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Research Article

Formulation and *In-vitro* Evaluation of Fexofenadine Floating Tablets using Natural and Synthetic Polymers

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ABSTRACT

The extent of therapeutic advantages led to the development of controlled drug delivery systems, which could be taken once a day. The prime objective of these dosage forms would be single dose, which releases the active ingredient over an extended period. Secondly, it should release the active entity directly to the site of action, thus, minimizing or eliminating side effects. In the present manuscript, fexofenadine was selected as drug of choice to design effervescent gastric floating matrix tablets (EGFMT) using natural polymers as well as synthetic polymers as matrix-forming agents. Natural polymers comprise bhara gum, grewia gum and mucuna gum, whereas synthetic polymers consist of hydroxypropyl methylcellulose (HPMC) K4M, K15M, and K100M. These were compared; it was found that low concentrations of natural gum were enough to produce prolonged release. Hence out of three natural gums that were available, bhara gum had given promising results. Therefore bhara gum was selected for further studies.

Introduction

The desire to develop a new drug delivery system (DDS) is to minimize the disadvantages associated with existing dosage form and optimize therapy. Despite tremendous advancements in drug delivery, the oral route remains the most promising route of drug delivery.[1]

Conventional DDS achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. Thus, several controlled release drug delivery systems (CRDDS) have been developed that could provide a number of therapeutic benefits when taken once a day. [2]

Due to its low bioavailability, multiple doses were needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance.[3,4]

Previous studies performed by Sudarshan Singh *et al.*[5] reported that LVT extended release matrix tablets were developed using hydroxypropyl methylcellulose (HPMC) K4M, K15M and K100M that could control the drug release for 18 hours; another work by Himanshu Paliwal *et al.*[6] reported that the levetina cetam tablets were developed using various grades of HPMC could control the drug release for 18 hours.

Effervescent gastric floating matrix tablets (EGFMT)of fexofenadine (FEX) was designed to retain the tablets in the stomach for longer periods and deliver the drugs effectively to the absorption window to maintain the effective plasma levels fora prolonged time.[7]

Direct compression method was used to prepare floating tablets of FEX. Bhara gum, grewia gum and mucuna gum were taken as CR polymers, sodium bicarbonate was used as gas generating agent. Floating properties and drug release studies were performed.

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Hence in the present study, FEX was selected as drug of choice to design the EGFMT using bhara gum, grewia gum and mucuna gum as matrix forming polymers. Low bioavailability of this drug from available conventional dosage forms may be due to its narrow absorption window in the stomach and upper parts of the small intestine.

MATERIALS AND METHODS

MATERIALS

FEX is a gift sample from Sreenivasa Pharmaceuticals Pvt. Ltd. Hyderabad, HPMC (K4M, K15M and K100M) are gift samples from Colorcon Asia Pvt. Ltd, Goa, gum gucuna, gum bhara, gum grewia are gift samples from Yarrow chem, Mumbai, India.

METHODS

Preformulation Studies[8, 9, 10, 11, 12]

Preformulation studies were performed on the obtained sample of drug for identification and compatibility studies.

Fourier transform infrared (FTIR) spectroscopic studies

The pure fexofenadine and polymers' FTIR spectra (400 to 4000 cm-1 and resolution of 4 cm-1) were measured by preparing dispersion in dry KBr using Shimadzu FTIR 8400S (Perkin-Elmer 1615 Series or Bruker, Germany).

Differential Scanning Calorimetric (DSC) Studies

The heat characteristics of fexofenadine and polymers were analyzed using a Shimadzu DSC-60 (Shimadzu, Kyoto, Japan).

Construction of calibration curve[13]

Determination of λ_{max}: FEX was dissolved in 0.1N HCl and scanned for maximum absorbance in UV-spectrophotometer in U V range, i.e., from 200 to 400 nm. FEX showed λ_{max} at 225 nm and shown in Fig. 1.

Calibration curve of FEX: To prepare the standard stock solution, accurately weighed 100 mg of FEX was dissolved in 100 mL of 0.1N HCl. Each mL of the above solution consists of 1000 µg/mL. The standard stock solution was diluted to give 100 µg/mL in 0.1N HCl. Aliquots of 1.0, 1.5, 2, 2.5, 3, 3.5 and 4 mL of stock solution was pipetted out into 10 mL volumetric flask and the volume was made up to the mark with 0.1N HCl to give a series of concentrations of 10, 15, 20, 25, 30, 35, 40 µg/mL of FEX, respectively. Table 3, Fig. 2 shows the calibration curve of pure drug FEX.

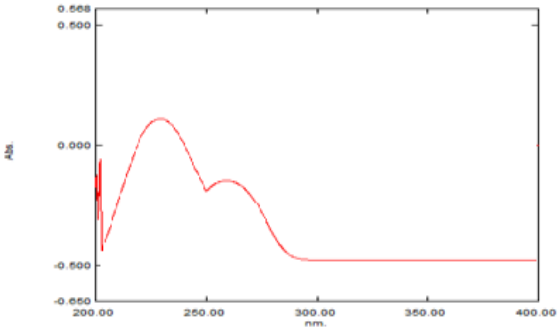

Fig. 1: UV spectra of fexofenadine at 225 nm

Pre-compression Evaluation of Powder Blend[14,15]

Bulk Density:

About 5 gm of blend was weighed and transferred to a measuring cylinder. Then bulk volume was noted. Bulk density was calculated using the following formula

Bulk density = Mass/Bulk Volume

Tapped Density

A blend of 5 gm was weighed, transferred to a measuring cylinder and subjected to 100 tapings. Then volume was noted as tapped volume. Tapped density was measured by using the following formula

Tapped density = Mass/Tapped volume

Hausner's Ratio

It is expressed in percentage and is expressed by

$$H = D_t/D_b$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Carr's Index

It is expressed in percentage and is expressed by the following formula,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Angle of repose

The angle of repose (θ) was calculated by the formula

Angle of Repose (Tan θ)=h/r

Dose Calculation of FEX

The total dose (D_T) consisting of initial (D_I) and maintenance doses (D_M) for formulating the FEX sustained release was calculated as per Robinson and Eriksen equation with a zero-order release principle.

