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Research Article

FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING MATRIX TABLETS OF NEVIRAPINE

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ABSTRACT

The purpose of the study was to formulate floating matrix tablets of Nevirapine (NVP), an Anti-HIV agent. Inspite of long half life (45 hrs) a Nevirapine extended release (NVP ER) once daily tablet formulation could be used to maintain optimum peak plasma concentration for effective viral suppression. Floating drug delivery system is suitable for NVP as the absorption and solubility of NVP is high at pH<3. The absorption rate of NVP was decreased from upper part to lower part of GIT and from jejunum to descending colon. Hence, the present investigation was aimed at developing floating drug delivery system for NVP at a dose of 400mg daily as they are not available in the market. NVP floating tablets were prepared by direct compression method employing rate controlling polymers like HPMC K_4M and Ethocel (7-10 cps). Prepared tablets were evaluated for weight variation, hardness, friability, drug content, invitro buoyancy studies and invitro dissolution studies. It was concluded that the formulation F13 was the best formulation as the extent of drug release was found to be 94.25 %. It also showed immediate flotation of about 15 secs with total flotation of about 24 hrs.

Keywords: Nevirapine**,** Gastro retentive**,** Floating matrix tablets, HPMC, Ethocel.

INTRODUCTION

The oral route is the most frequently used route for drug administration. Oral dosage forms are intended for systemic effects resulting from drug absorption through gastro intestinal tract. Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose. [1] Therefore, different approaches have been proposed to retain the dosage form in the stomach. These include floating systems, bioadhesive systems, swelling, expanding systems, delayed gastric emptying systems and low density super porous systems. [2-8] Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance, non-evasive in nature and flexibility formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. A gastric drug delivery system (GFDDS) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. [9], [10]

Nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immuno-deficiency virus type 1 (HIV-1), block polymerase activity after binding directly to the HIV-1 reverse transcriptase leading to disruption of the enzyme's catalytic site.[11] NVP is a weak base with low water solubility, and belongs to BCS class II drug. In human, NVP is well absorbed orally with an estimated absolute bioavailability of about 90%. [12, 13]

Floating drug delivery system is suitable for NVP as the absorption and solubility of NVP is high at pH<3 [14]. The absorption rate of NVP was decreased from upper part to lower part of GIT and from jejunum to descending colon [15]. Thus, floating oral delivery system is expected to remain buoyant in a lasting way upon the gastric contents and enhance bioavailability. The major objective of the present investigation was to develop a gastroretentive drug delivery system containing NVP using different polymers.

MATERIALS AND METHODS

Materials

Nevirapine obtained as a gift sample from Aurobindo Pharma Pvt. Ltd, Hyderabad; Ethyl cellulose (7-10 cps) obtained from Lobba Chemie, Mumbai; Hydroxy Propyl Methyl cellulose (K_4M grade) was obtained from Colorcon, India; Micro crystalline cellulose (Avicel PH 102, PH 101) was obtained from FMC, Ireland/U.S.A; Di-calcium Phosphate was obtained from Finar; Sodium Bicarbonate was obtained from Hi pure fine chem, Chennai; Talc and Magnesium stearate was obtained from SD-Fine Chemicals.

METHODS

Solubility studies

Solubility of drug was determined at 25 ± 0.5°C, in distilled water and wide range of pH solutions of 0.1 N HCl , pH 4.6, pH 6.8 and 7.2. The solubility results are displayed in Figure 1. Because NVP is weak basic drug (pKa 2.8), an increase in solubility was anticipated with decrease in pH. The pH solubility profile indicated a gradual decline in solubility with an increase in pH from 0.1 N HCl (1.703 mg/mL) to 4 .6 (0.252 mg/mL) and remained steady at pH 7 and 7.2 (0.1 mg/mL). The solubility of NVP decreased by approximately, 85% with an increase in pH from 1.2 to 4.6. These results (Table1, Fig: 1) revealed that the solubility of NVP was pH dependent, which was in accordance with the reported literature.

FTIR Studies

The FTIR studies were done to characterize the drug. The infra red spectrum for pure drug and polymers are given in fig. 2 - 7.The peak observed at 758.787 cm^{-1} is characteristic of the C-H bending of aromatic group. The peak produced at 1289 cm^{-1} is characteristic of C=O stretching seen in alcohols. The peak observed at 1461 cm^{-1} is typical of C=C stretching of aromatic group. The peaks observed at 1585 cm^{-1} and at 1643 cm^{-1} are characteristic of N=N and C=N stretching. The peak observed at 3184 cm^{-1} is characteristic of C-H alkene group present in the molecule. No interactions between polymers and drug were observed from the spectrum.

