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Formulation and Evaluation of Floating Bioadhesive Tablets of Nevirapine

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ABSTRACT

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 thus the purpose of our study was formulation of floating bioadhesive tablets to increase the retention time of drug in its absorption area and decrease the dosing interval by increasing the bioavailability. The formulations were prepared by polymer such as hydroxyl propyl methyl cellulose (HPMC) and carbopol 934 in different ratio using direct compression technique. The effervescent base sodium bi carbonate and citric acid was used in 7.5% ratio. The present was concluded that the floating-bioadhesive tablets of Nevirapine can increase the gastric residence time as well as bioavailability. Thus better patient compliance can be achieved.

Keywords: Nevirapine, gastric retention, floating, bioadhesion

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INTRODUCTION

Among all drug delivery systems oral drug delivery system is the most popular route due to their several advantages over the conventional systems like; enhance patient compliance, less dosing frequency, non-interfering in nature, flexibility in designing of dosage form than the other route. Oral drug delivery is the most advantageous option as the oral route provides maximum active surface area than the all drug delivery system for administration of various drugs. In market more than 50% of drug deliveries available are oral drug delivery system.

Using various pharmaceutical dosage forms, like tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectable, as drug carriers for the treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients from many decades. Even today in the prescriptions these conventional drug delivery systems are the primary pharmaceutical products commonly seen; this type of drug delivery system is known to fulfil a motivate release of drug. It is often to take this type of delivery system several times a day to achieve as well as to maintain the drug concentration within the therapeutic range need for the treatment. This results in a significant deviation in the drug delivery [1].

Various technical advancements have been made and resulted in the development of new techniques for drug delivery to overcome this problem recently, which are capable of controlling the rate of drug release, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue [2, 3]. History tells that, Although these advancements have led to the development various novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic advantages and also draw some confusion in the terminology between “controlled release” and “sustained release”.

Floating drug delivery systems are useful for those drugs that are poorly soluble or unstable in intestinal fluids and goal of the system is to retain the drug in the stomach. The fundamental principle of the system is very simple i.e., to make the dosage form less dense than the gastric fluid so that it can float on them. The major disadvantage of the floating system is that they are efficient only when the fluid level in the stomach is sufficiently high. However, as the stomach empties and the tablet reaches the pylorus, the buoyancy of the dosage form may be obstructed[4]. This serious disadvantage can be overcome by making the system finally adhere to the mucous lining of the stomach wall[5]. Floating and bioadhesive drug delivery systems have the advantages of increased contact time with stomach mucosa, more effective and efficient absorption and bioavailability of

drugs with absorption windows near proximal intestine and stomach, with low dosing frequencies[4].

HIV Type 1

HIV-1 is the most common and pathogenic strain of the virus. Scientists divide HIV-1 into a major group (Group M) and two or more minor groups, namely Group N, O and possibly a group P. Each group is believed to represent an independent transmission of SIV into humans (but subtypes within a group are not).

Group M (major) this is the most common type of HIV, with more than 90% of HIV/AIDS cases deriving from infection with HIV-1 group M. The M group is subdivided further into clades, called subtypes.

Group N (non-M) patients suffering from this type were found only in Cameroon.

Group O (outlier) patients found within west central Africa. And it could not be detected in the early version of HIV-1 test kits.

Group P (pending the identification of further human cases) it has great similarity to a simian immune deficiency virus found in wild gorillas.

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. 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% [6].

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[6]. 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 METHOD

Materials

Nevirapine was procured as a gift sample from Ranbaxy laboratories Ponta sahib, Himanchal Pradesh. HPMC K4M, carbopol 934, magnesium stearate, talc, citric acid, sodium bi carbonate and lactose were supplied from Central drug house (P) LT.

Methods

The Preformulation studies include the observation of color, odor, taste, solubility analysis, melting point and compatibility studies. All the observations provide over all information that could help in the formulation. The Preformulation parameters may be sub divided into following parts:

Preformulation studies

A. Identification of API (Drug)

- Organoleptic properties
- FTIR spectroscopy study of ISDN sample with reference standard.

