FORMULATION AND IN-VITRO EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM FOR NEVIRAPINE

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Abstract-

Floating matrix tablets of nvirapine were developed to prolong gastric residence time and increase its bioavailability. In the present investigation it was thought worthwhile to develop a gastric floating drug delivery system of nevirapine to improve the efficacy of dosage form. Inevirapine a potent antiviral drug with low toxicity used in treatment of HIV. It has maximum absorption in stomach and upper part of small intestine. Due to low gastric retention time, the bioavailability of drug is low as large portion of drug misses the absorption window. The tablets were prepared by direct compression technique, using polymers such as Hydroxy propyl methylcellulose(HPMC, Methocel K100M), Carbopol and Sodium alginate alone or in combination. Sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. The effects of sodium bicarbonate and citric acid on drug release profile and floating properties were investigated. All the tablets passed the compendial tests and other tests like weight variation, drug content, hardness, friability. The floating time was found to be more than 12 hrs. All the tablets showed the floating lag time of less than 10minute. The dissolution study was carried out in 0.1 N HCL using USP type II apparatus.

Keywords: Floating matrix, nevirapine, potent antiviral, direct compression, floating lag time.

INTRODUCTION

A significant obstacle may arise in development of oral controlled drug delivery if there is a narrow absorption window for drug in GIT, if a stability problem exists in gastrointestinal fluid and if the drug is poorly soluble in stomach or degrades colonic microbial environment. Thus the real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hrs but to prolong the presence of the dosage form in the stomach or somewhere in the upper small intestine until the drug is released for the desired period of time.Acquired Immuno Deficiency Syndrome (AIDS), which threatens to cause a great plague in the present generation. In reality AIDS is not a disease but a collection of seventy or more conditions which result from the damage done to the immune system and other parts of the body as a result of infection by HIV1. It is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment. There are a number of drugs that have been considered as to be anti HIV. The drugs like nevirapine appears most promising because it crosses the blood brain barrier and can be taken orally and in treaties they do not cause serious side effects nevirapine is the first approved compound for the treatment of AIDS; however the main limitation to therapeutic effectiveness of nevirapine is its dose-dependent toxicity, short biological half-life and poor bioavailability. This limitation can be overcome by formulating gastroretentive drug delivery systems which retained in the stomach and help in continuously releasing the drug, thus ensuring optimal bioavailability. The objective of this study was to develop a gastric floating drug delivery system (GFDDS) containing nevirapine.

MATERIALS AND METHODS

Nevirapine was obtained as gift sample from Mylan Pharmaceutical Ltd. Metolose was obtain from jitendra scientific, Jalgaon. Sodium CMC was obtained from commercial sources. Citric acid and Sodium Bicarbonate were gifts from SD Fine Chemicals, Mumbai, India. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Acyclovir floating matrix tablets

Sustained release nevirapine floating matrix tablets were prepared by direct compression method. Nevirapine with various concentrations of Metolose and SCMC were used as a Release retardant polymer. Sodium bicarbonate and citric acid were used as gas generating agent. The other excipient used was Micro crystalline cellulose for its diluent property. They were first sieved and then blended in mortar with pestle to obtain uniform mixing. Finally 1% talc and 0.5% magnesium stearate was mixed for lubrication which was then compressed by

Cadmach single punch machine by using 12mm flat punch. The weight of tablet was adjusted to 500 mg and each tablet contained 200 mg nevirapine. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability.

Evaluation of nevirapine floating matrix tablets

STUDY OF FLOATING PROPERTY

The floating behavior was determined by the method described by Rosa et al. The floating lag time and the total floating duration was determined by placing the tablets in a 100 ml flask containing pH 1.2 solutions. The time required for dosage form to emerge on surface of the medium is called total floating lag time. The duration of time by which the dosage forms constantly emerge on surface of the medium called is total floating time.

IN-VITRO RELEASE STUDIES

In-vitro release study was carried out according to USP XXIII dissolution type II apparatus (Electro Lab.DTD – 06P) using paddles. 0.1 N HCl solution was selected as a dissolution medium. The study was conducted by keeping 100 rpm paddle rotation at the temperature of 37 ± 0.5 0C. The samples were withdrawn at predetermined time interval and same volume of fresh medium was replaced. The withdrawn samples were suitably diluted and the amount of drug release was estimated using UV spectrophotometer (Shimadzu-1700)

Drug content and physical evaluation*:* The drug content of the tablets was determined using 0.1N HCl as a solvent, and the samples were analyzed spectrophotometrically (Shimadzu, SPD-10AVP, Kyoto, Japan) at 290nm. Tablets were also examined with regard to their weight variation (n = 10), friability (n = 10) and hardness (n = 3).