Table 1: Solubility study of Nevirapine

Solubility	Concentration (mg/1ml) ± SD
0.1 N HCl	1.703 ± 0.004
pH 4.6	0.252 ± 0.001
pH 6.8	0.114 ± 0.003
Distilled water	0.1 ± 0.004
pH 7.2	0.1 ± 0.006

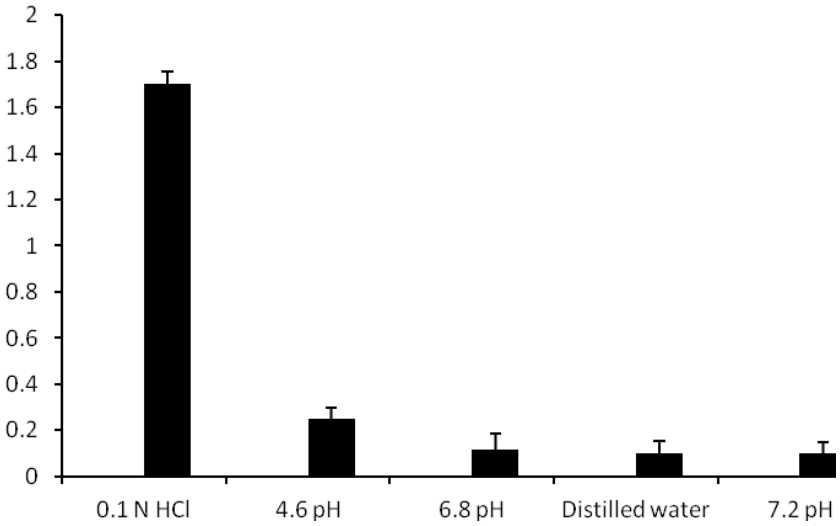

Fig. 1: Solubility study of NVP

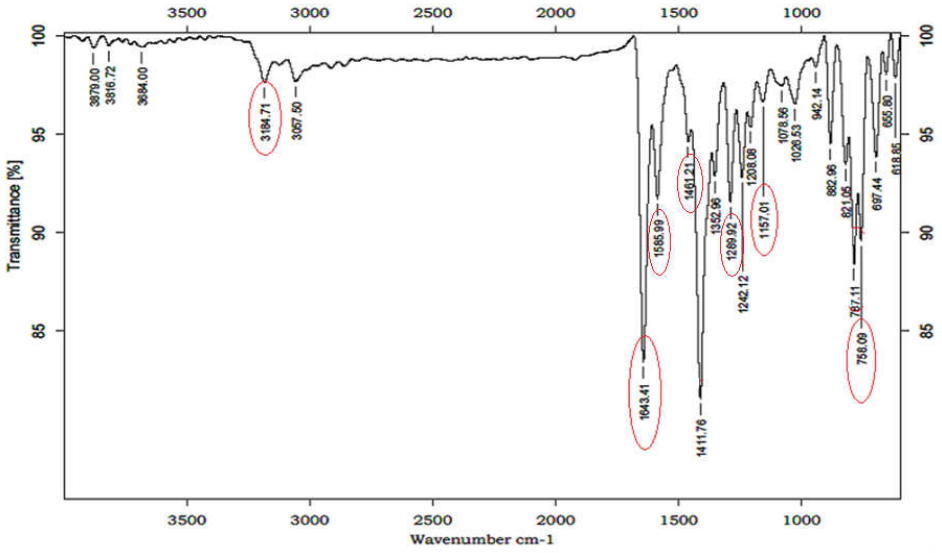

Fig. 2: FTIR spectrum of NVP (pure drug)