B. Solubility analysis.

C. Melting point.

D. UV spectroscopy of the drug.

E. Drug-excipients compatibility studies by FTIR spectroscopy studies.

Pre-compression parameters

A. Angle of repose

B. Bulk density

C. Tapped density

D. Hausner's ratio

E. Cars ratio

Post compression parameters

A. General appearance including shape, color, marking.

B. Weight variation

C. Thickness

D. Hardness

E. Friability

F. Disintegration time

G. Drug content (assay)

H. In vitro dissolution studies.

Preparation of Floating Bioadhesive Tablets

Direct compression method:

For the preparation of nevirapine bioadhesive floating tablets all the polymers and the active ingredients were passed through sieve no. 80 separately. Than the quantity of drug (nevirapine), polymer (HPMC K4M, carbopol 934), effervescent agents and excipients were accurately weighed and mixed using glass motar pestle. Automatic punching machine was used to prepare tablet with

desired hardness, shape and size. Direct Compression technique was employed for batch code from F_1 to F_6.

Table 1: formulation composition of different batches

S.no.	Ingredients (quantity/tablet) mg.	Batch code					
		F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)
1	Nevirapine	200	200	200	200	200	200
2	HPMC K4M	200	300	400	-	-	-
3	Carbopol 934	-		-	200	300	400
4	Sodium bicarbonate	30	30	30	30	30	30
5	Citric acid	15	15	15	15	15	15
6	Magnesium Stearate	2	2	2	2	2	2
7	Talc	3	3	3	3	3	3
8	Lactose	200	100	-	200	100	-

EVALUATION PARAMETER OF TABLETS

General appearance [7]:

The tablets were observing visually and evaluated. Appearance of the product is the crucial parameter of patient compliance also factors like size, shape, color, texture plays an important role. Tablets ware randomly pic and evaluated in the presence of light. To ensure that no chemical reaction occur between the drug and the excipients.

Weight variation [8]:

Twenty tablets selected at the random were weighed accurately and the average weight of the tablet was calculated. The standard of IP was followed to check the uniformity of tablets.

Uniformity of thickness [8]:

The thickness of the tablet was determined by using Vernier caliper that accurately measures the thickness of tablets. 10 tablets were selected and evaluated.

Hardness [8]:

A hardness of the tablets plays an important role in the manufacturing. The hardness test is performed to check the possible breakage that could occur due to any reason. As tablet should have strength to maintain its shape and size. Pfizer hardness tester was used to check the hardness.

Friability [7]:

Friability of the tablets was done to check the mechanical strength. Roche friabilator is used to check the friability. 20 pre weight tablets were placed in the fiabilator. The tablets were made to fall from a height of 6 inches for 4 minutes. The speed of the friabilator at 25 rpm. The loss in the weight of the tablets is the measure of friability and expressed in percentage as following:

% friability = {(initial weight – final weight) / initial weight}*100

% Friability of tablets less than 1% is considered as acceptable.

Measurement of Floating Capacity [9]:

The floating efficiency of the tablet defines the efficiency of the tablet to float due to the bouncy force. For testing the floating capability of the tablet three individual tablets were taken. The tablets were allowed to sink in a solution containing 400ml of 0.1(N) HCL solutions. The time taken by the tablet to come up from the base to the top was noted (floating lag time). The time for which the tablets float on the water surface (duration of floating) was measured. The sample mean and standard deviation were calculated.

Measurement of the Density of the formulation: [10]

The volume and the mass of the tablets were used to calculate the density. Thus the volumes V of the tablets were calculated from their height *h* and radius *r*. following formula was used to calculate the density of the tablet.

($\boldsymbol{V = \pi \times r^2 \times h}$).

Measurement of Bioadhesive Strength of the floating formulation [11]:

The modified balance was used to calculate the force required to separate the sample disk from a model substrate. The method was reported by Parodi et al. (1996). The formulation was made to come in contact with mucosal membrane of goat tongue; the tablets were left for 5 minute for hydrate. A beaker was placed on a moving platform. The beaker was then slowly raised until the substrate came in the contact with the formulation. A preload of 50g was placed into the stopper for 6min so that the adhesion bonding could be established. After this time, the preload was removed and was added at a constant rate. The addition was stopped as soon as the detachment of the two surfaces was obtained

Drug content:

Three tablets from each batch were selected randomly and crushed. The powder obtain was transferred to a 100ml volumetric flask containing 0.1(N) HCL. It was allowed to stand for 48hours. 1ml solution from each volumetric flask was transferred to the test tubes. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

***In-vitro* study:**

USP –II type dissolution apparatus (paddle type) was used for the study. The study was performed at 50 rpm in 900ml 0.1(N) HCL. 5ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium.