Swelling characteristics*:* The swelling properties matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900ml0.1N HCL at 37±0.5°C. The tablets were removed periodically from the dissolution medium and, after removing free water, the weight gain was measured. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to the equation5.

Data analysis*:* To analyse the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into zero order first order Higuchi matrix and Korsemeyer-peppas model, based on the r value the best fit model was selected.

Stability studies*:* The stability studies were carried out according to ICH and WHO guidelines12 to assess the drug and formulation stability. Optimized B7 formulations were sealed in aluminum packaging having a polyethylene coating on the inside. Samples were kept in a humidity chamber maintained at 45°C and 75% RH for 3 months. At every one month of the study period, samples were analyzed for drug content, buoyancy lag-time, buoyancy time and detachment stress and drug release characteristics.

RESULTS AND DISCUSSION

Floating Matrix tablets of nevirapine were mainly prepared by using different polymers like Metolose and SCMC either alone or in combination Effervescent base of tablets were prepared by using sodium bicarbonate and citric acid. The tablets were fabricated using direct compression technique. The Micromeritic property of drug and polymers were characterized with respect to the angle of repose, bulk density, tap density and Carr's index (table no.2)

The formulated tablets were subjected for various evaluation parameters like hardness, thickness, density, weight variation, drug content, floating capabilityand dissolution study. Our experimental results (Table **3**) revealed that all the formulated tablets were of good quality with regard to hardness (5- 6 kg/cm2), density (~1 g/cm3), drug content (> 90%) and floating lag time (4-10 min). Swelling index was calculated with respect to time. Maximum swelling was seen with the batches B1, B4 and B7 containing Metolose in alone and in combination with SCMC respectively (Figure **1**). *In-vitro* drug release showed (Figure **2**, **3**, **4** and **5**) that the release increased with increase of polymer. The maximum drug release and fast release was obtained with the formulations contains the Sodium CMC in the more amount then the other polymer or as alone, this was due to high swelling capacity of the polymer. Kinetic models describe drug release from immediate and modified release dosage forms.

To predict the mechanism of diffusional release, equation $Mt / M\infty = ktn$ was used. Different kinetic was applied to interpret the release rate of nevirapine from Floating matrix tablets of batch F2 the coefficient of determination were (r2) determined

Result indicated that release of B7 best fitted square root kinetics(Table **5**). Formulation B7 was selected as a most promising formulation for further study depending on its swelling study and drug release properties. Results of stability studies of formulation B7 indicate that it is stable at 40°C, 75±5% relative humidity as there was no significant difference observed for dissolution, floating time and Swelling characteristics.(Figure **5** and **6**)

CONCLUSION

This study suggests that the polymers maltose and SCMC can produce a controlled pattern of drug release in the prepared nevirapine tablets. The high mucoadhesive strength of this formulation is likely to increase its residence time in the gastrointestinal tract, which eventually improves the extent of bioavailability. However, an appropriate balance between various levels of the two polymers is needed to acquire proper release and mucoadhesion. In this formulation the amount of maltose mainly affects on the Mucoadhesion and Swelling of tablets. It can be concluded that by formulating gastroretentive sustained release tablets ofnevirapine, its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption can be solved by increasing the retention time of drug in GIT for a longer duration of time.

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Tables and figers

Table 1. Formulation Chart of nevirapine floating matrix tablets

Batch/ Ingredients (mg)	Drug	Metolose	Sodium CMC	Sodium Bicarbonate	Citric acid	MCC	Total Weight
B1	200	160	-	50	25	65	500
B2	200	140	-	50	25	85	500
B3	200	120	-	50	25	105	500
B4	200	-	80	50	25	145	500
B5	200	-	70	50	25	155	500
B6	200	-	60	50	25	165	500
B7	200	80	40	50	25	105	500
B8	200	70	35	50	25	120	500
B9	200	60	30	50	25	135	500

Table no.2 Micromeritic characterization of drug and polymers

Parameters/Polymers	Nevirapine	Metolose	Sodium CMC
bulk density (g/cm3)	0.41±0.03	0.304±0.020	0.363±0.017
Tapped density (g/cm3)	0.49±0.03	0.478±0.029	0.572±0.151
Carr's Index	16.32±0.014	36.40	36.34
Hausner's ratio	1.19	1.57	1.57
Angle of repose	20±0.4	17±0.3	18±0.5