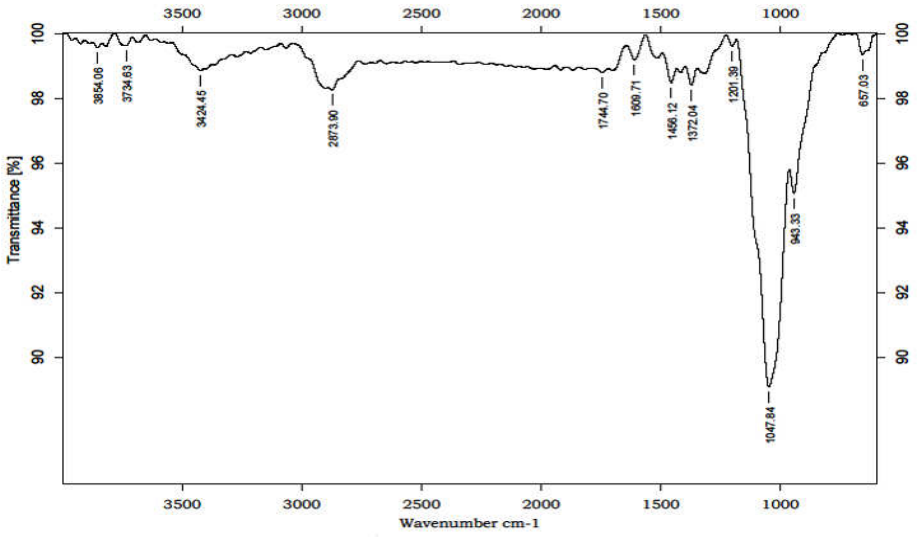

Fig. 3: FTIR spectrum of HPMC

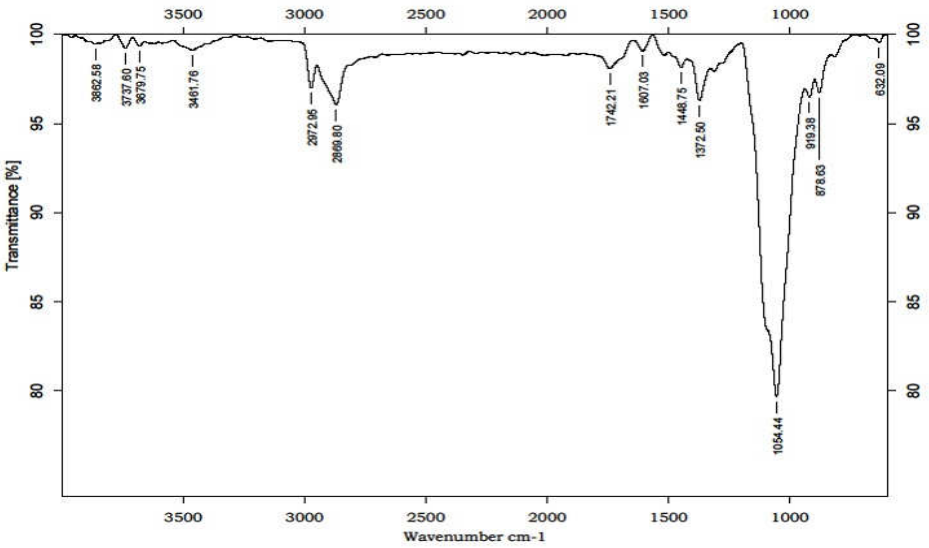

Fig. 4: FTIR spectrum of Ethyl Cellulose

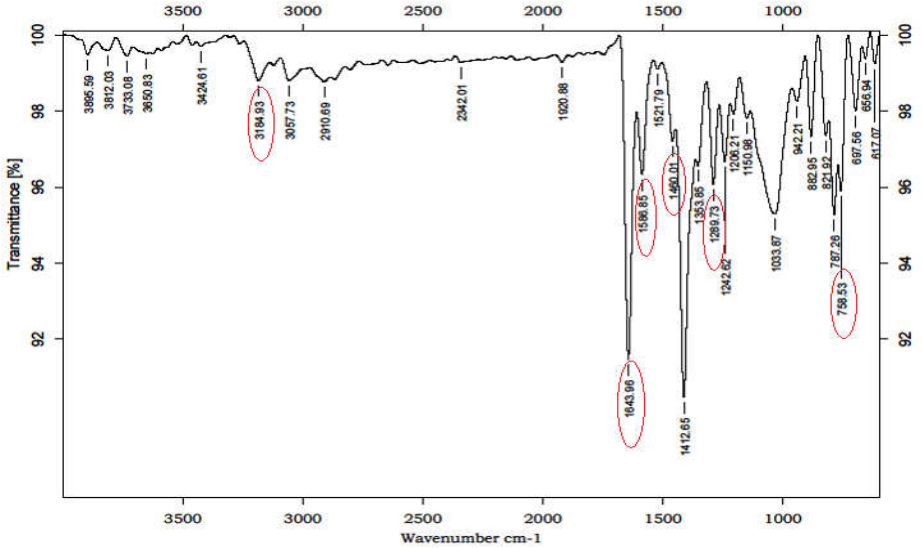

Fig. 5: FTIR spectrum of NVP+HPMC

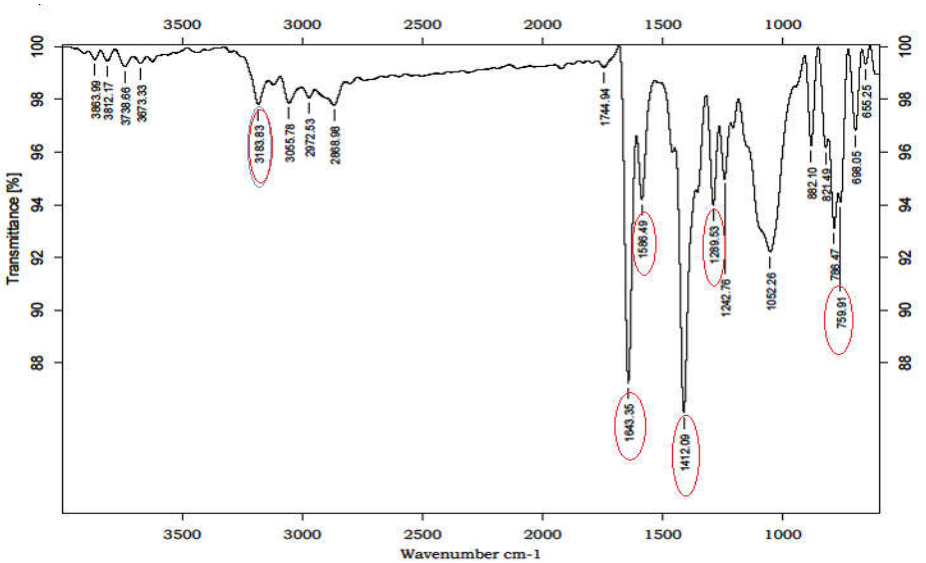

Fig. 6: FTIR spectrum of NVP+ Ethyl cellulose

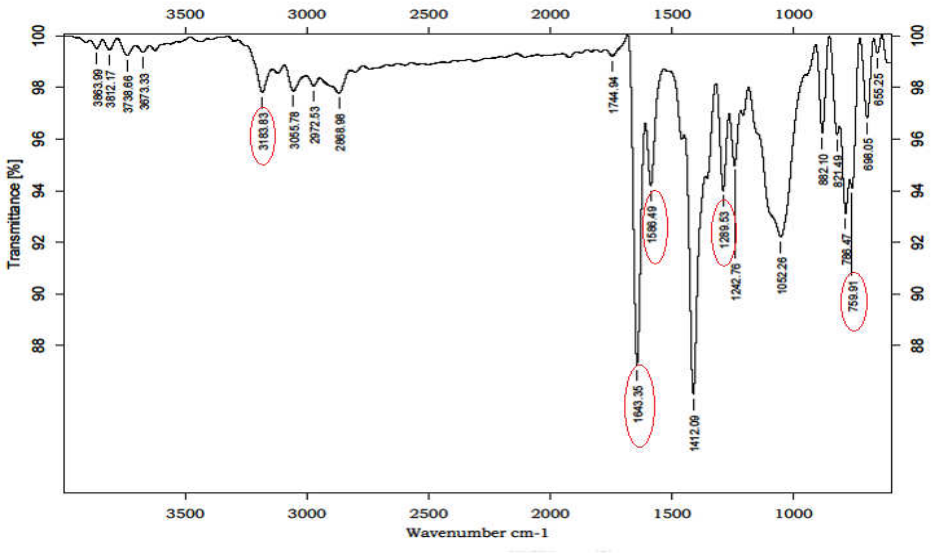

Fig. 7: FTIR spectrum of NVP+$NAHCO_3$

Table 2: Composition of floating matrix tablets for F1-F4

Formulation Ingredients	FI (mg)	F II (mg)	F III (mg)	F IV (mg)
Nevirapine (NVP)	400	400	400	400
HPMC K_4M	180	160	160	155
$NAHCO_3$	300	320	300	300
ETHOCEL	-	-	-	-
MCC (AVICEL PH 102)	-	-	-	-
MCC (AVICEL PH 101)	-	-	-	-
DCP	16	16	36	41
Magnesium Stearate, Talc	4	4	4	4

