtures of various polymers and excipients on different physicochemical properties was evaluated. Full factorial design (3²) was used to develop optimized GRDDS using the floatation technology. The formulations were evaluated for floating time, floating lag time, percent drug release, and stability studies. *In vitro* dissolution kinetic studies were performed to assess the improvement in the solubility and dissolution rate of EFV. [13]

MATERIALS AND METHODS

Materials

EFV was gifted by Mylan Laboratories, Nashik, India. HPMC K100 Abitech Corporation (Columbus, OH, USA). Sodium bicarbonate was purchased from BASF Corporation 3000 Continental Drive - North Mount Olive, NJ 07828-1234. Citric acid, Poly vinyl pyrrolidone k-30, Sodium carboxy methyl cellulose, Talc was purchased from Loba Chemicals, Mumbai, India. Hydrochloric acid (HCl) was purchased from Merck Specialities, Mumbai, India. Methanol, acetonitrile, and water of high performance liquid chromatography (HPLC) grade were used in UV spectrophotometer studies purchased from Merck, Mumbai, India. Freshly prepared double distilled water was used whenever required.

Methods

Preparation of solid dispersions

Preliminary trials were conducted to select the polymer for SD which included HPMC E5, Eudragit RS 100 and Soluplus in different ratios. Solvent evaporation method was used to prepare solid dispersions. Different solvent systems were used depending on solubility of the components of the mixtures. The solvents were evaporated using electric water bath and subsequently the moist mass was dried at room temperature. [14] The samples were triturated until a soft powder was obtained using a mortar and pestle and which was then passed through sieve no. 22 of 150µm pore size. These samples were evaluated for saturation solubility. [15] Based on the increase in solubility further studies were conducted with HPMC as polymer as it produced greater increase in EFV solubility than other polymers. Hence 03 ratios of drug: HPMC E5 were used to prepare SD1 (1:1), SD2 (1:0.75) and SD3 (1:0.5).

Evaluation of solid dispersions

Drug content

The percentage drug content in SDs was estimated by dissolving 20 mg of SD in methanol and filtered. The filtrate was diluted with methanol and drug content was determined against blank by UV spectrophotometer (Jasco V-730) at 247 nm. [16-17]

Saturation solubility studies

Saturation solubility was determined by adding excess drug/binary SD into 20 ml of DW, 0.1 N HCl, separately and were placed in an orbital shaker (CIS-24 Remi, India) at 37 ± 0.5°C for 24 h. The equilibrated suspensions were centrifuged and filtered through Whatman filter paper (0.45µm) and analysed for drug content by UV-spectrophotometer (Jasco V-730) at 247 nm. [17]

Dissolution test

USP dissolution test apparatus (Lab India DS 8000) type II (Paddle) operating at 50 rpm was used for the study. Dissolution of the drug and SDs was performed in triplicate. SDs equivalent to 200 mg of the EFV were subjected to these studies in 900 ml of 0.1N HCl as dissolution media at 37 ± 0.2°C, respectively. The sample (10 ml) of the dissolution media was removed at predetermined time intervals and was

simultaneously analysed UV spectrophotometrically at a λ_{max} of 247 nm. The SDs i.e, SD1, SD2, SD3 which displayed the most increase in saturation solubility and dissolution rate was subjected to further evaluation. [18]

Micrometric flow property of solid dispersions

The various powder flow properties of solid dispersion like angle of repose, bulk density, tapped density; Hausner's ratio and Carr's index were evaluated. [19]

Fourier transform infrared (FT-IR) Spectroscopy

Fourier transform infrared spectra of powdered samples of EFV and SDs were obtained using a FTIR spectrophotometer (Jasco FTIR - 460 plus spectrophotometer). The scanning range was 400–4000 cm^{-1} and the resolution was 2.4 cm^{-1} . [20]

Differential Scanning Calorimetric Analysis (DSC)

The thermograms were recorded for EFV and SD using a differential scanning calorimeter. A heating rate 10°/min was employed in the 30–300°C temperature range. Samples were placed in aluminium sample pans and an empty pan was used as a reference standard. The analysis was performed on 5mg samples in a nitrogen atmosphere (40 ml/min). [21]

Powder X-ray diffraction study (PXRD)

The PXRD spectra of EFV and SD were recorded using high power powder X-ray diffractometer (Ru-200B). Cu was used as target filter and voltage/current of 40 kV/40 mA was applied. The scan speed was 40/min. The samples were analyzed at 2 θ angle range of 5°–50°. Step time was 0.5 s and time of acquisition was 1 h. [22]

Preparation of Floating Tablets with Solid Dispersion

The solid dispersion which displayed greater increase in solubility was used for the formulation of gas generating floating tablets. HPMC K 100 a water soluble polymer was selected as a hydrophilic matrix. The solid dispersion and other tablet ingredients were individually passed through sieve # 60 and mixed thoroughly by triturating up to 15 min. Then ethanol solution containing PVP K30 were added dropwise to above mixture & the doughy mass was passed through sieve no 18. Granules were dried at room temperature. Further it was lubricated with talc. [23]

Experimental design

A 3² full factorial design was used to formulate the tablets. The designs consist of two factors at three levels. Two factors i.e, HPMC K 100 (A) and citric acid (B) were evaluated each at three levels lag time (Y1), floating time (Y2), % drug release (Y3)& experimental trials were performed at all possible nine combinations.