Table 3. Standard Physical Tests for Matrix Tablets

Formulation	Hardness (kg/cm2)	Percent friability	Thickness (mm)	Content uniformity (%)	Wt. variation
B1	5.1±0.3	0.61±0.02	3.22±0.01	99.23%	Passes
B2	5.4.±0.2	0.55±0.03	3.25±0.04	100.16%	Passes
B3	5.3±0.2	0.54±0.01	3.23±0.02	99.41%	Passes
B4	5.5±0.1	0.52±0.03	3.24±0.01	99.37%	Passes
B5	5.5±0.2	0.51±0.03	3.22±0.01	100.13%	Passes
B6	5.3±0.3	0.48±0.04	3.22±0.03	99.74%	Passes
B7	5.4.±0.2	0.52±0.05	3.27±0.05	100.26%	Passes
B8	5.2±0.3	0.51±0.02	3.25±0.01	99.63%	Passes
B9	5.5±0.4	0.49±0.03	3.22±0.04	99.85%	Passes

Table no 4. Floating lag time

Batches	Floating lag time(min)	Total floating time
B1	8	More than 12 hr
B2	6	More than 12 hr
B3	10	More than 12 hr
B4	8	More than 12 hr
B5	9	More than 12 hr
B6	9	More than 12 hr
B7	4	More than 12 hr
B8	5	More than 12 hr
B9	7	More than 12 hr

Table 5. Kinetic Data of nevirapine floating Matrix Tablets

Batch	Zero Order (R2)	First order (R2)	Matrix Model (R2)	Korsemeyer-peppas model (R2)
B1	0.8251	0.9599	0.9960	0.9912
B2	0.8626	0.9669	0.9964	0.9911
B3	0.8036	0.9513	0.9944	0.9917
B4	0.8687	0.9716	0.9966	0.9882
B5	0.8924	0.9766	0.9968	0.9911
B6	0.7847	0.9280	0.9931	0.9910
B7	0.8547	0.9665	0.9964	0.9888
B8	0.8785	0.9721	0.9967	0.9878
B9	0.8686	0.9628	0.9978	0.9910