Table 3: Composition of floating matrix tablets for F5-F13

Formulation Ingredients	FV (mg)	FVI (mg)	FVII (mg)	FVIII (mg)	FIX (mg)	FX (mg)	FXI (mg)	FXII (mg)	FXIII (mg)
NVP	400	400	400	400	400	400	400	400	400
HPMC K_4M	150	150	150	140	145	110	120	140	130
$NAHCO_3$	300	300	300	300	300	300	300	300	300
ETHOCEL (7-10 cps)	-	-	-	-	-	45	45	45	45
MCC (AVICEL PH 102)	-	-	46	56	51	40	30	10	20
MCC (AVICEL PH 101)	-	46	-	-	-	-	-	-	-
DCP	46	-	-	-	-	-	-	-	4
Mg stearate, Talc	4	4	4	4	4	5	5	5	5

Preparation of floating matrix tablets [4], [7], [16], [17]

Accurately weighed quantities of API, polymer was passed through sieve no #40 and remaining ingredients were added to the blend in a polybag and mixed well for 10 minutes. Sufficient quantities of diluents (Micro crystalline cellulose, Dicalcium phosphate) were used to raise the total bulk of the tablets to a weight of 900mg each.

The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 12 mm round punches to the hardness of 4-6 kg/cm^2. These fabricated tablets were evaluated. The tablets were white round and the details of composition are given in Table 2, 3.

Post Evaluation parameters

Weight variation test[2], [6], [15]

20 tablets were selected at random, individually weighed and the average weight was calculated. None of the tablets deviated from the average weight by more than ±7.5%.

Hardness test[5], [8]

Tablets require a certain amount of strength or hardness and resistance to friability to with stand mechanical shocks. The hardness of tablet was measured by Monsanto hardness tester.

Friability[2], [8], [11]

Twenty tablets were weighed and placed in a Roche friabilator and the equipment was rotated at 25 rpm for 4 min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated by:

$$\% \text{ Friability} = \frac{\text{Initial friability- Final friability} \times 100}{\text{Final friability}}$$

Drug content[16], [17], [18]

Twenty tablets were selected randomly and transferred to a suitable tare container and weighed, and then average weight per tablet was calculated, the tablets were powdered with the help ofmortarand pestle. NVP solution was prepared by dissolving the required amount of powder in a suitable solvent. Absorbances of the resultant solutions were measured after suitable dilutions at 313 nm by UV/Visible spectrophotometer. The results were given in Table 4.

In-vitro buoyancy studies[19]

The in-vitro buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100 ml glass beaker containing simulated 0.1N Hydrochloric acid, as per USP. The time required for the tablet to rise to the surface and float was determined as the floating lag time. Total floating time was also determined and the results were given in Table 5.

In-vitro dissolution studies[7], [19]

In vitro dissolution studies were performed using type II (paddle) dissolution apparatus at 50 rpm and 900 ml of 0.1 N Hydrochloric acid (pH 1.2) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37±0.5°C. Five millilitres aliquot of the dissolution medium was withdrawn at specific time intervals. Absorbance of filtered solution was measured by UV–visible spectrophotometer at 313 nm, and the percent of drug released was determined using standard curve. Dissolution rate was studied for the prepared formulations and were given in Tables 5, 6 and represented in Fig 2, 3.

Table 4: Formulation Evaluation parameters (n=3)

Parameters Formulations	Hardness (kg/cm^2) ± S D	Percent Friability	Weight Variation ± SD	Drug content (mg/tab) ± SD
FI	4.47±0.15	0.6	900±0.15	400±1.25
FII	4.40±0.10	0.8	900±0.10	399±1.98
FIII	4.57±0.15	0.6	900±0.18	400±1.67
FIV	4.51±0.10	0.6	900±0.12	398±1.25
FV	4.50±0.10	0.9	898±0.04	400±0.98
FVI	4.32±0.12	0.7	900±0.06	400±0.65
FVII	4.21±0.08	0.9	900±0.08	400±0.54
FVIII	4.53±0.06	1.1	899±0.04	399±0.78
FIX	4.63±0.15	0.8	900±0.01	400±0.85
FX	4.71±0.12	0.8	900±0.02	400±0.97
FXI	4.52±0.11	0.6	899±0.05	400±0.36
FXII	4.50±0.10	1.2	900±0.05	399±0.84
FXIII	4.37±0.10	0.9	900±0.03	399±0.97