Characterization of factorial batches

Precompression evaluation parameters

The various powder flow properties were evaluated like angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index. [24]

Floating lag time

Floating lag time was determined by placing each tablet to the 100 ml of 0.1N HCl in beaker. Time required for tablet to float was recorded. The experiment was conducted in triplicates. [25–26]

Table 1: Relationship between angle of repose (θ) and flowability

Angle of Repose (θ)	Flowability
< 25	Excellent
25–30	Good
30–40	Passable
> 40	Very Poor

Table 2: Composition of preliminary trial batches (all quantities in mg)

S. No	Ingredients	PT1	PT2	PT3	PT4	PT5	PT6	PT7
1	Solid dispersion	400	400	400	400	400	400	400
2	HPMC	19.34	19.34	24.34	24.34	19.34	19.34	19
3	Sodium bicarbonate	147	117	132	132	80	80	100
4	Citric acid	9.75	9.75	9.75	19	26	15.75	26.75
5	PVP K30	20	15	15	5	10	10	-
6	Sodium CMC	25	100	50	50	100	100	75
7	Talc	29.75	19.25	19.25	10	15.25	25.25	29.25

Table 3:

S. No	Independent variable	Dependent variable
1	HPMC	Floating time
2	Citric acid	Lag time
		Percent drug release in 8 h.

Table 4: Actual & coded levels of the factors

Factor	Actual values (mg)			Coded values		
	low	Mid	High	Low	Mid	High
Factor A HPMC	19.34	21.84	24.34	-1	0	1
Factor B Citric acid	19	22.5	26	-1	0	1

Table 5: Composition of the formulations in terms of coded values

S. No	Batch codes	Coded factor levels	
		X1	X2
1	F1	1	1
2	F2	0	1
3	F3	1	1
4	F4	1	0
5	F5	0	0
6	F6	1	0
7	F7	1	1
8	F8	0	1
9	F9	1	1

Table 6: Composition of formulations of optimization (all quantities in mg)

S. No	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Solid dispersion	400	400	400	400	400	400	400	400	400
2	HPMC	21.84	19.34	21.84	21.84	19.34	24.34	19.34	24.34	24.34
3	Sodium bicarbonate	80.00	59.00	80.00	77.00	80.00	54.00	77.00	80.00	51.00
4	Citric acid	22.50	19.00	19.00	26.00	22.50	19.00	26.00	26.00	22.50
5	PVP K30	65.00	42.00	43.00	65.00	42.00	42.00	42.00	59.00	42.00
6	Sodium CMC	50.00	100.00	75.00	50.00	75.00	100.00	75.00	50.00	100.00
7	Talc	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00

Floating time

The tablets from optimised batch were placed in a 100 ml glass beaker containing 0.1N HCl. The duration for which the tablets remained floating on the surface of medium was determined as floating time. [27]

In vitro dissolution studies

The *in vitro* dissolution studies were carried out using USP apparatus type II (DA 8000, Lab India) in 0.1N HCl (900 ml) at paddle speed of 100 rpm at 37°C ± 0.5°C. Aliquots of 10 ml of samples were withdrawn at 1 h interval till 8 h and analyzed by UV spectrophotometer at 247 nm. The release studies were conducted and the values were plotted versus time with standard deviation of less than 3, indicating the reproducibility of the results. [28]

Post compression evaluation parameters

Hardness, thickness, friability, drug content, uniformity of weight was evaluated for floating tablets. [23, 28]

Optimization and validation model

The drug release data and floating lag time was input in Design expert software 11.0 and polynomial equations were generated. Based on desirability function numerical optimization was done to generate the optimized formula. The optimized formulation predicted by the software was prepared and analysed to assess similarity with predicted responses.

Stability studies

Optimized floating tablet was subjected to physical stability studies for 3 months at 40°C ± 75% RH (Remi, CHM 6 S). Samples were evaluated for physical appearance, hardness, drug content and floating lag time. ICH Q1A (R2) guidelines were followed for stability studies. [23]

Table 7: IP standards of uniformity of weight

S. No	Average Wt. of tablet	% deviation
1	80 mg or < 80	10
2	>80 to <250 mg	7.5
3	>250 or more	5

Table 8: Melting point of EFV

Property	Observation	
	Reported	Observed
Melting point	139-141°C	138-140°C

Table 9: Linearity of plain EFV in methanol AR Grade (N=3, Mean ± SD)

Concentration (µg/ml)	Absorbance (247 nm)
5	0.2611 ± 0.001
10	0.4857 ± 0.005
15	0.7272 ± 0.0001
20	0.9654 ± 0.0001
25	0.1985 ± 0.0001

Table 10: Linearity validation data UV spectrophotometric analysis of EFV (N=3, Mean ± SD)

Concentration (µg/ml)	Absorbance (247 nm)			
	Linearity 1	Linearity 2	Linearity 3	Average ± SD
5	0.2611	0.261	0.2613	0.2612 ± 0.0002
10	0.4857	0.4861	0.4862	0.4756 ± 0.0003
15	0.7272	0.7273	0.7274	0.7275 ± 0.0001
20	0.9654	0.9652	0.9654	0.9653 ± 0.0001
25	1.1985	0.1987	1.1985	1.1987 ± 0.0001
R ²	0.9999	0.9999	0.9999	0.9999

Table 11: Interday precision data for UV spectrophotometric analysis of EFV

Concentration (µg/ml)	Mean Absorbance* (247 nm)	SD	%RSD
5	0.2540	0.00011547	0.045
10	0.4862	0.0002	0.0411

Table 12: Intraday precision data for UV spectrophotometric analysis of EFV

Concentration (µg/ml)	Mean Absorbance* (247 nm)	SD	%RSD
5	0.2538	0.000288	0.113
10	0.4861	0.00023	0.047

Table 13: Percent recovery data for UV spectrophotometric analysis of EFV

Level	Concentration (µg/ml)	Total Concentration (µg/ml)	Mean Absorbance* ± SD (247 nm)	Practical Concentration	Recovery (%)
50%	10+5	15	0.7273	14.98	99.86
100%	10+10	20	0.9653	20.08	100.4
150%	10+15	25	1.1986	24.99	99.98

RESULTS AND DISCUSSION

Preparation of Solid Dispersions

Numbers of methods are used to prepare solid dispersions depending on the nature of drug and polymer. These include solvent evaporation, melt method, hot melt extrusion and gel entrapment method. [13] Melt method and melt extrusion method involve heating to melt the carriers and this may cause unwanted changes in the physicochemical profile of the drug such as degradation, crystallographic changes, etc. [17] Hence in present study solid dispersions of EFV were prepared by solvent evaporation method using different polymer i.e., HPMC E5, Eudragit RS 100 and Soluplus in three ratios i.e., (1:1) (1:0.75) (1:0.5) respectively. Different solvent systems were used depending on solubility of the components of the mixtures. In this method the drug is in molecular form resulting in an intimate mixture between drug and polymer. [14] Solid dispersions were evaluated for saturation solubility & percent drug release in 0.1N HCl. Saturation solubility and percent release showed an increase with increase in concentration of polymers. Solid dispersions i.e., A (Drug + HPMC E 5), B (Drug + Eudragit RS 100) and C (Drug + Soluplus) containing (1:1) ratio showed an almost 11 fold, 7 fold and 8 fold increase in solubility as compared to plain drug EFV respectively. From the study, it was found that all solid dispersions displayed higher release than plain drug. SD A showed nearly 89% release in 90 min. SD B and SD C exhibited 77% and 73% release at 90 min respectively. All ratios of drug with HPMC E5 displayed higher solubility than SDs of other polymers in different ratios. Hence, the SD A i.e., A (Drug + HPMC E 5), was selected for further studies.