Estimation of Controlled Release Parameters of FEX

From the above calculations the total dose obtained for sustained release of fexofenadine for 24 hours is 85 mg (Table 1).

Table 1: Estimation of controlled release parameters of FEX

Pharmacokinetic parameters	*FEX*
Time to reach peak plasma (t_p) in hr	2
Bioavailability (F)	0.35
Elimination rate constant (K_{el}) in hr^{-1}	0.05
Initial dose (C_{ss}*V_d/F) mg	60
Desired input rate (k_0) in mg/hr	2.88
Maintenance dose (D_M) in mg	28.8
Corrected Initial dose D_I*: in mg	55.5
Total dose (D_T) = D_I* + D_M	84.3=85

Preparation of Tablets[16, 17]

Preparation of Floating Tablets using Synthetic and Natural Polymers

In the present investigation, wet granulation technique was employed to prepare tablets of HPMC, direct compression technique was employed to prepare tablets using natural polymers at different drug to polymer ratios as per the composition given in tables, respectively. Microcrystalline cellulose was used as diluent along with sodium bicarbonate as gas generating agent. Compression was done using karnavathi tablet compression machine (R & D type) using B type punch (for FEX tablets) sizes with corresponding dies. Table 2 and 3 shows the composition of FEX floating tablets using natural and synthetic polymers (Figs 3 to 5).

Post-compression Physicochemical Evaluation of FEX Floating Tablets[18]

Visual Inspection: The tablets were smooth with uniform in size, shape and colour. There was no lamination or chipping in all the tablets which indicated that the tablet-instrumentation was compatible with the powder blends and resulting in good tablet characteristics.

Weight Variation: Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X100$$

Hardness: The hardness of the tablet was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability: The Roche friability test apparatus was used to determine the friability of the tablets. Total of 20 pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

Drug Content Uniformity: Ten tablets were weighed and powdered. The powder weight equivalent to 85 mg of fexofenadine was dissolved in 100 mL of 0.1N HCl separately and filtered using 0.45 µm whatman filter paper. 5 mL of this was diluted to 50 mL with 0.1N HCl and drug content was estimated at 225 nm.

***In-vitro* Buoyancy Studies:** *In-vitro* buoyancy was determined by floating lag time**.** Tablets were placed in a 250 mL beaker containing 100 mL of 0.1N HCl. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

Swelling Studies: Formulated tablets were weighed individually (W_0) and placed separately in a petri dish containing 50 mL of 0.1N HCl. The petri dishes were placed in an incubator maintained at 37 ± 0.5°C. The tablets were removed from the petri dish at predefined intervals of time and reweighed (W_t), and the % swelling index was calculated using the following formula

$$\% W_U = (W_t\text{-}W_o/W_o) \times 100$$

Where: W_U – Water uptake, W_t – Weight of tablet at time t, W_o – Weight of tablet before immersion.

Table 2: Formulation of Fexofenadine floating tablets prepared using synthetic polymers

Ingredients(mg)	*FES1*	*FES2*	*FES3*	*FES4*	*FES5*	*FES6*	*FES7*	*FES8*	*FES9*	*FES10*	*FES11*	*FES12*
Fexofenadine	85	85	85	85	85	85	85	85	85	85	85	85
HPMC K4M	21.25	42.5	63.75	85	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	21.25	42.5	63.75	85	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	21.25	42.5	63.75	85
Microcrystalline cellulose	88	66.5	45.25	24	88	66.5	45.25	24	88	66.5	45.25	24
Sodium Bicarbonate	35	35	35	35	35	35	35	35	35	35	35	35
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	250	250	250	250	250	250	250	250	250	250	250	250

Table 3: Formulation of Fexofenadine floating tablets prepared using natural polymers

Ingredients (mg)	*FEN1*	*FEN2*	*FEN3*	*FEN4*	*FEN5*	*FEN6*	*FEN7*	*FEN8*	*FEN9*	*FEN10*	*FEN11*	*FEN12*
Fexofenadine	85	85	85	85	85	85	85	85	85	85	85	85
Bhara gum	21.25	42.5	63.75	85	-	-	-	-	-	-	-	-
Grewia gum	-	-	-	-	21.25	42.5	63.75	85	-	-	-	-
Mucuna gum	-	-	-	-	-	-	-	-	21.25	42.5	63.75	85
Microcrystalline cellulose	88	66.5	45.25	24	88	66.5	45.25	24	88	66.5	45.25	24
Sodium Bicarbonate	35	35	35	35	35	35	35	35	35	35	35	35
PVP K30	15	15	15	15	15	15	15	15	15	15	15	15
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	250	250	250	250	250	250	250	250	250	250	250	250

In-vitro Dissolution, Studies[19]

Drug release profiles were carried out in 900 mL of 0.1N HCl maintained at 37 ± 0.5°C temperature at 100 rpm. A 5 mL of samples were withdrawn at regular time intervals up to 12 hours. The samples were replaced by equivalent dissolution medium volume and filtered through 0.45 µm Whatman filter paper. Drug release plots were shown in Figs 8 to 13.