Table 5: In-vitro buoyancy study of Formulations

Batch	Floating lag time	Total floating time (hour)
F1	30 min	24
F2	15 secs	24
F3	doesn't float	24
F4	48 secs	24
F5	40 secs	24
F6	35secs	24
F7	35secs	24
F8	20secs	24
F9	15secs	24
F10	Fail	4
F11	Fail	4
F12	15secs	24
F13	15secs	24

RESULTS

Formulations were prepared by direct compression method using different polymers. Parameters like weight variation, hardness, friability, drug content, in-vitro buoyancy and in-vitro dissolution studies were performed and results are described in Table3, 4 and 5. All formulations evaluated for variation in weight and results indicated that for all formulations exhibit very low weight variation which lies within the pharmacopoeial limits i.e. Average weight ±7.5%. The hardness of the tablets was found to be in the range of 4.2 to 5.3 kg/cm^2. The percentage friability was less than 1% for all formulation ensuring mechanical stability of the formulated tablets. Content uniformity in all the formulations were found in the range of 98.32 ± 0.76 to 99.92 ± 0.57 indicating the compliance with the pharmacopoeia limits.

The FI formulation with polymer concentration of HPMC K_4M (20% w/w), and effervescent concentration of $NAHCO_3$ (33.3%) found to have a release percent of approximately 50%. The polymer concentration showed high retarding effect but the floating lag time for the formulation was found to be nearly more than 30 min. So the polymer concentration and effervescent concentration was changed to HPMC K_4M (17.7% w/w), $NAHCO_3$ (36.6%) in FII formulation. The release percent was found to be 66% in 24 hours with a lag time of 15secs, but the tablet was found to be dispersed slightly and does not retained till 24 hours due to increase in effervescent concentration. Hence, in the FIII formulation the effervescent concentration was reduced to $NAHCO_3$ (33.3% w/w) with same polymer concentration. The release percent was found to be 52%. However, the tablet didn't float.

To clearly visualize the effect of effervescent and polymer ratio on the flotation of tablet, the FIV formulation was formulated to contain HPMC K_4M (17.2% w/w), $NAHCO_3$ (33.3%) and the release percent was found to be only 54% in 24 hours with floating lag time of nearly 48secs. The formulation FV release was observed to be approximately 51% in 24 hours with floating lag time of about

40secs. The rate controlling polymers used were HPMC K_4M (16.6% w/w) along with $NaHCO_3$ (33%) and DCP (5.1%) as diluent.

The FI to FV formulations are prepared using Di-calcium phosphate (DCP) as diluent. In order to compare the effect of diluent on the release of the drug, the formulations FVI and FVII were prepared with Micro-crystalline cellulose of different grades (101,102) as a diluent along with HPMC K_4M (16.6 % w/w) and $NaHCO_3$ (33%). The floating lag time for the formulations FVI and FVII, were found to be nearly 35secs but the release was found to be more (nearly 75%) in formulation containing Avicel (102) as a diluent rather than formulations containing DCP (51%) or Avicel 101 (71%).

As Avicel 102 has a fast wicking rate of water than 101, it enhances drug dissolution by speeding tablet disintegration, using disintegration mechanism of wicking. Hence, the remaining FVIII to FXIII formulations are prepared using MCC 102 as a diluent. In order to increase the release, FVIII formulation was formulated with polymer concentration reduced to HPMC K_4M (16.11% w/w), the release was found to be about 72% with floating lag time of 20secs. The formulation FIX was formulated with HPMC K_4M (15.5%) and the release was found to be nearly 73% with a lag time of 15secs.

The formulations FX, FXI and FXII were formulated using the hydrophobic polymer Ethocel (7-10 cps) of about 5% along with hydrophilic polymer HPMC K_4M of about 12.2% w/w, 13.3% w/w, and 15 % w/w respectively. The FX, and FXI formulation tablets got dispersed with in 1hr and 100% release was found with in 4hrs in FX and FXI formulations due to decrease in the polymer concentration. The release percent was found to be approximately 76% with a floating lag time of 15secs in FXII formulation. In order to increase the release the polymer concentration was reduced in FXIII formulation.