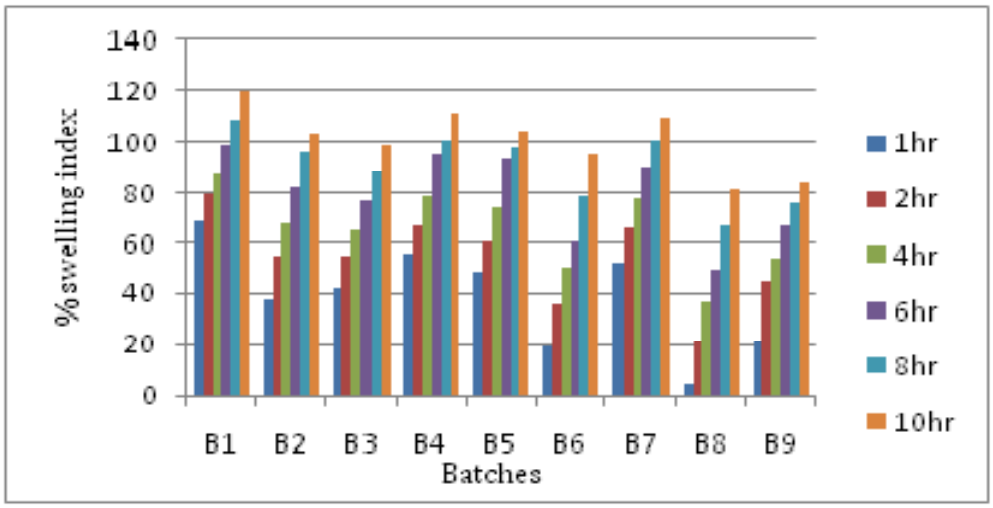

Figure 1. % swelling index of formulated batches

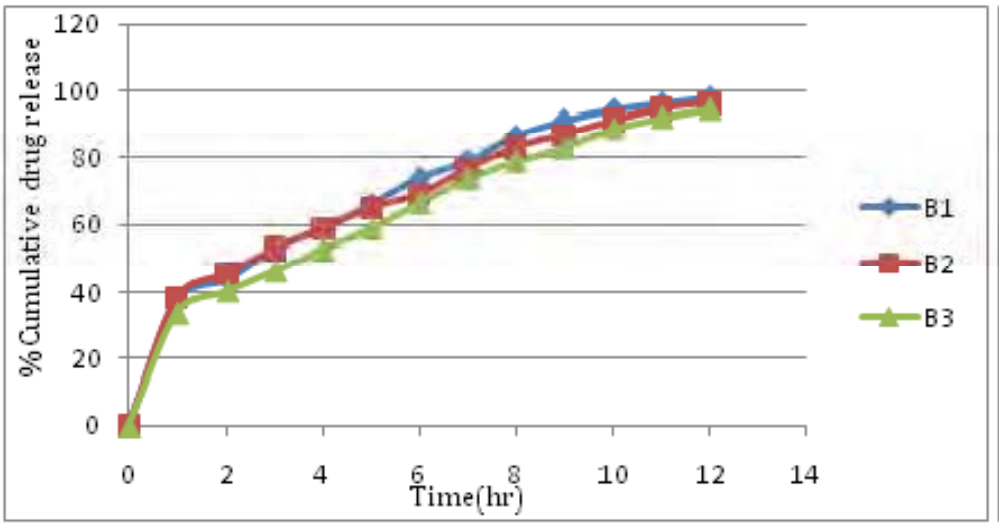

Figure 2. Dissolution profile of Batch B1, B2 and B3

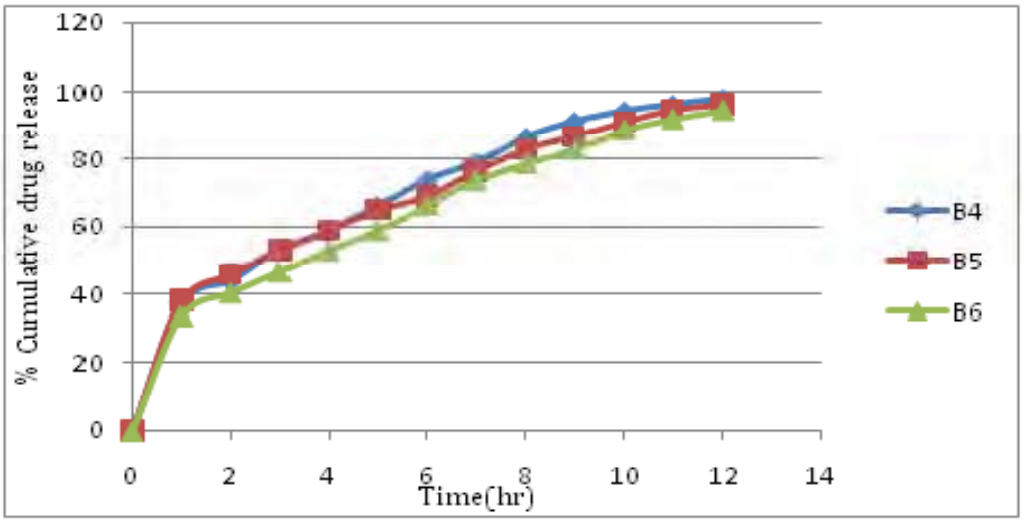

Figure 3. Dissolution profile of Batch B4, B5 and B6