Kinetic Modeling Studies [20, 21]

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into zero order, first order, Higuchi and Korsmeyer-Peppas equations. Based on the obtained R^2 values, the best-fit model was selected.

Zero Order Equation for Drug Release

$$Qt = Q0+K0t$$

Where, Q_t is the amount of drug released at time t, K_0 is the apparent dissolution rate constant or zero- order release constant and Q_0 is the initial concentration of the drug in the solution resulting from a burst effect;

Higuchi Equation

$$Q = K_H t^{1/2}$$

Where, Q is the cumulative amount of drug release at time "t", K_H is Higuchi constant.

Korsmeyer-Peppas Equation

$$F = (M_t/M) = K_m t^n$$

Where, F is fraction of drug released at time 't', Mt is the amount of drug release at time 't', M is the total amount of drug in dosage form, K_m is kinetic constant, 'n' is diffusion or release exponent and 't' is time in h.

Stability studies of optimized floating matrix tablets

The optimized floating matrix tablets were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 40 ± 5°C/75% RH for three months and every month

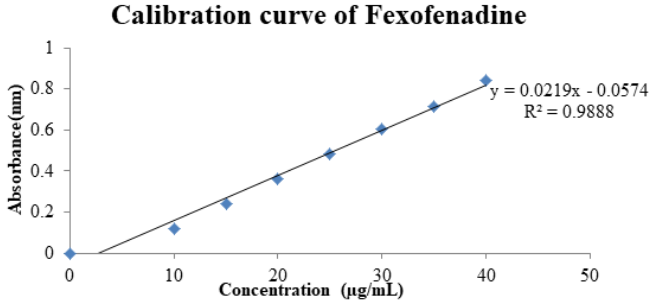

Fig. 2: Standard Plot of Fexofenadine

the formulations from each group were subjected to dissolution studies and % drug release was calculated. The drug content, floating lag-time and drug dissolution profile of the exposed samples were determined.

RESULTS

Preformulation Studies

Preformulation studies were performed on the obtained sample of drug for solubility analysis, it was clearly observed that it has good solubility in pH 1.2. It appears as a white to off-white crystalline powder. From the compatability studies it was proved that there was no change in melting point.

Compatability Studies

FTIR

FEX was studied for FTIR, it was found that from the functional groups analysis, it was FEX. The excipients used were also compatable since there were no new functional groups formed. (from Figs 3 to 5)

DSC

From the above DSC curves it was clearly evident that the optimized formulation of FEX had also showed a melting point of 148°C (Fig. 6). This was clearly found in literature that it was within the range. The optimized formulation

Table 4: Calibration curve of Fexofenadine

Concentration (µg/mL)	*Absorbance (nm)*
0	0
10	0.120 ± 0.001
15	0.242 ± 0.007
20	0.363 ± 0.005
25	0.481 ± 0.003
30	0.605 ± 0.002
35	0.716 ± 0.012
40	0.839 ± 0.047

Data is expressed as mean ± SD (n=3)

Table 5: FTIR of pure FEX

Alcholic-OH group	*3613.21*
Acid C=O	1697.63
Acid-OH	3395.11
=CH	3067.11
-CH	2932.09
Aromatic C=C	1515.02

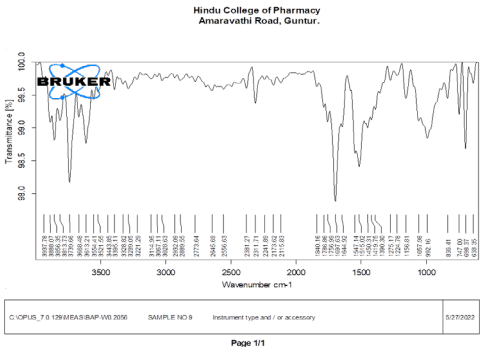

Fig. 3: FTIR of Pure FEX

Table 6: FTIR of Optimized formulation using synthetic polymers

Alcholic-OH streching	*3614.33*
Acid C=O streching	1694.56
Acid-OH	3330.29
Aromatic=CH streching	3038.59
Alkane-CH	2977.41
Ether C-O	1026.35
Aromatic C=C	1515.40

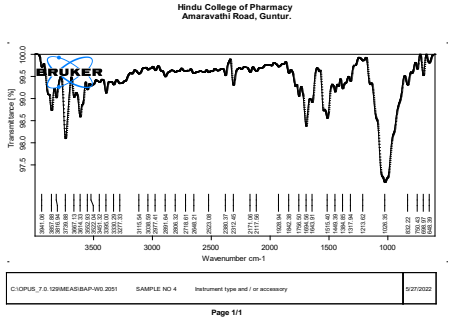

Fig 4: FTIR of Optimized formulation using synthetic polymers

Table 7: FTIR of Optimized Formulation using natural polymer

Alcholic-OH streching	*3666.75*
Acid C=O streching	1700.85
Acid-OH	3394.08
Aromatic=CH streching	3034.09
Alkane-CH	2985.93
Ether C-O	997.74
C=O	1756.98
Aromatic C=C	1543.29