Micrometric properties of solid dispersions

The prepared solid dispersions were evaluated for micrometric properties. The angle of repose was found to be excellent thus pointing to excellent flow properties (Table 14) for all the dispersions prepared. However Hausner's ratio for SD2 and SD3 was found

to be less than or equal to 1.15 which indicates presence of significant interparticle frictions. [18] Moreover, SDs having Carr's index below 15 were considered to have good flow properties and could be successfully compressed into tablets with uniform weight. [29]

Drug content

The percentage drug content was determined by UV/Visible spectrophotometer (Make Lab UV 3000) at 247 nm. [29] Drug content in all SDs was found to be between 95%-102% indicating no or negligible loss of drug during the process. [30]

Table 14: Micrometric flow properties of solid dispersions. Mean $\pm$ SD (N=3)

Formula code	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Carr's index
SD1	25.44 $\pm$ 2.41	0.440 $\pm$ 0.12	0.483 $\pm$ 0.26	1.09 $\pm$ 0.66	8.33 $\pm$ 4.45
SD2	30.96 $\pm$ 3.12	0.489 $\pm$ 0.25	0.558 $\pm$ 0.23	1.16 $\pm$ 0.2	12.54 $\pm$ 3.5
SD3	29.24 $\pm$ 3.33	0.464 $\pm$ 0.18	0.583 $\pm$ 0.12	1.256 $\pm$ 0.45	11.9 $\pm$ 3.89

Table 15: Saturation solubility of EFV in different solvent. Mean $\pm$ SD (N=3)

S. No	Media	Plain drug	SD 1	SD 2	SD 3
1	Water	4.6 $\pm$ 2.5	34.19 $\pm$ 2.3	32.54 $\pm$ 2.8	29.6 $\pm$ 2.5
2	0.1 N HCl	7.54 $\pm$ 3.1	77.82 $\pm$ 1.5	69.23 $\pm$ 2.7	65.08 $\pm$ 2.2

Saturation solubility studies

Saturated solubility studies for EFV and SDs in different media (Fig. 7) showed that solubility of SDs increase with increasing polymer proportion. The improved solubility of the drug may be due to its entrapment within the carrier during the solvent evaporation process, or due to the molecularly dispersed form of the drug in the solid dispersion. Also the drug is converted into amorphous state and its wetting property is improved due to presence of hydrophilic polymer which leads to improvement in solubility. [12] The SD1 (1:1) showed an almost 7 fold increase in solubility in water, 8 fold increase in 0.1 N HCl as compared to plain EFV. SD2 (1:0.75) and SD3 (1:0.5) also displayed higher solubility than plain drug however the increase was not very significant. [17, 29]

In-vitro dissolution of solid dispersions

The *in-vitro* dissolution studies revealed that dissolution rate of solid dispersions was higher as compared to that of drug alone (Fig. 8). From the study, it was found that all solid dispersions displayed higher release than plain drug. [17] SD1 showed nearly 89% release in 90 min. SD2 and SD3 exhibited 73 and 61% release at 90 min respectively. Hence, SD1 was selected for further studies. The slower release in presence of higher polymer concentration could be attributed to the matrix forming ability of HPMC E 5 which results in slower drug diffusion through the tortuous channels formed in the matrix. [12, 30] The improvement in the dissolution of the drug may be due to its entrapment within the carrier during the solvent evaporation process, or due to the molecularly dispersed state of the drug in the solid dispersion. Also the drug is converted into amorphous state and its wetting property is improved. [12, 31] Thus the cumulative effect is

improvement in dissolution rate. SD1 displayed the highest increase in saturation solubility and dissolution rate; hence it was subjected to further evaluation.

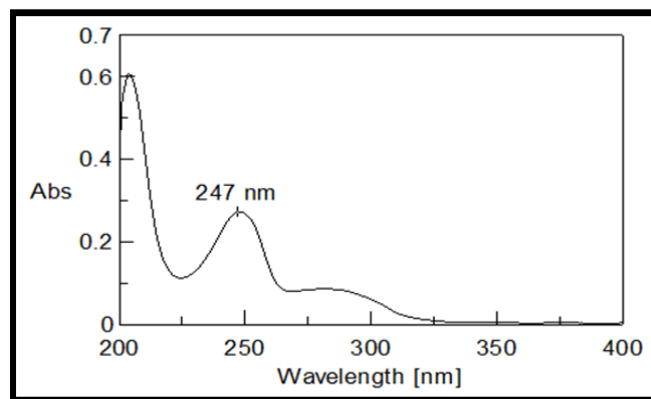


Fig. 1: UV spectrum of EFV (10 µg/ml) in methanol AR grade.

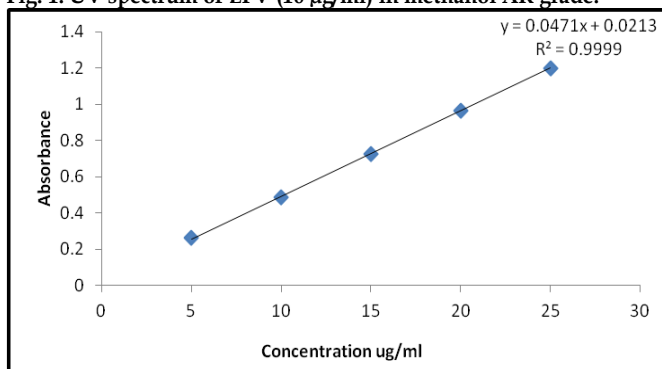


Fig. 2: Calibration curve of EFV in Methanol AR grade. (n=3, mean $\pm$ SD)