The optimized formulae FXIII formulation with polymer concentrations of HPMC K_4M (14.4% w/w) and Ethocel (5%) showed better release profile with release of 94% in 24 hours with a floating lag time of 15secs.

Floating lag time from all the prepared formulations was found to be in the following order: **F1< F4< F5< F6, F7< F8< F9, F12, F13.**

% Cumulative drug release from all the prepared formulation was found to be in following order **F13> F12> F7> F9> F8> F6> F2> F4> F1> F3> F5.** % Cumulative drug release from F10 and F11 was found to be for 4 hours. Formulation F13 shows high % Cumulative drug release.

Table 6: Comparative drug dissolution profile mean± SD, (n=3) for F1-F6 Formulations

Time	% Cumulative drug release					
(hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	7.24± 0.33	8.24±0.58	6.09±0.62	7.35±0.33	6.94±0.40	8.90±0.66
1	16.75±0.25	10.93±0.74	9.49±1.35	9.44±0.51	12.06±0.80	10.64±0.42
2	22.60±0.41	21.25±0.073	13.33±3.61	15.11±0.53	18.78±1.03	15.73±1.00
3	31.28±0.23	31.10±0.36	16.97±3.39	21.94± 0.14	22.87±1.28	19.03 ±1.13
4	33.63±0.29	34.44±0.21	21.20±4.99	26.22±0.48	30.71±4.81	21.96±1.86
6	37.71±0.36	42.97±0.29	27.07±4.10	32.84±0.93	33.80±3.20	27.44±2.73
8	43.53±0.15	50.77±0.26	33.55±4.01	39.52±0.40	41.60±2.33	37.80±4.04
10	50.55±0.37	55.54±0.36	39.13±3.16	46.20± 0.71	44.32±0.94	44.58±4.06
12	52.71±1.00	64.71±0.25	48.69±4.08	50.75±0.85	49.04±1.65	46.76±5.34
24	53.96±0.23	66.33±0.37	53.66±0.99	54.08± 0.69	51.68 ± 0.84	71.72± 2.64

Table 7: Comparative drug dissolution profile mean± SD, (n=3) for F7- F13 Formulations

Time	% Cumulative drug release						
(hr)	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0
0.5	8.51±0.22	6.72±0.14	7.33±1.29	68.74±1.46	62.63±2.23	9.17±0.15	14.37±1.36
1	10.37±1.18	9.10±0.54	9.78± 2.05	81.77±0.42	84.45±11.72	13.45±0.87	18.22±1.88
2	15.14±1.98	11.94±1.71	13.18± 3.35	86.18±1.69	86.18±2.77	22.74±1.24	23.40±0.90
3	19.69±3.92	14.90±2.96	16.58± 3.02	88.62±1.46	87.65±3.35	29.79± 0.53	25.00±2.11
4	21.28±3.93	19.81±3.55	19.54± 3.15	94.49±3.30	94.49±2.96	32.41±1.90	32.52±2.29
6	27.73±4.34	26.70±5.35	25.51± 3.04	-	-	40.28±2.73	38.10±1.75
8	35.95±4.65	32.65±7.11	31.69± 3.91	-	-	44.37±0.25	45.83±4.06
10	43.92±4.37	39.62±8.37	39.37± 2.94	-	-	53.84±2.64	62.65±10.0
12	50.89±5.03	44.18±4.56	45.71± 2.38	-	-	62.45±4.03	88.11±1.13
24	75.90±1.28	72.90±0.68	73.40± 1.50	-	-	76.63±3.30	94.25±1.12

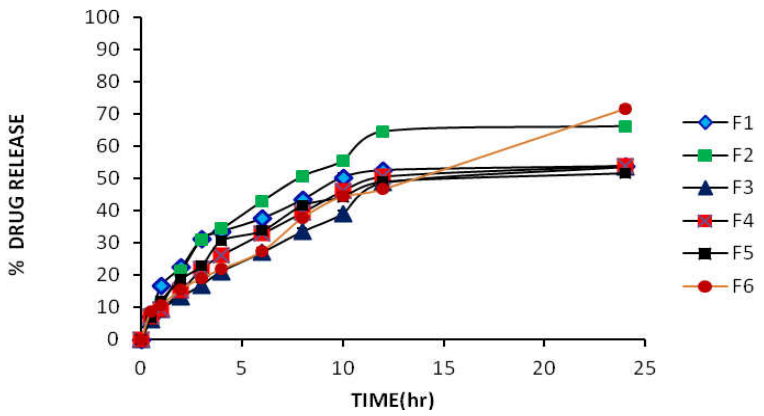

Fig. 2: Comparative drug dissolution profile mean± SD, (n=3) for F1-F6 formulations