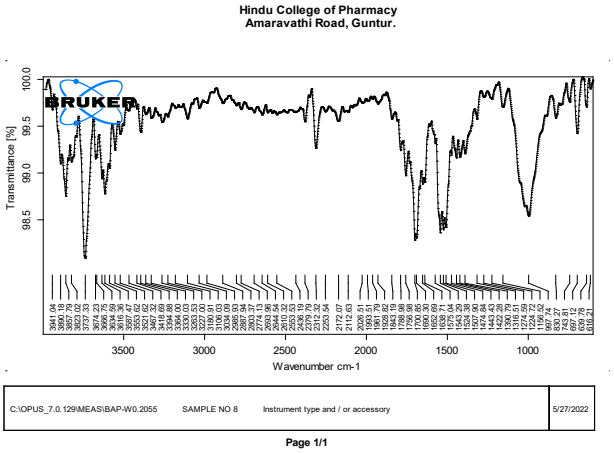

Fig 5: FTIR of Optimized Formulation using natural polymer

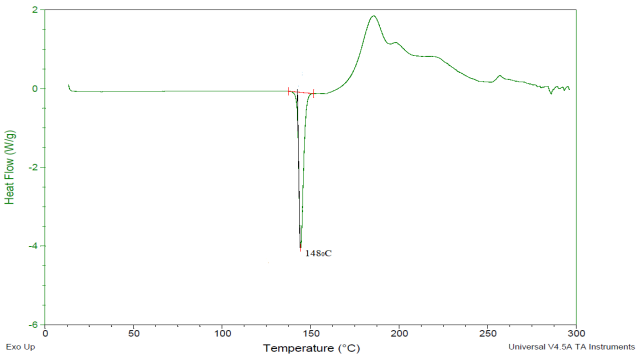

Fig. 6: DSC of pure fexofenadine

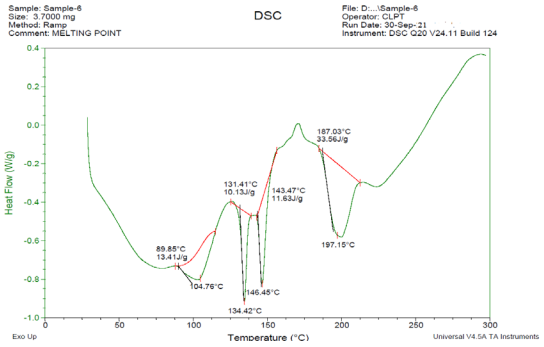

Fig. 7: DSC of optimized formulation of fexofenadine

Table 8: Pre-compression flow properties of Fexofenadine GRDDS tablets using Synthetic polymers

Formulation	*Bulk density (gm/cm^3)*	*Tapped density (gm/cm^3)*	*Carr's index (%)*	*Hausner'sratio*	*Angle ofrepose (°) ± SD*
FES1	0.462 ± 0.98	0.580 ± 0.67	20.69	1.261	27.76 ± 1.16
FES2	0.47 ± 0.99	0.575 ± 1.98	18.26	1.223	25.90 ± 1.01
FES3	0.452 ± 0.98	0.568 ± 2.90	20.42	1.257	25.41 ± 0.16
FES4	0.486 ± 1.98	0.557 ± 1.98	12.75	1.146	22.29 ± 2.16
FES5	0.46 ± 0.90	0.540 ± 1.45	16.21	1.193	26.11 ± 1.96
FES6	0.474 ± 0.70	0.540 ± 0.43	12.22	1.190	25.39 ± 0.13
FES7	0.455 ± 0.87	0.537 ± 2.23	15.27	1.180	25.30 ± 1.14
FES8	0.488 ± 0.85	0.521 ± 1.78	06.15	1.066	23.09 ± 0.16
FES9	0.425 ± 0.45	0.496 ± 0.09	14.31	1.167	25.11 ± 1.59
FES10	0.472 ± 0.53	0.524 ± 2.56	09.61	1.156	23.01 ± 1.10
FES11	0.465 ± 0.09	0.555 ± 2.56	16.22	1.144	22.17 ± 1.18
FES12	0.445 ± 0.12	0.542 ± 0.90	17.59	1.310	21.07 ± 1.76

Table 9: Pre-compression flow properties of Fexofenadine GRDDS tablets using Natural polymers

Formulation	*Bulk density (gm/cm^3)*	*Tapped density (gm/cm^3)*	*Carr's index(%)*	*Hausner'sratio*	*Angle of repose (°)*
FEN1	0.520 ± 0.12	0.616 ± 0.43	15.58	1.184	26.72 ± 0.78
FEN2	0.523 ± 0.23	0.617 ± 0.23	15.23	1.180	25.90 ± 0.76
FEN3	0.527 ± 0.95	0.619 ± 0.65	14.86	1.175	25.41 ± 0.65
FEN4	0.516 ± 0.34	0.611 ± 0.43	15.54	1.184	27.32 ± 0.54
FEN5	0.519 ± 0.34	0.613 ± 0.56	15.49	1.183	26.94 ± 0.43
FEN6	0.521 ± 0.56	0.615 ± 0.77	15.28	1.180	26.31 ± 0.32
FEN7	0.514 ± 0.76	0.611 ± 0.65	15.87	1.188	27.64 ± 0.21
FEN8	0.519 ± 0.78	0.614 ± 0.54	15.49	1.183	26.93 ± 0.67
FEN9	0.521 ± 0.89	0.616 ± 0.43	15.42	1.182	26.10 ± 0.54
FEN10	0.513 ± 0.54	0.608 ± 0.23	15.62	1.185	27.43 ± 0.43
FEN11	0.516 ± 0.12	0.610 ± 0.32	15.40	1.182	26.81 ± 0.23
FEN12	0.520 ± 0.23	0.614 ± 0.21	15.30	1.180	26.42 ± 0.12

Post-compression physicochemical evaluation of floating tablets

Table 10: Post compression parameters of fexofenadine floating tablets prepared by using semi synthetic polymers