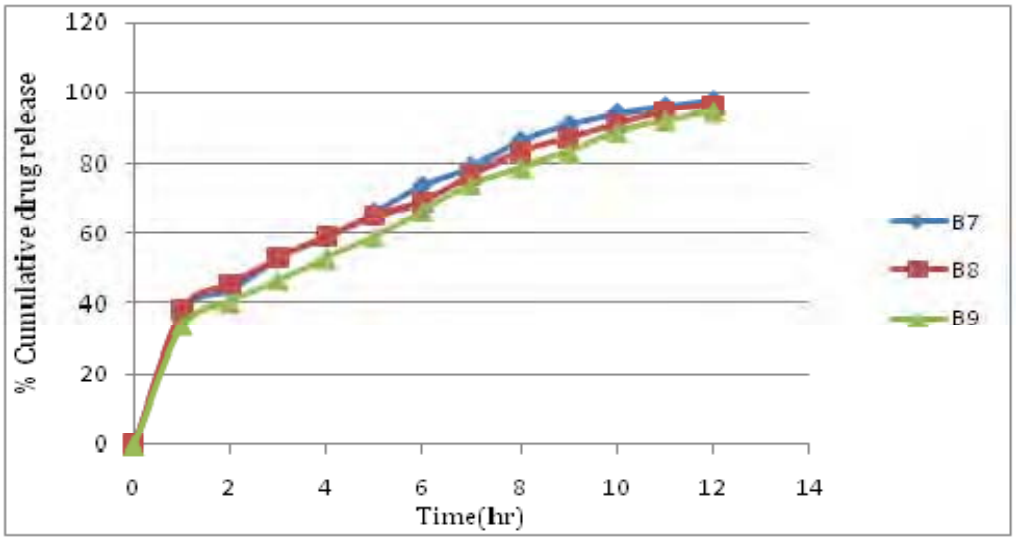

Figure 4. Dissolution profile of Batch B7, B8 and B9

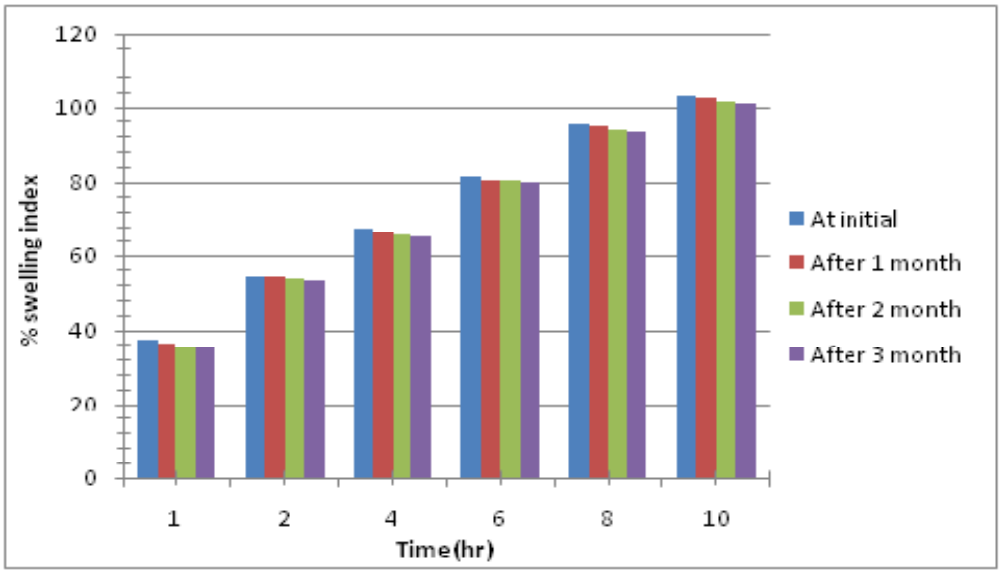

Figure 5. % swelling of B11 after Stability Study

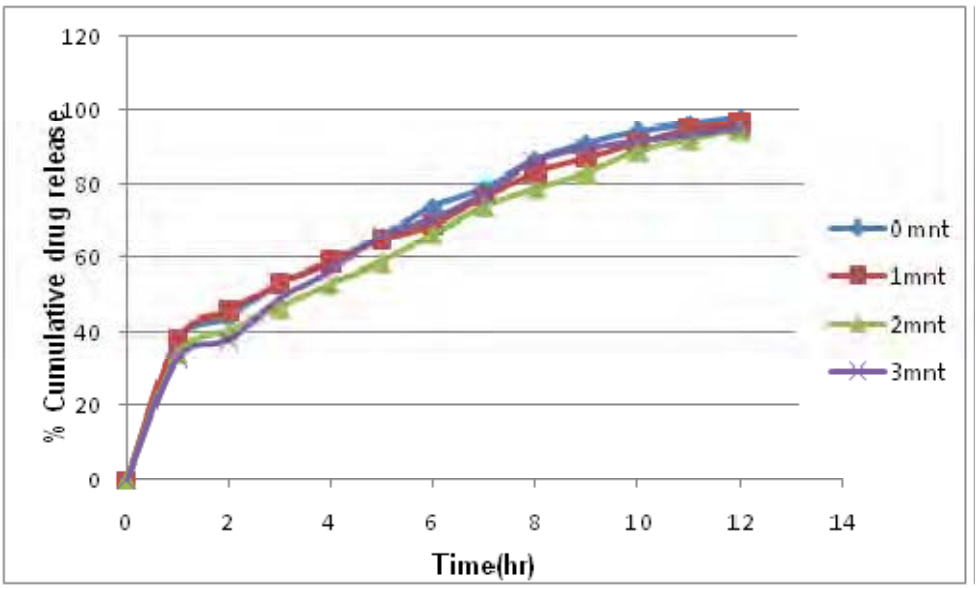

Figure 6. Dissolution study of B11 after Stability Study