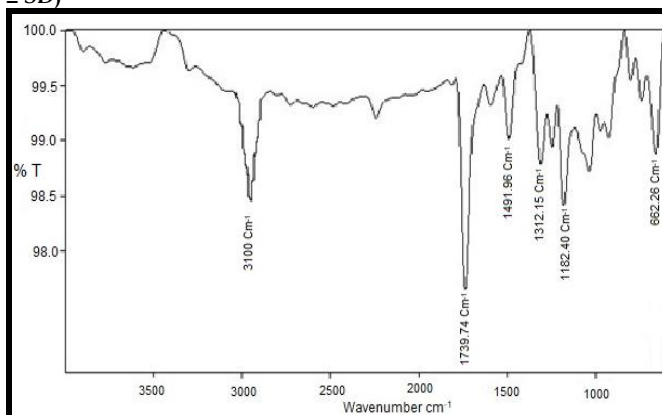
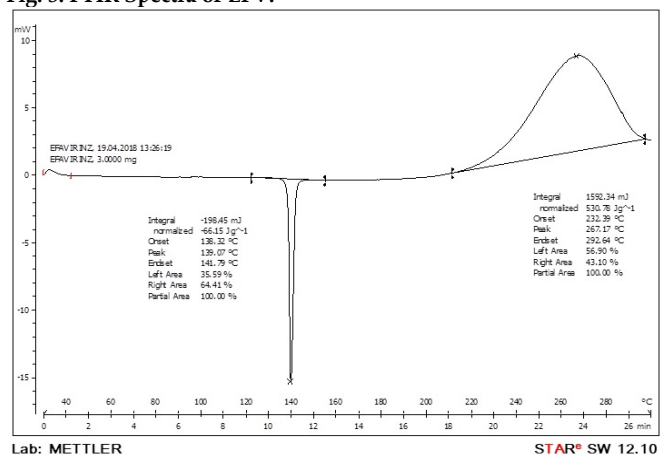


Fig. 3: FTIR Spectra of EFV.



Lab: METTLER

STAR® SW 12.10

Fig. 4: DSC thermogram of EFV.

Table 16: Granular properties of the optimization formulations: the values represent Mean $\pm$ S.D.

Formulation	Tapped density (g/ml)	Bulk density (g/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose (°)
F1	0.65 $\pm$ 2.9	0.624 $\pm$ 3.1	4.86 $\pm$ 3.2	1.051 $\pm$ 4.5	27.75 $\pm$ 2.1
F2	0.6121 $\pm$ 2.7	0.5768 $\pm$ 2.9	5.77 $\pm$ 2.5	1.061 $\pm$ 2.5	32.03 $\pm$ 1.5
F3	0.5768 $\pm$ 2.5	0.5356 $\pm$ 3.5	7.14 $\pm$ 3.2	1.076 $\pm$ 3.2	27.14 $\pm$ 1.8
F4	0.5769 $\pm$ 2.2	0.5454 $\pm$ 2.4	5.46 $\pm$ 4.5	1.057 $\pm$ 3.3	27.75 $\pm$ 3.4
F5	0.5769 $\pm$ 2.8	0.5083 $\pm$ 3.2	11.87 $\pm$ 4.3	1.134 $\pm$ 4.5	30.22 $\pm$ 3.7
F6	0.603 $\pm$ 2.6	0.5453 $\pm$ 3.6	9.55 $\pm$ 3.8	1.106 $\pm$ 3.9	31.04 $\pm$ 2.7
F7	0.565 $\pm$ 3.1	0.5366 $\pm$ 2.9	5.16 $\pm$ 3.5	1.054 $\pm$ 3.5	29.02 $\pm$ 2.9
F8	0.588 $\pm$ 3.4	0.5457 $\pm$ 2.5	7.27 $\pm$ 4.1	1.077 $\pm$ 3.8	27.75 $\pm$ 3.5
F9	0.566 $\pm$ 2.9	0.5084 $\pm$ 2.5	10.19 $\pm$ 4.3	1.113 $\pm$ 2.7	31.42 $\pm$ 3.2

Table 17: Experimental run & responses for optimization of floating tablet using 3² full factorial design

Std	Run	Factor 1	Factor 2	Response (Y ₁)	Response (Y ₂)	Response (Y ₃)
		A: HPMC	B: Citric acid	Lag Time	Floating Time	% Drug Release (8 h)
		Conc	Conc	Sec	Hour	%
5	1	21.84	22.5	70 $\pm$ 1.6	6 $\pm$ 2.1	79 $\pm$ 1.25
1	2	19.34	19	120 $\pm$ 1.4	5 $\pm$ 2.5	72 $\pm$ 4.62
2	3	21.84	19	125 $\pm$ 1.4	6 $\pm$ 1.5	76 $\pm$ 2.33
8	4	21.84	26	48 $\pm$ 1.7	8 $\pm$ 1.8	85 $\pm$ 4.6
4	5	19.34	22.5	75 $\pm$ 2.1	6 $\pm$ 1.6	77 $\pm$ 3.33
3	6	24.34	19	121 $\pm$ 1.6	7 $\pm$ 2.2	85 $\pm$ 1.33
7	7	19.34	26	44 $\pm$ 2.4	8 $\pm$ 2.2	89 $\pm$ 5.3
9	8	24.34	26	41 $\pm$ 2.7	8.7 $\pm$ 1.4	89.5 $\pm$ 2.33
6	9	24.34	22.5	68 $\pm$ 2.5	8 $\pm$ 1.6	87 $\pm$ 5.12

Table 18: Selection of optimized batch

Batches	Amount of HPMC (mg)	Amount of Citric acid (mg)	Lag Time (sec)	Floating Time (h)	Cumulative % Drug Release
X1	24.34	26	40.08	9.083	90.111
X2	24.34	25.88	40.63	9.02	89.91
X3	24.09	26	40.92	8.93	89.39
X4	19.34	26	45.91	7.91	88.111

Table 19: Validation of batches

Formulation Code	Composition of optimized formulation		Responses	Predicted Value	Actual Value	% Error
	Amount of HPMC (mg)	Amount of Citric acid (mg)				(%)
X1	24.34	26	Lag Time	40.08	41	2.24
			Floating Time	9.083	8.7	4.36
			Cumulative % Drug Release	90.111	89.5	0.68

Table 20: Evaluation of post compression parameters of optimization formulations. the values represent Mean $\pm$ S.D.