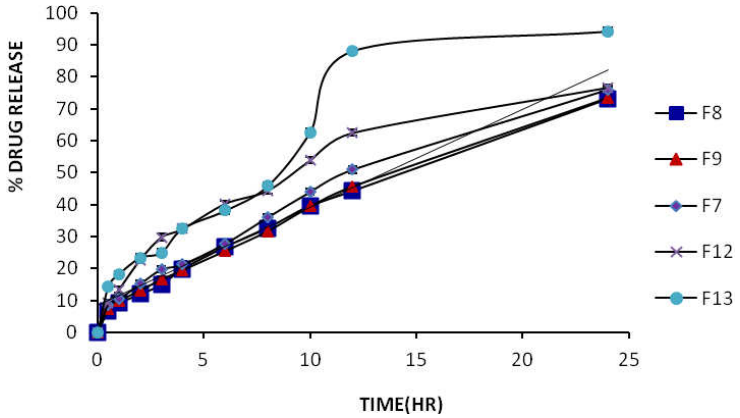

Fig. 3: Comparative drug dissolution profile mean± SD, (n=3) for F7-F13 formulations

DISCUSSION

Different formulations were prepared using different polymers like HPMC K_4M, Ethyl cellulose (7-10 cps). The tablets prepared by dry granulation technique were found to have adequate hardness, friability, content uniformity, floating lag time and total floating time.

Preformulation studies: Preformulation studies of the API showed that the drug has poor flow property. However, the flow property is good with blend in direct compression method.

FTIR studies were carried out on drug and polymers used. From the obtained spectra, it was clear that there was no drug-polymer interaction.

Hardness is maintained at 4kg/cm² approximately which is required for floating tablets (4-6kg/cm²). Friability and weight variation were within the limits.

In vitro drug release studies: Among the formulations used, FXIII shows maximum release of about 94% with a floating lag time of 15secs and the tablet was retained for 24 hrs.

Higuchi's plot showed that the release is by diffusion model. On extending this by using Peppas plot it is known that the release is by Non-Fickian transport.

Combination of hydrophobic polymer (EC) hydrophilic polymer (Methocel) increases the release rate. This is because of swelling of hydrophilic polymer was low in combination which helps in migration of the drug from the matrix.

Among the three diluents, drug release was found to be more with Avicel 102. The order of release with various diluents was:

Avicel 102 > Avicel 101 > DCP

Avicel 102 has a fast wicking rate of water than Avicel 101 which is best suited for direct tableting. It enhances drug dissolution by speeding tablet disintegration, using dual disintegration mechanisms of wicking and swelling for more rapid disintegration.

Tablets of all batches remained floatable throughout the study. It was concluded that the formulation F13 is the best formulations as the extent of drug release was found to be 94.5 % in 24 hours and total floating time was 24 hours.

Based on the results we can certainly say that floating type gastroretentive drug delivery system holds a lot of potential for drug having stability problem in alkaline pH or which mainly absorb in acidic pH. This route of drug delivery can certainly be explored for improved bioavailability and increased stability those drugs which degrades in intestinal pH for many existing drugs.

CONCLUSION

It was concluded from the above study that the floating matrix tablets of Nevirapine was successfully developed in order to sustain the drug release rate by using combination of Ethocel and HPMC as effective rate controlling polymers. Combination of hydrophobic polymer (Ethocel) and hydrophilic polymer (HPMC K_4M) increases the release rate. This is because of swelling of hydrophilic polymer was low in combination which helps in migration of the drug from the matrix. Ethocel was found to have profound influence on the in-vitro release profile of Nevirapine from the hydrophilic matrices. The buoyancy of tablets depends on the content of sodium bicarbonate and swelling property of the polymers. The tablets released the drug by Non-Fickian diffusion following First order release mechanism.

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