Formulation	*Hardness (kg/cm^2)*	*Weight variation(mg)*	*Friability (%)*	*Uniformity of drug content (%)*	*FloatingLag time (minutes)*	*Total floating time (hours)*
FES1	4.5 ± 0.13	250.16 ± 0.33	0.62 ± 0.01	99.40 ± 0.65	1.8	10
FES2	4.5 ± 0.11	250.69 ± 0.77	0.63 ± 0.02	99.62 ± 0.12	1.6	20
FES3	4.6 ± 0.07	250.71 ± 0.98	0.55 ± 0.01	100.85 ± 0.54	1.0	24
FES4	4.7 ± 0.04	250.61 ± 0.02	0.58 ± 0.01	99.07 ± 0.86	1.0	26
FES5	4.3 ± 0.05	250.51 ± 0.66	0.72 ± 0.02	97.45 ± 0.76	1.2	16
FES6	4.7 ± 0.05	250.23 ± 0.76	0.68 ± 0.02	98.62 ± 0.86	1.6	26
FES7	4.9 ± 0.04	250.11 ± 0.94	0.62 ± 0.01	99.15 ± 0.78	1.4	28
FES8	4.9 ± 0.05	250.93 ± 0.28	0.65 ± 0.01	100.42 ± 0.87	1.5	30
FES9	4.7 ± 0.06	250.08 ± 0.16	0.56 ± 0.02	99.72 ± 1.21	2.0	22
FES10	4.8 ± 0.03	250.05 ± 0.85	0.54 ± 0.01	99.25 ± 0.85	1.40	28
FES11	4.9 ± 0.04	250.30 ± 0.05	0.58 ± 0.02	99.50 ± 0.94	1.18	30
FES12	5.0 ± 0.02	250.90 ± 0.10	0.65 ± 0.018	98.97 ± 0.80	1.10	32

Table 11: Post compression parameters of fexofenadine floating tablets prepared by using natural polymers

Formulation	*Hardness (kg/cm²)*	*Weight variation (mg)*	*Friability(%)*	*Drug content (%)*	*Floating lag time (minutes)*	*Total floatingtime (hours)*
FEN1	4.5 ± 0.021	250.32 ± 0.24	0.40 ± 0.010	100.14 ± 0.13	2.25	14
FEN2	4.7 ± 0.025	250.65 ± 0.28	0.34 ± 0.018	99.78 ± 0.15	1.23	24
FEN3	4.8 ± 0.032	250.83 ± 0.39	0.25 ± 0.024	99.56 ± 0.11	2.12	26
FEN4	4.3 ± 0.011	250.23 ± 0.13	0.45 ± 0.015	99.54 ± 0.12	2.36	28
FEN5	4.5 ± 0.022	250.12 ± 0.18	0.36 ± 0.021	99.68 ± 0.11	2.17	8
FEN6	4.7 ± 0.016	250.66 ± 0.23	0.28 ± 0.013	99.73 ± 0.17	1.52	12
FEN7	4.3 ± 0.015	250.21 ± 0.15	0.64 ± 0.006	99.78 ± 0.13	2.34	14
FEN8	4.5 ± 0.008	250.18 ± 0.12	0.49 ± 0.012	99.83 ± 0.10	2.21	18
FEN9	4.6 ± 0.012	250.86 ± 0.13	0.38 ± 0.011	99.92 ± 0.13	1.89	14
FEN10	4.5 ± 0.011	250.16 ± 0.11	0.69 ± 0.008	99.83 ± 0.11	2.21	16
FEN11	4.7 ± 0.013	250.12 ± 0.19	0.56 ± 0.011	99.78 ± 0.14	2.02	18
FEN12	4.9 ± 0.010	250.73 ± 0.09	0.43 ± 0.007	99.97 ± 0.09	1.76	20

Table 12: Swelling studies of fexofenadine floating tablets formulated with different grades of HPMC

Formulation	*Swelling index*		
	After 1 hours	*After 2 hours*	*After 8 hours*
FES1	69.46	92.48	178.36
FES2	74.2	97.29	212.04
FES3	93.93	110.14	240.19
FES4	99.22	130.14	223.19
FES5	76.3	118.42	192.63
FES6	84.68	124.7	201.6
FES7	86.2	130.91	218.96
FES8	88.43	146.32	224.61
FES9	56.88	110.06	196.5
FES10	77.96	128.07	210.68
FES11	86.88	130.9	220.8
FES12	98.04	144.87	280.46

Table 13: Swelling studies of fexofenadine floating tablets formulated with different natural polymers

Formulation	*Swelling index*		
	After 1 hours	*After 2 hours*	*After 8 hours*
FEN1	54.34	78.93	149.24
FEN2	57.45	91.46	171.39
FEN3	60.12	98.56	157.23
FEN4	62.69	96.64	145.00
FEN5	50.24	76.89	144.00
FEN6	55.26	86.10	150.50
FEN7	59.56	96.46	159.34
FEN8	61.37	102.12	163.30
FEN9	51.32	74.40	142.29
FEN10	53.69	87.12	151.67
FEN11	55.34	92.54	163.43
FEN12	57.43	94.74	165.26

also consisted of 146°C. Therefore it was brought to confirmation that drug and excipients were compatable (Fig. 7).

Precompression Parameters

The drug and polymer powders blends of different combinations were evaluated for bulk density, tapped density, carr's index, hausner's ratio and angle of repose using standard procedures, from the results obtained it was observed that there were no deviations from standard, the results were shown in Tables 9 and 10.