Batches	Hardness (kg/cm ²)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug content (%)	Weight variation (g)
F1	8.2 $\pm$ 2.5	12.49 $\pm$ 2.5	5.16 $\pm$ 1.8	0.15 $\pm$ 1.23	99.39 $\pm$ 1.12	0.649 $\pm$ 0.53
F2	8.2 $\pm$ 3.5	12.49 $\pm$ 2.8	5.16 $\pm$ 2.5	0.28 $\pm$ 3.45	99.77 $\pm$ 2.11	0.649 $\pm$ 0.590
F3	8.16 $\pm$ 3.3	12.496 $\pm$ 2.1	5.16 $\pm$ 2.8	0.153 $\pm$ 2.11	98.65 $\pm$ 2.41	0.6497 $\pm$ 0.42
F4	8.2 $\pm$ 3.8	12.499 $\pm$ 2.7	5.17 $\pm$ 2.7	0.153 $\pm$ 3.77	99.97 $\pm$ 3.66	0.6496 $\pm$ 0.52
F5	8.19 $\pm$ 4.2	12.499 $\pm$ 3.2	5.17 $\pm$ 3.2	0.153 $\pm$ 3.45	99.9 $\pm$ 2.41	0.65 $\pm$ 0.554
F6	8.16 $\pm$ 4.5	12.493 $\pm$ 3.5	5.16 $\pm$ 4.1	0.154 $\pm$ 4.65	98.85 $\pm$ 1.45	0.649 $\pm$ 0.48
F7	8.2 $\pm$ 4.3	12.499 $\pm$ 4.8	5.168 $\pm$ 4.6	0.416 $\pm$ 4.23	99.83 $\pm$ 3.55	0.649 $\pm$ 0.52
F8	8.2 $\pm$ 4.2	12.495 $\pm$ 3.5	5.164 $\pm$ 2.5	0.266 $\pm$ 2.11	99.55 $\pm$ 2.25	0.65 $\pm$ 0.53
F9	8.16 $\pm$ 4.8	12.499 $\pm$ 3.2	5.17 $\pm$ 2.7	0.333 $\pm$ 2.56	99.94 $\pm$ 4.45	0.649 $\pm$ 0.53

Table 21: Stability data

Formulation F8	0 Month	1 st Month	2 nd Month	3 rd Month
Hardness (kg/cm ²)	8.2 $\pm$ 0.0	8.2 $\pm$ 0.0	8.1 $\pm$ 0.0001	8.1 $\pm$ 0.0001
Drug content (%)	99.57	99.49	99.49	99.46
Buoyancy lag time (sec)	40	40	42	44
Floating time (h)	>12	>12	>12	>12

Differential Scanning Calorimetry

The DSC thermograms of EFV showed in (Fig. 9), shows a sharp endotherm at 147°C (melting point), indicating the crystalline nature of the drug. The drug peak in SD1 has shifted due to its dilution effects which points to amorphization of the drug and is molecularly

dispersed in the polymer matrix which supports the FTIR results. [32] Amorphization of the drug could be another reason for enhanced solubility and dissolution rate of poorly water soluble drug. [17]

FT-IR studies of solid dispersions

The key peaks of EFV was observed (Fig. 10) in the region of 1749.7 cm⁻¹ due to the C=O aliphatic stretching, a peak at 1500.83 cm⁻¹ due to C=C stretching and a peak at 3100 cm⁻¹ due to aliphatic N-H stretching. The broadening of the peak in the spectra of SD1 indicates that EFV is molecularly dispersed in the polymer matrix. However other peaks related to C-O-C, N-H, C=C stretching remains unchanged. This indicates that overall stereochemistry of the molecule might not be significantly changed. [17]

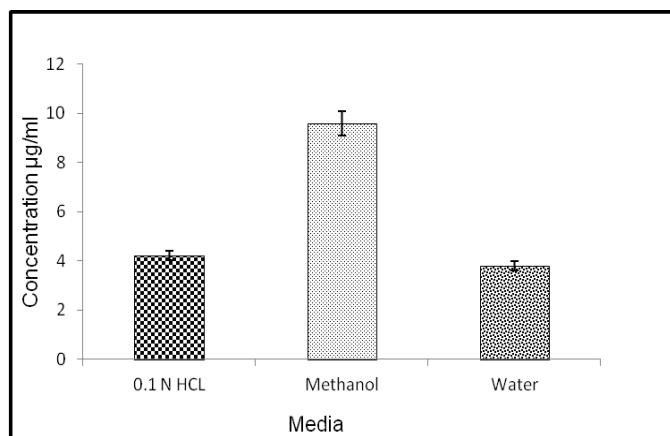


Fig. 5: Solubility of EFV in various solvents such as HCl, methanol, water.(n=3, mean $\pm$ SD)

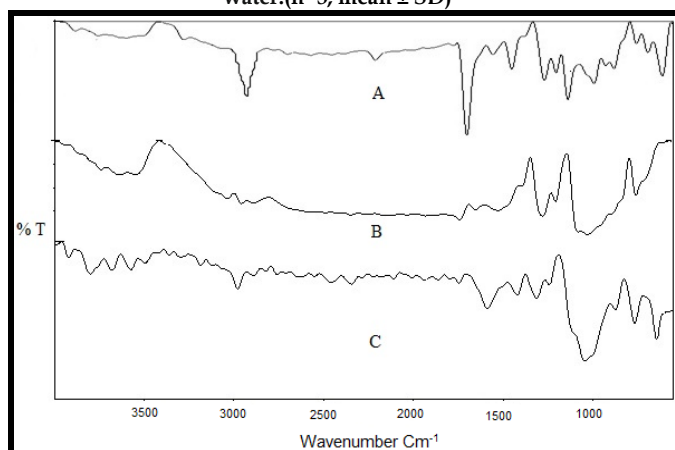


Fig. 6: FTIR spectra (after 30 days) for drug-excipients compatibility studies. A= EFV, B= EFV + HPMC, C= EFV + NaCMC