The absorption of withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the respective calibration curve

RESULTS AND DISCUSSION

Pre-formulation results:

Table 2: Result of Organoleptic properties.

S.No.	Organoleptic properties	
1.	Description	Solid
2.	Color	White to almost white colored
3.	Odor	Odorless
4.	Taste	Unpleasant
5.	Appearance	Crystalline

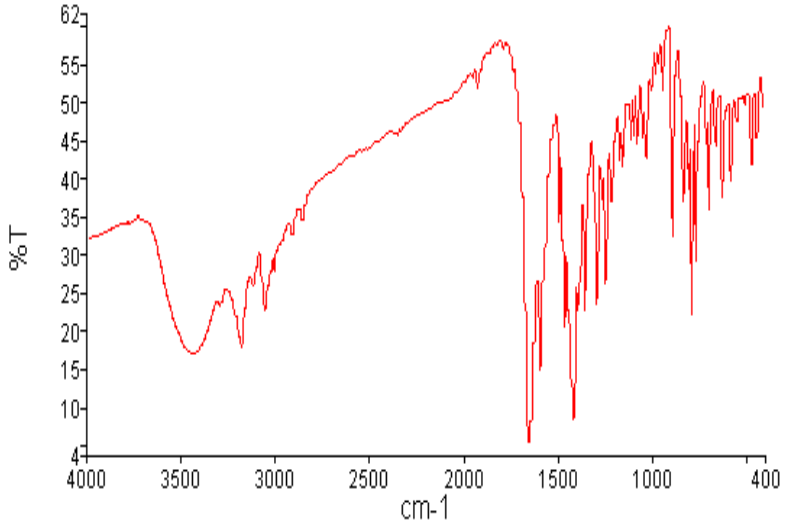

Figure 1: FTIR of the sample drug under investigation

Solubility analysis:

Table 3: Solubility analysis:

S.No.	Solvent	Solubility
1.	0.1N HCl	Soluble
2.	Di methyl sulphoxamide	Soluble
3.	Dichloromethane	Spirangly soluble
4.	Water	Practically insoluble

Melting point determination:

The temperature at which the powder of the drug starts to melt was found to be 240-244 ^{o}C.

UV Spectroscopy: Preparation of standard curve of Nevirapine in 0.1N HCl:

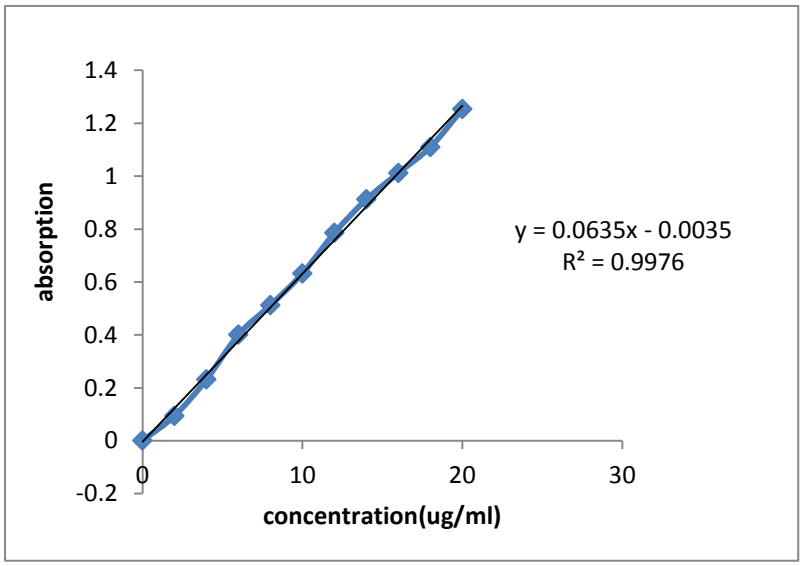

Figure 2:Calibration curve of nevirapine

Drug excipients compatibility studies:

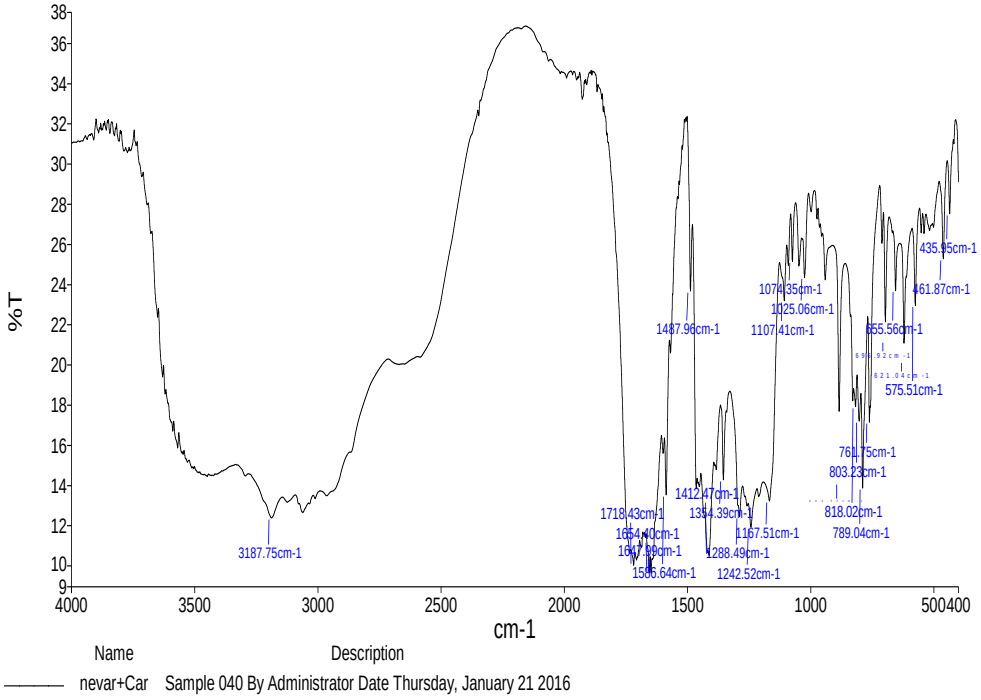

Figure3:FTIR of Nevirapine + HPMC K4M

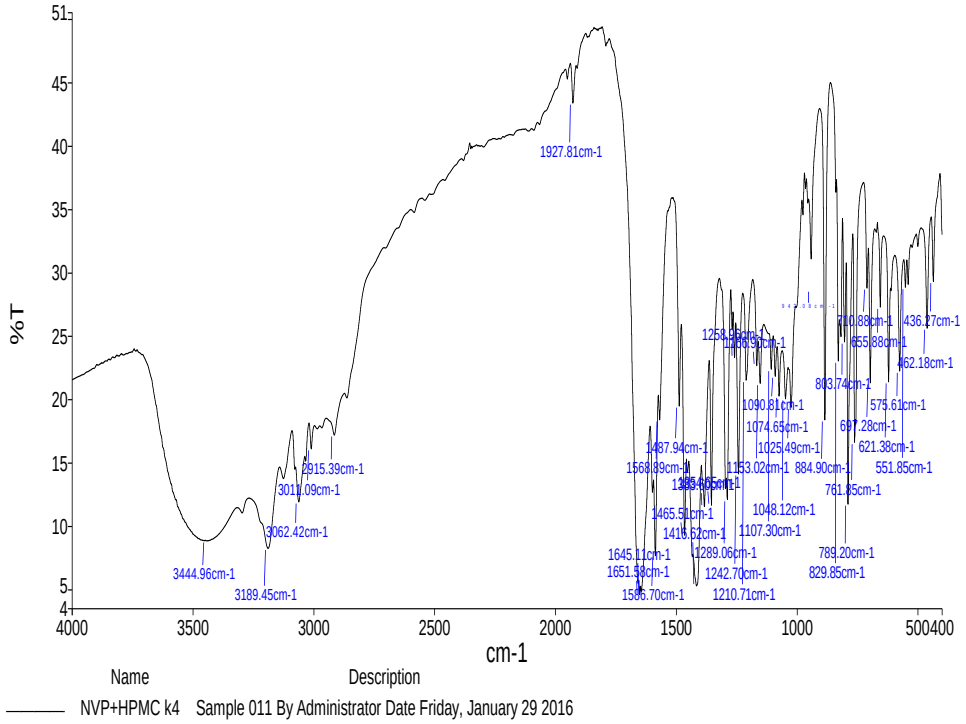

Figure 4: FTIR of Nevirapine + carbopol 934

Table 4: Pre-compression parameters

Drug	Angle of repose	Bulk density	Tapped density	Carr's ratio	Hausner's ratio
Nevirapine	38±3.1	0.28±0.015	0.40±0.019	28.57±0.32	1.40±0.32