In-vitro Dissolution Studies of Semi Synthetic Polymers

In vitro dissolution studies of Fexofenadine, floating tablets were evaluated in 0.1 N HCl (pH 1.2) for 24 hours. The cumulative percentage of drug released from the tablets containing three natural polymers in (bhara gum, grewia gum and mucuna gum,) in specified ratios (1:0.25, 1:0.5, 1: 0.75 and 1:1) was compared.

The in vitro drug release profiles for the formulations FEN1–FEN12, FBN1-FBN12 were summarized. The curves of cumulative percentage of drug released vs. time (hours) for all the formulations were plotted and are depicted in Figs 11 to 13.

The floating drug delivery systems can extend the drug release and thus increase the overall drug bioavailability. The formulations (FEN1–FEN4) containing bhara gum showed decrease in drug release with increase in concentration of bhara gum. The drug release from the formulation FEN2 containing drug and natural polymer in 1:0.5 ratios exhibited nearly 100% (99.47 ± 0.23) drug release at 24 hours. For all the other formulations FEN6 and FEN10 prepared with grewia gum, mucuna gum in 1:0.5 ratio, respectively showed nearly 100% of drug release at the end of 12th and 16th hours, respectively.

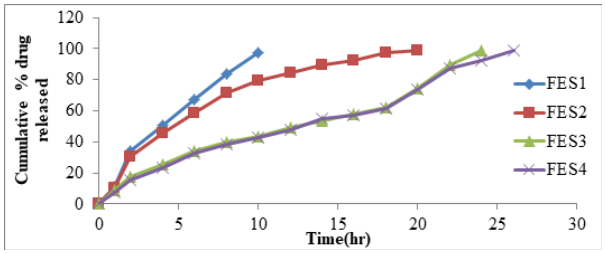

Fig. 8: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using HPMC K4M

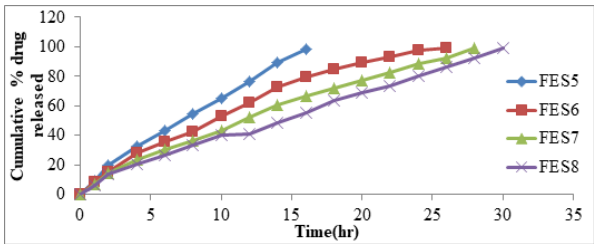

Fig. 9: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using HPMC K15M

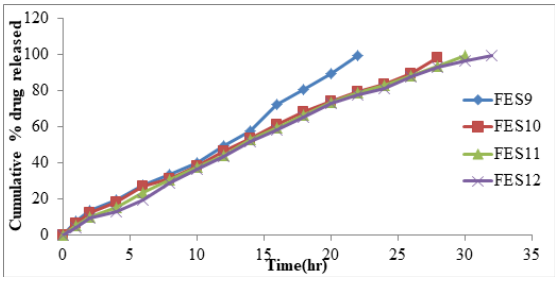

Fig. 10: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using HPMC K100M

Out of all the three set of natural polymers used, bhara gum had maximum release at the end of 24 hours using 1:0.5 ratio, where as other gums like mucuna and grewia gum had shown maximum release at the end of 18, 20 hours even after using 1:1 ratio, therefore it may require even more concentration to extend the drug release for 24 hours.

In-vitro Dissolution Studies of Natural Polymers

In vitro dissolution studies of FEX, Febuxostat floating tablet were evaluated in 0.1 N HCl (pH 1.2) for 12 hours. The cumulative percentage of drug released from the tablets containing three viscosity grades of HPMC (K4M, K15M and K100M) in specified ratios (1:0.25, 1:0.5, 1:0.75 and 1:1) were compared.

The *in-vitro* drug release profiles for the formulations FES1–FES12 were summarized. The curves of cumulative percentage of drug released vs. time (hours) for all the formulations were plotted and are depicted in Figs 7 to 9. Drug release was found to decrease with an increase in polymer concentration. Drug release was maximum (99.38 ± 0.72%) for formulation FES3, FBS4 (99.44 ± 0.29%) at the end of 24 hours, which was constituted with low viscosity HPMC K4M. The increased density of polymer at higher concentration results in an increased diffusional

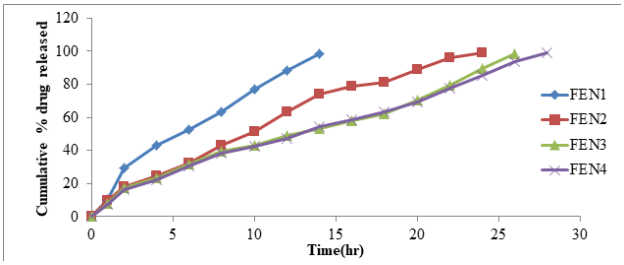

Fig. 11: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using Bhara gum

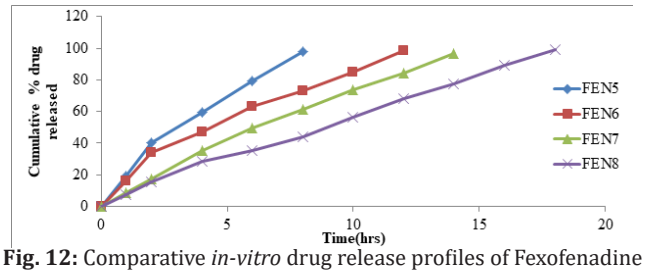

Fig. 12: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using Grewia gum

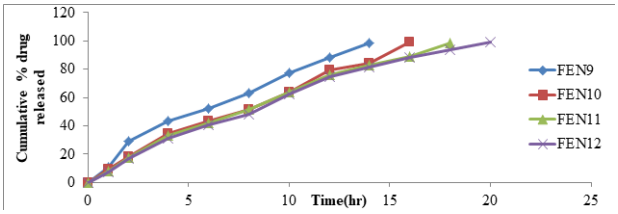

Fig. 13: Comparative *in-vitro* drug release profiles of Fexofenadine floating tablets formulated using Mucuna gum

pathlength, which leads to an overall decrease in release of the drug. Although composition of HPMC K15M and HPMC K100M sustains the drug release for a longer period of time up to 15 hours, this controlled release of drug could be attributed to the formation of a thick gel structure that delays the drug release from the tablet matrix.