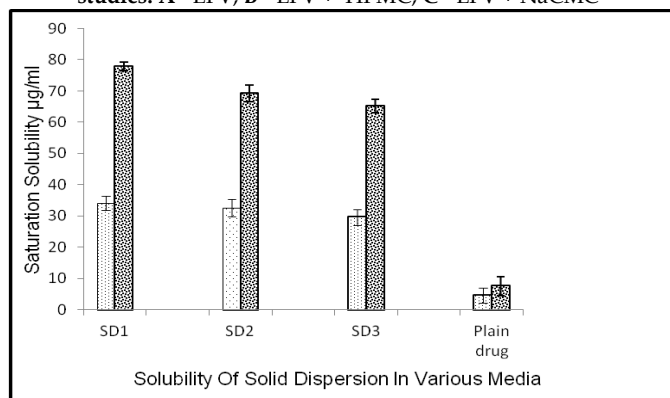


Fig. 7: Saturation solubility in different media i.e., 0.1 N HCl and water. Mean $\pm$ SD (n=3)

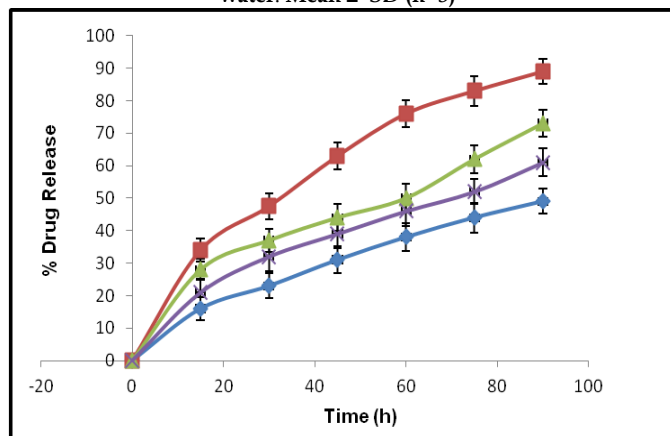


Fig. 8: Percent Drug release profile in 0.1 N HCl. Mean $\pm$ SD (n=3),

—●— Drug, —■— SD1, —▲— SD2, —×— SD3.

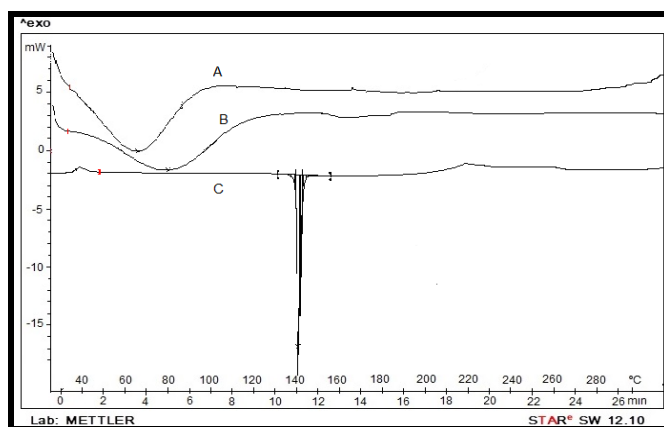


Fig. 9: DSC thermograms of pure A =HPMC E5, B= SD(1:1), C=EFV.

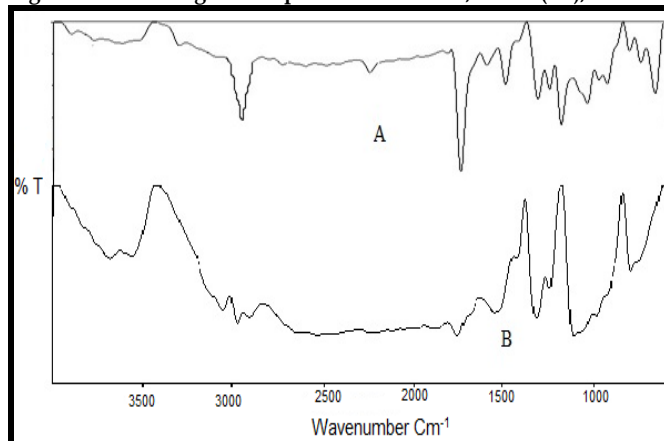


Fig. 10: FTIR spectra for compatibility studies. A= EFV, B = Solid dispersion

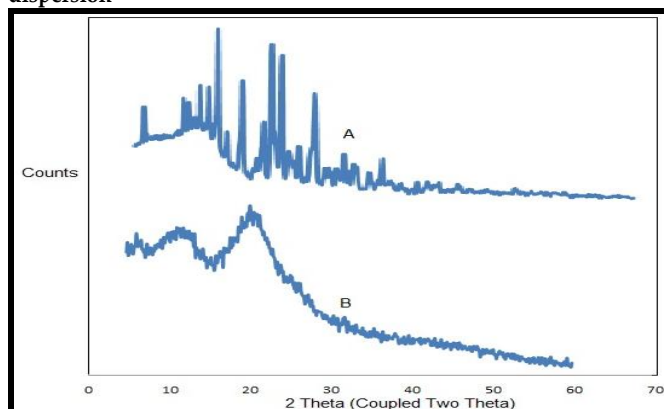


Fig. 11: Powder X-ray diffraction patterns of A = plain drug, B = solid dispersion.

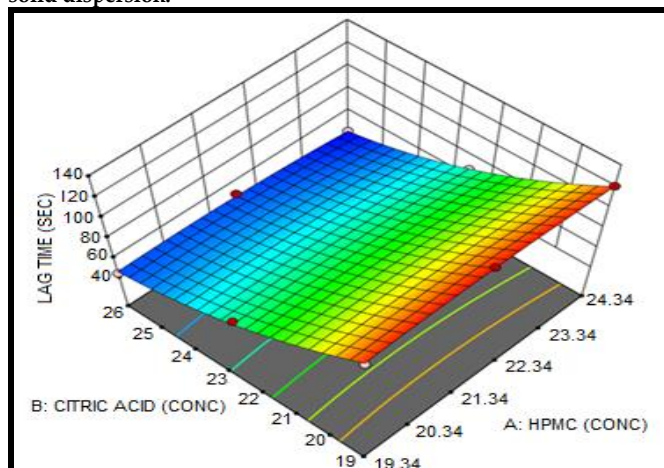


Fig. 12: Response surface plot (3D) showing the effect of HPMC & citric acid on lag time.(n=3, mean $\pm$ SD)