Table 5: Post compression parameters

Parameters	F1	F2	F3	F4	F5	F6
Weight variation (mg) n=20	651.1±1.04	651.5±1.12	650.3±0.64	649.5±0.81	651.1±1.04	650.1±0.7
Thickness (mm) n=10	6.2±.02	6.1± .08	6.2±.03	6.3±.04	6.3±.01	6.2± .01
Hardness (kg/cm^2) n=5	3.24±0.102	3.46±0.16	4±0.08	3.6±0.11	4±0.08	4±0.04
Friability (%) n=20	0.6	0.5	0.6	0.7	0.5	0.6
Density	1.056±0.1	1.099±0.02	1.007±0.09	1.056±0.1	1.085±0.03	0.055±0.04
Floating lag time (min)	1.5±0.12	2.2±0.24	3±0.08	1.2±0.12	23±0.47	2.6±0.12
Floating duration (hrs.)	10±0.47	14±1.25	17±1.41	8±0.94	13±1.25	18±0.47

***In- vitro* profile of formulation 1 to 6:**

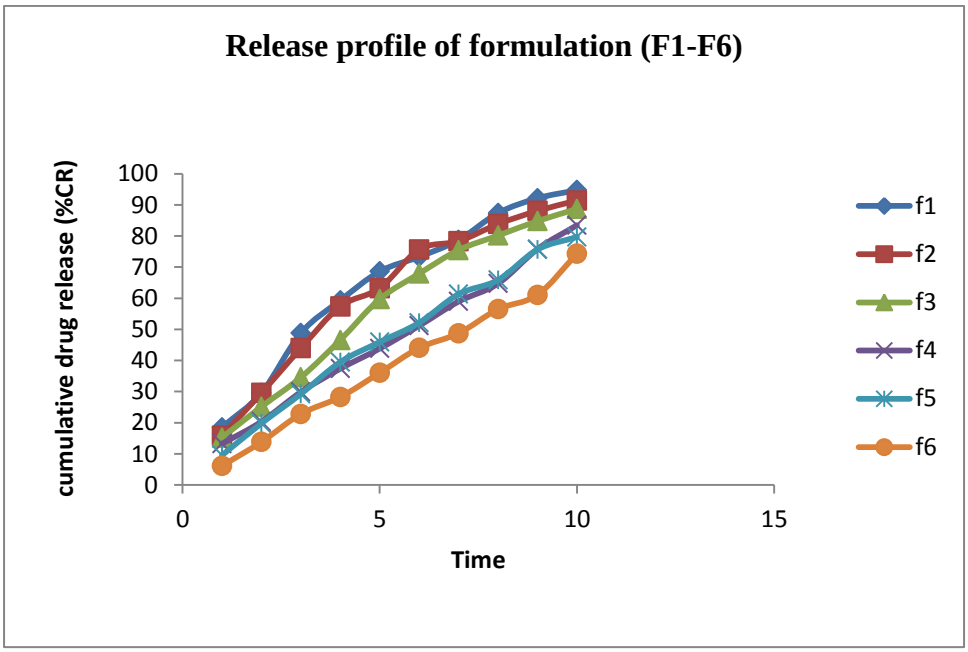

Figure 5: FTIR of Nevirapine + carbopol 934

Table 6: Table of correlation factor

Formulation code	Correlation Factor			Korsmeyer and Peppas (N)
	Zero (R^2)	First (R^2)	Higuchi (R^2)	
F1	0.945	0.965	0.988	0.721
F2	0.948	0.994	0.949	0.073
F3	0.969	0.997	0.969	0.079
F4	0.998	0.935	0.975	0.807
F5	0.991	0.985	0.991	0.089
F6	0.994	0.985	0.994	0.103

Photographic documents of formulation (F1 to F6) captured during floating capability study are shown below:

F1 F2 F3 F4 F5 F6

Figure 6: Photographic documents of formulation (F1 to F6)