Mathematical Model Fitting of Obtained Drug Release Data

The mechanism of drug release for the above formulations was determined by calculating the correlation coefficient for the kinetic models, viz., zero-order, first-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation.

Stability Studies

Stability studies results were depicted in Table 11 and 12.

Discussion

Preformulation studies were performed and it clearly infers that the drug showed maximum absorbance at 225 nm and Fig. 1. From the compatibility studies, it was evident that the drug selected is FEX as shown in Fig. 2, similarly from the Figs 3 and 4 it was observed that drug was compatible with other ingredients such as HPMC and bhara gum. From DSC studies it was observed that the formulation

Table 14: Zero order and first order release rate constants and correlation coefficient (r) values of Fexofenadine matrix tablets using Semisynthetic polymers and Natural polymers

Formulation code	Zero order		First order		Formulation code	Zero order		First order	
	K_0 (mg/hr)	R^2	K_1 (hr^{-1})	R		K_0 (mg/hr)	R^2	K_1 (hr^{-1})	R
FES1	9.59	0.9740	0.323	0.8704	FEN1	6.71	0.9741	0.237	0.8219
FES2	7.80	0.9552	0.200	0.9411	FEN2	5.35	0.9801	0.152	0.8404
FES3	4.20	0.9630	0.119	0.6306	FEN3	4.34	0.9823	0.109	0.7047
FES4	3.81	0.9340	0.117	0.7097	FEN4	3.26	0.9898	0.103	0.7258
FES5	5.98	0.9938	0.202	0.7997	FEN5	11.81	0.9747	0.440	0.8563
FES6	3.97	0.9687	0.151	0.8926	FEN6	7.65	0.9651	0.278	0.8195
FES7	3.42	0.9878	0.115	0.7936	FEN7	6.8	0.9919	0.200	0.8645
FES8	3.12	0.9950	0.101	0.7394	FEN8	5.3	0.9968	0.185	0.7344
FES9	4.34	0.9925	0.143	0.6997	FEN9	6.71	0.9741	0.237	0.8219
FES10	3.38	0.9956	0.111	0.7840	FEN10	5.90	0.9904	0.208	0.7275
FES11	3.33	0.9924	0.106	0.7890	FEN11	5.38	0.9843	0.181	0.8411
FES12	3.20	0.9905	0.101	0.8330	FEN12	5.01	0.9789	0.175	0.8469

Table 15: Floating characteristics before and after Storage

Formulations	*Floating characteristics*			
	Before Storage		*After Storage*	
	Floating Lag time (min)	*Floating time (hr)*	*Floating Lag time (min)*	*Floating time (hr)*
FES3	1	24	1	24
FEN2	1.23	24	1.23	24
FBS4	1.0	24	1.0	24
FBN3	1.56	24	1.56	24

Table 16: *In-vitro* dissolution data of optimized Fexofenadine floating tablets (FES3) tested at 40 ± 2°C/75 ± 5% RH for 3 months

Time(h)	*- Percentage of FEX Released ($\bar{x}$ ± sd)*	
	Test	*Reference*
0	0	0
1	8.52 ± 0.71	8.51 ± 0.33
2	17.40 ± 0.47	17.15 ± 0.54
4	25.32 ± 0.19	25.19 ± 0.33
6	34.21 ± 0.42	33.20 ± 0.55
8	39.86 ± 0.51	38.55 ± 0.29
10	43.73 ± 0.61	42.99 ± 0.20
12	49.21 ± 0.52	48.44 ± 0.29
14	53.44 ± 0.76	53.99 ± 0.02
16	57.86 ± 0.48	57.44 ± 0.19
18	62.32 ± 0.62	62.20 ± 0.33
20	74.47 ± 0.18	74.99 ± 0.25
22	89.51 ± 0.57	89.22 ± 0.44
24	99.38 ± 0.72	99.15 ± 0.26

Table 17: *In-vitro* dissolution data of optimized Fexofenadine floating tablets (FEN2) tested at 40 ± 20 C/75 ± 5% RH for 3 months

Time (h)	*- Percentage of FEX Released (x ± sd)*	
	Test	*Reference*
0	0	0
1	9.44 ± 0.33	9.01 ± 0.67
2	18.33 ± 0.19	18.01 ± 0.88
4	24.36 ± 0.41	24.45 ± 0.39
6	32.19 ± 0.20	32.25 ± 0.66
8	43.22 ± 0.67	43.37 ± 0.39
10	51.47 ± 0.24	51.52 ± 0.57
12	63.44 ± 0.72	63.37 ± 0.36
14	74.20 ± 0.15	74.33 ± 0.19
16	79.07 ± 0.48	79.12 ± 0.63
18	81.47 ± 0.64	81.20 ± 0.64
20	89.23 ± 0.77	88.69 ± 0.41
22	96.29 ± 0.43	95.43 ± 0.29
24	99.47 ± 0.23	99.63 ± 0.47

of FEX had showed a melting point of 148°C. This was clearly found in literature that it was within the range. The optimized formulation also consisted of 146°C. Therefore it was brought to confirmation that drug and excipients were compatible. Fig. 5 shows the melting point of pure drug, Fig 6 shows that