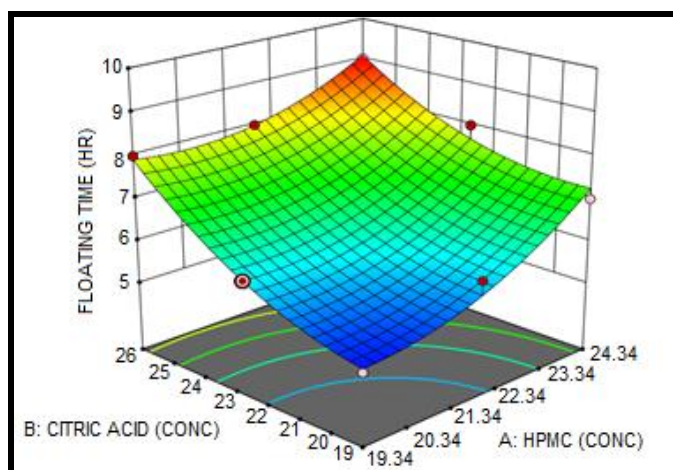


Fig. 13: Response surface plot (3D) showing the effect of HPMC & citric acid on floating time. (N=3, mean $\pm$ SD)

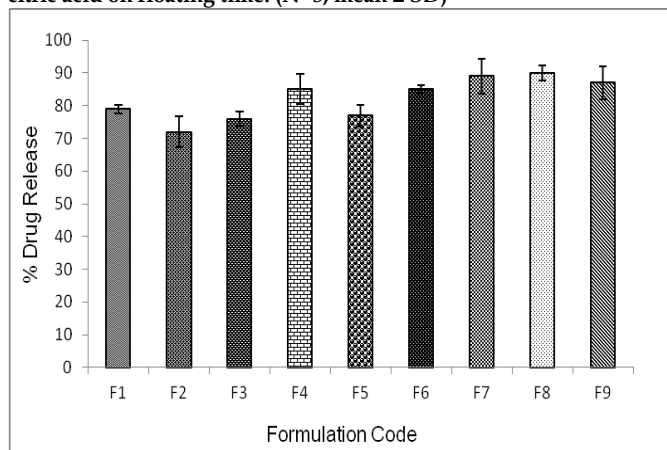


Fig. 14: *In vitro* drug release data of optimization formulation (in 8 h). The values represent mean $\pm$ S.D

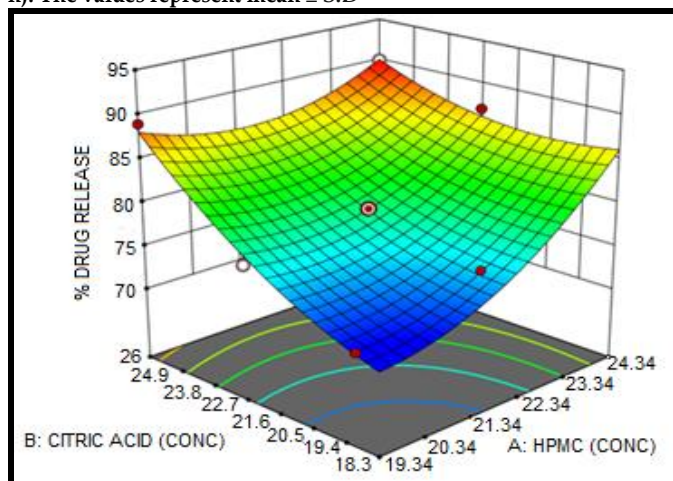


Fig. 15: Response surface plot (3D) showing the effect of HPMC & citric acid on % drug release (N=3, mean $\pm$ SD)

Powder X-Ray diffraction patterns

The PXRD of EFV consist of sharp multiple peaks at 2θ angles of 6° , 10.31° , 12° , 15° and 17° , 20° , 22° , 24° , 28° , indicating crystalline nature of the drug. The diffractogram of SD1 exhibited a halo pattern with reduced peak intensities.^[17] Generally this partial loss of crystallinity supports DSC results and confirms partial amorphization of the drug.^[33]

Evaluation of floating tablet

SD1 ratio of solid dispersion was selected based on percent drug release and drug content and further used

for the formulation of gas generating floating tablets.^[5] HPMC K100, a water soluble polymer was selected as a hydrophilic matrix. Citric acid and sodium bicarbonate were used as the gas generating agents. The solid dispersion and all other ingredients were separately passed through sieve # 60 and triturated to ensure thorough mixing. Then ethanolic solution containing PVP K30 was added drop wise to above mixture & the wet mass was passed through sieve no 18 and granules so obtained were dried and lubricated with talc and compressed using 12 mm punch and die (Rimek Mini Press-II MT).^[23, 25]

Pre compression parameters

The bulk density and tap density values of the powder ranged from 0.50 ± 3.2 g/ml to 0.62 ± 3.1 g/ml and 0.56 ± 3.1 g/ml to 0.65 ± 2.9 g/ml. Moreover, powders having Carr's index below 15 were considered to have good flow properties and could be successfully compressed into tablets with uniform weight.^[30] Angle of repose ranged from 27.14 ± 1.8 to 32.03 ± 1.5 which indicates excellent flow properties and Hausner's ratio below 1.15 which indicates excellent flow properties with less interparticle frictions between particles.^[18] The granular properties like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose for all formulations were determined and the results are reported as shown in the (Table 15).