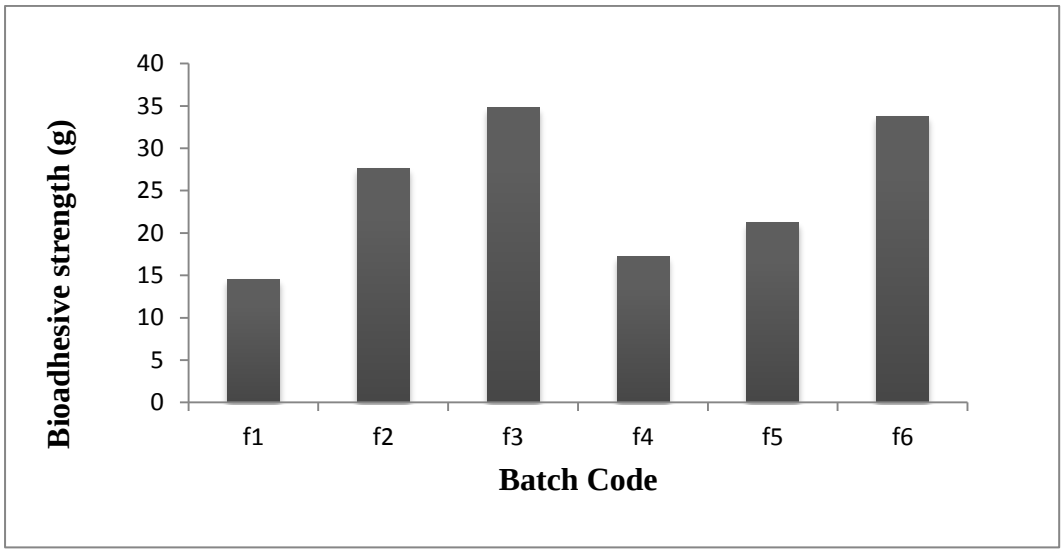

Figure 7: Bioadhesion strength of floating tablets of nevirapine measured by modified balance method (n = 3)

DISCUSSION

All the formulated floating tablets of Nevirapine were prepared by using different polymer like HPMC-K4M and Cabopol-934. The tablets were prepared by using direct compression technique. The tablets were found to be good quality in respect of size, hardness, and drug content as well as floating capability. Effervescent base of tablets were prepared by sodium bicarbonate and citric acid with combination in a ratio 7.5%.

Different formulation shows different values of floating lag time and floating duration was observed from the results of floating capability study. The result shows the floating lag time from about 1.5 to 3 min with effervescent base of tablets from 7.5%

The formulation batches F_1, to F_6 shows floating lag time. This was due to the use of 7.5% effervescent base that reduced the floating lag time. HPMC K4M may help to reduce the bulk density and increase the floating duration due to the porous structure of the polymer.

In case of F_3 the HPMC K4M was used in greater amount that may produce strong polymer integrity and create more porous structure than F_1 and F_2. Because of the light weight of carbopol 934 the F_6 formulation may have done the trick.

By using USP-II type dissolution apparatus the different batches of the prepared formulation of nevirapine were studied. The release rate and cumulative percentage drug release of the different formulations were observed.

Kinetic models describe drug release from immediate and modified release dosage forms [(12)]. From the result (table 6) obtained it was observed that the formulation shows the value of R^2 over

0.9 for zero order, higuchi and 1st order kinetic model. To predict the mechanism of diffusional release, equation **$M_t/ M_\infty = kt^n$** was used. Considering the **n** values calculated for the studied tablets (table no.6), in all cases fickian and non-fickian mechanism is dominant. Applying ANOVA (using stat plus 2007) to the formulation, it was found that all the formulation were statistically significant ($p \leq 0.05$). The excellent concept of floating system suffers from a disadvantage that it is effective only when the fluid level in the stomach is sufficiently high; however, as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage from may be impeded [13].

Floating and bioadhesive drug delivery systems offer the advantages of increased contact time with stomach mucosa, more effective absorption and bioavailability of drugs with absorption windows near proximal intestine and stomach, and low dosing frequencies[14]. The serious limitation can be overcome by using bioadhesive polymers to enable it to adhere to the mucous lining of the stomach wall. Bioadhesive strength was measured by modified balance method as reported by Parodi et al. for the prepared formulations. The result of the bioadhesion test (figure 7) shows that all the formulations pusses' good bioadhesive strength.

CONCLUSION

The present study concluded that the floating bioadhesive tablets of nevirapine can increase the gastric residence time as well as the bioavailability. The study also shows that the patient compliance can be achieved.

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