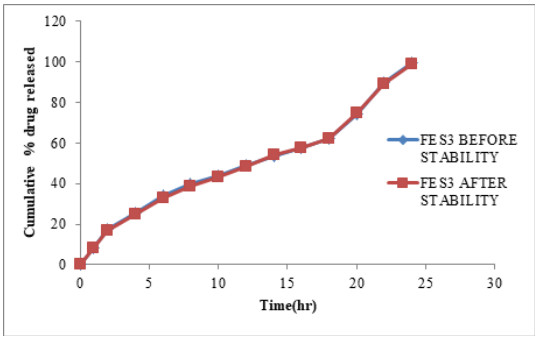

Fig. 14: Cumulative % drug released before and after storage

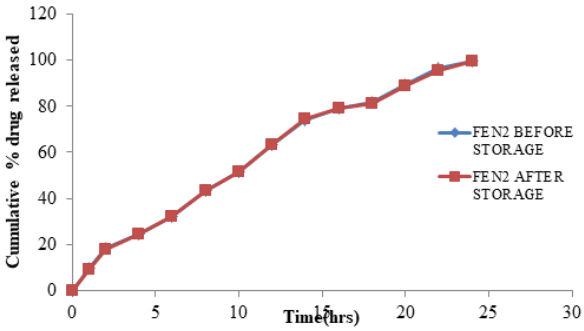

Fig 15: Cumulative % drug released before and after storage

other excipients were also found compatible.

The drug and polymer powders blends of different combinations were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures and consistency in data obtained as indicated by their standard deviation values shown in Tables 5 and 6.

The obtained values of all the derived properties of powder combinations were within the limits, indicating that the powder blends possessed the required flow property for tablet compression.

The formulated floating tablets were subjected for post compressional evaluation such as hardness, weight variation, friability, uniformity of drug content, *in-vitro* buoyancy, swelling, *in-vitro* dissolution and stability. The results are summarized in Tables 7 and 8. It was found that the values obtained were with in the limits.

The floating tablets with low-viscosity grade HPMC K4M exhibited shortest floating lag time of 1-minute and maximum 1.8 minutes. Whereas other grades of HPMC like HPMC K15M and K100M showed floating lag time in between 1.18-2.12 which is high compared to HPMCK4M. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer (HPMC) influenced the *in-vitro* buoyancy. An increase in HPMC concentration in the formulations decreased the floating lag time. Therefore polymer type and concentration affected the *in-vitro* buoyancy of floating tablets. Similarly with regard to natural polymers, it was clearly observed that Bhara gum had shown promising results. In case of FEN2 and FBN3 the FLT were 1.23 and 1.56 second, respectively, which were relatively shortest when compared to other natural polymers. These values infer that the carbon dioxide generated from gas generating in presence of dissolution medium (0.1N HCl) was trapped in the polymer gel matrix formed by the hydration of polymer which decreases the density (<1) and makes the tablet buoyant.

The swelling index of floating tablets of FES1–FES12, FEN1-FEN12 were shown in Tables 9 and 10. Floating tablets prepared using HPMC K4M and HPMC K15M (FES1 to FES8) swelled rapidly at the beginning in 0.1 N HCl and could remain their matrix integrity up to 8 hours. The swelling index was increased with concentration of HPMC since this polymer gradually absorbs buffer due to hydrophilic nature. The HPMC grade affects the swelling and hydration with considerably higher swelling index for HPMC K4M than HPMC K15M and HPMCK100M. HPMC K100M (FES9-FES12) exhibited low swelling index which could be due to its high viscosity and high water retention property. It was observed that FES3 had swelling index of 240.19% at the end of 8^{th} hours.

The swelling index of all the formulations prepared by natural polymers were determined by water uptake of the floating tablets. The percent swelling was evaluated at 1, 2 and 8^{th} hours. The complete swelling was achieved by the end of 8^{th} hours. The highest swelling (171.39%) was found in formulation FEN2 when compared to other formulations and least percentage of swelling (142.29%) was observed in formulation FEN9 at 8^{th} hours time. There was significant difference observedon swelling property by varying the concentration and type of natural polymers used. Similarly, in case of FBN3 the swelling index was 107.9% at end of 8^{th} hours.

There was considerably increase in percent swelling of the floating tablets with an increase in the concentration of bhara gum. Similarly, increasing concentration of other two gums used in this study also increased swelling but was relatively lesser than Bhara gum.

The results of the kinetic models are summarized in Table 14. For most of the formulations the correlation coefficient value of Korsmeyer–Peppas and zero-order model was nearer to one than those of other kinetic models. Thus, it could be drawn from the results that the drug release follows zero-order and Korsmeyer–Peppas model mechanisms.

An inverse correlation was observed between zero order release rate constant and drug-polymer ratio. As the polymer concentration increased, a decrease in the release rate was observed indicating the good correlation with a correlation value of 0.9956 and 0.9047 for FEX. It was clearly understood that natural polymer had performed better from correlation values compared to semisynthetic polymer.

The 'n' values of Korsmeyer–Peppas model for the best formulations were in the range of 0.45–0.85. Therefore, the most probable mechanism of release was found tobe non-Fickian diffusion or anomalous diffusion for the formulations tested. It was observed that the best formulations were by using HPMCK4M and bhara gum. These were further studied for stability. The optimized formulations FES3, FEN2 were subjected to accelerated stability studies as per ICH guidelines and the results of floating characteristics and drug