Experimental design

For formulation of floating tablets as per 3^2 full factorial design the concentrations of citric acid and HPMC K100 were considered as the two independent factors. Design comprised of 9 experimental runs to evaluate the significance of individual and combined effects of the citric acid and HPMC K100 on floating time, lag time and percent drug release in 8 h. The response data for the factorial design trials were fitted in the 3^2 factorial design to get model equations for responses analysed.^[34] Quantitative effect of independent variable in the obtained equation are mean results obtained by changing one factor from its low to high value keeping another factor constant. The polynomial equations obtained were visualized with the help of 3D response surface graphs.^[25, 34]

Characterization of factorial batches

Lag Time (Y1)

Lag time is one of the important characteristics in floating gastroretentive formulations and it is the time taken by tablet to emerge on surface of media. When citric acid liberated CO_2 after reaction with gastric acid, the combination of effervescence and swelling of the polymer enables the dosage form to achieve lower density than the gastric fluid i.e, (1.004 to 1.010 g/ml) and results in an upward motion of the tablet which maintains the buoyancy. The floating time and percent drug release is dependent on lag time.^[8, 4]

$$\text{Lag time} = 73.00 + 1.67 A - 39.00B - 1.25AB - 3.00 A^2 + 12.00 B^2 \dots \dots \text{Equation 1}$$

The lag time of factorial batches was found to be between 40 to 125 sec. The linear effect of the amount of

(B) was found to be significant ($p < 0.05$). The negative coefficient implied that an increase in the amount of Citric acid (B) led to a decrease in lag time (Y1). In contrast, the quadratic effect of amount of Citric acid (B^2) was found to be significant ($p < 0.05$) having negative coefficient. Though the effect of the amount of HPMC K 100 (A) was found to be significant ($p < 0.05$) with positive coefficient (Eq.1), indicating an increase in lag time (Y1) with an increase in the amount of HPMC K 100(A). The high negative coefficient for term AB ($p < 0.05$) indicated interaction between HPMC K 100 and citric acid. This implied that a judicious selection of the amount of HPMC K 100 and Citric acid is essential to ensure stability, and decrease in lag time.

Floating Time (Y2)

Floating time is the time span for which the dosage form remains on surface of medium. Effervescence, due to reaction between sodium bicarbonate and gastric medium, besides citric acid in the formulation caused CO_2 to get entrapped in the swelling polymer to improve the floating time. [8, 4]

$$\text{Floating time} = 6.33 + 0.8333 A - 1.17 B - 0.2500 AB + 0.5000 A^2 - 0.5000 B^2 \dots \text{Equation 2}$$

The floating time of factorial batches was found to be between 5 to 9 h. The linear effect of the amount of (B) was found to be significant ($p < 0.05$). The negative coefficient implied that an increase in the amount of Citric acid (B) led to increase in floating time (Y2). In contrast, the quadratic effect of amount of Citric acid (B^2) was found to be significant ($p < 0.05$) having negative coefficient. Though the effect of the amount of HPMC K 100 (A) was found to be significant ($p < 0.05$) with positive coefficient (Eq.2), indicating an increase in floating time (Y2) with an increase in the amount of HPMC K 100 (A). The high negative coefficient for term AB ($p < 0.05$) indicated interaction between HPMC K 100 and citric acid. This implied that a judicious selection of the amount of HPMC K 100 and citric acid is essential to ensure stability, and increase in floating time. [27-28]

Percent Cumulative Drug Release at 8 Hours (Y3)

The gastric contents and citric acid releases carbon dioxide (CO_2) by reacting with sodium bicarbonate which becomes trapped within the gellified hydrocolloid system. The combination of effervescence and swelling causes floatation of the tablet for extended time period and ensures slow release of the drug. [34]

$$\% \text{ Drug Release} = 172.29 - 13.98 A + 2.22 B - 0.34 AB - 0.533 A^2 + 0.1496 B^2 \dots \text{Equation 3}$$

The cumulative percent release of factorial batches was found to be between 72 to 89.5% in 8 h. The linear effect of the amount of (A) was found to be significant ($p < 0.05$). The negative coefficient implied that an increase in the amount of HPMC K 100 (A) led to increase in percent drug release (Y3). In contrast, the quadratic effect of amount of HPMC K 100 (A^2) was found to be significant ($p < 0.05$) having negative coefficient. Though the effect of the amount of HPMC K 100 (A) was found to be significant ($p < 0.05$) with positive coefficient (Eq.3), indicating an increase in

percent drug release (Y3) with an increase in the amount of HPMC K 100 (A). The high negative coefficient for term AB ($p < 0.05$) indicated interaction between HPMC K 100 and citric acid. This implied that a judicious selection of the amount of HPMC K 100 and Citric acid is essential to ensure stability, and increase in percent drug release.

Selection of optimized formulation and validation studies

Selection of optimized formulation of floating tablet was carried out; where the various trials were made to attain the goals like minimization of lag time and maximization of floating time and cumulative percent drug release. The optimized batch was chosen by numeric optimization using the desirability function. The constraints set for numerical optimization of floating tablet included lag time ($Y1 < 180$ sec), floating time ($Y2 > 8$ h) and cumulative percent drug release ($Y3 > 90\%$). Based on these three responses (Y1, Y2 and Y3), there were four different optimized batches of floating tablet given by the software and among these four batches of floating tablet, one batch was selected as an optimized batch of floating tablet based on their desirability function. Validation of the optimization methodology by comparing the observed responses with those of the predicted responses understood that percent prediction error for both the responses (Y1, Y2 and Y3) ranged between 0.98% and 0.99% of floating tablet. Thus, the formulation batch giving minimum lag time (Y1), maximum floating time (Y2) and the maximum cumulative percent drug release (Y3) was chosen as the optimized batch.

Post compression evaluation

The tablets weighing above 650 mg have the limit of $\pm 5\%$ variation according to Indian Pharmacopoeia. [35] The weight variation was within specified limits. The hardness of the tablet was found to be between 8.00 to 8.2 kg/sq cm. The thickness was between 5.16 mm to 5.17 mm. The friability of the tablets was found to be less than 1% which was considered within the limit. [26] These two parameters gives a measure of the strength of the tablets during handling, packaging and shipping. The percentage drug content estimations showed values in the range of $98.65 \pm 2.41\%$ to $99.97 \pm 3.66\%$ which reflects content uniformity in different formulations. [27] The average percentage weight variation of each formulation remained within $\pm 5\%$ and hence all formulations pass the test for uniformity of weight as per I.P. [35]

Stability studies

The stability studies conducted as per ICH guidelines revealed that there is no change in physical appearance, hardness, drug content and floating lag time.

The authors conclude that the development of gastroretentive drug delivery system with enhanced solubility can improve the therapeutic benefits of EFV. SDs of EFV prepared by a solvent evaporation method showed enhanced drug dissolution in comparison with pure drug. FTIR and DSC studies showed absence of

interaction between the drug and carrier. PXRD study confirmed amorphization of drug. Further the optimized batch of gas generating floating tablet consist of Citric acid and HPMC K100 which results in desirable lag time, floating time and percent drug release. From the *in vitro* studies, it was also shows that there was an increase in the solubility.

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