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Research Article

DEVELOPMENT AND EVALUATION OF FLOATING TABLET CONTAINING NEVIRAPINE USING A 3^2 FULL FACTORIAL DESIGN OPTIMIZATION METHOD

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ABSTRACT

Floating oral drug delivery system is retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Nevirapine are the suitable drug candidates for the formulation of floating sustained drug delivery system. Nevirapine is a non-peptic, protease inhibitor antiretroviral drug used in the treatment of the human immune deficiency virus. Floating tablet of Nevirapine is prepared with a view to attain early onset of action and giving prolonged release of Nevirapine by enhancing gastric retention time. A 3^2 full factorial design by Design Expert software was used for the development of floating sustained release tablet in which the composition of release retardant polymer and effervescent agent were incorporated as two independent variables or factors. Compatibility study was carried out by FTIR study. The regression coefficients and the analysis of variance information is well exposed. It was observed that as the concentration of the HPMC K4M increased the percentage of swelling also increased. The percentage of swelling was determined at the end of 8 h for all the developed formulations. The buoyancy lag time was measured by using stop watch and total floating time was observed visually. Floating lag time was observed less than 78 sec for all batches. Total floating time was observed more than 12 h. Hence, this new type of floating sustained release tablet which can transfer to industry scale production with high output rates by considering the need of nevirapine.

KEYWORDS: Nevirapine, gastric retention time, factorial design, ANOVA, dependent and independent variables, lag time.

INTRODUCTION

The primary aim for designing oral sustained release dosage form should be achieving predetermined and predictable drug release and thereby increasing bioavailability. But there are several physiological difficulties, which include restraining and localizing the drug delivery system within the regions of the gastrointestinal tract and the highly variable nature of gastric emptying process (a few minutes to 12 h) [1]. This variability, in turn may lead to unpredictable bioavailability and the time to achieve peak plasma levels, since the majority of drugs are preferentially absorbed from the upper part of small intestine. In human, drug remains 2-3 h only in major absorption zone as stomach or upper part of GIT. Various type drug degrade in small intestine or colon for such type of drug it is beneficial to design gastroretentive devices to avoid further consequences [2]. The conventional dosage forms retained in the stomach for 0.5- 2 h and passes to small intestine and where it gets absorbed within 3-6 h. Therefore it is difficult to adjust release retardation and stomach retention of drug for longer period of time. The concept of gastro retentive drug delivery system came from the need to localize the drug at a certain site in the body [3]. The majority of drugs are preferentially absorbed from the upper part of GIT hence, drug release at site of absorption can improve therapeutic efficacy of drug [4]. Floating oral drug delivery system (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids [5]. Drugs having pH dependent solubility i.e. highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH), drugs having short biological half-life e.g. Nevirapine are the suitable drug candidates for the formulation of floating sustained drug delivery system. Nevirapine (NVP) is a non-peptic, protease inhibitor (IP) antiretroviral drug used in the treatment of the human immune deficiency virus (HIV). NVP belongs to class II drug as per biopharmaceutical classification system. Oral bioavailability rendering to 29-43 %, having 4.1 log P value. Nevirapine is soluble in acidic environment of stomach since it is a weak basic drug and its therapeutic efficacy is limited by its poor aqueous solubility with half-life 3.5-5 h [6]. Moreover a tablet formulation of NVP is not available worldwide, preventing appropriate dose adjustment and more convenient administration. Even today a parenteral formulation has also not available in spite of their reported disadvantages. The gastro-retentive drug delivery systems can be able to retain the dosage unit in the stomach, get absorbed from stomach and thereby assist in improvement of drugs bioavailability. The purpose of this investigation was to develop a novel gastroretentive tablet formulation of Nevirapine for prolonged release. Floating tablet of Nevirapine is prepared with a view to attain early onset of action and giving prolonged release of Nevirapine by enhancing GRT.

MATERIALS AND METHODS

Nevirapine (NVP) was kindly gifted by Mylan Pharmaceutical ltd Waluj (Dist), Aurangabad, India. Hydroxypropyl methylcellulose K4M was obtained from Colorcon Asia Pvt. Ltd. Goa, India. Magnesium stearate and sodium bicarbonate were procured from S. D. Fine Chemicals, Mumbai, India.

DRUG -EXCIPIENTS INTERACTION STUDY

The drug-excipients interaction study was carried out using Fourier Transform-Infrared spectroscopy (FTIR). FTIR spectra of NVP, HPMC K4M, Lactose and physical mixture of lipids with NVP were studied. Above samples were compressed using KBr pellet technique using FTIR (Model-200, Thermo Electron, Shimadzu, Japan). The spectrum was scanned over the frequency range between 4000 and 400 cm–1. The FTIR spectra of mixtures were compared with that of the FTIR spectra of pure drug and lipid, to confirm any changes in the principle peaks of spectra of plain drug and lipid.

DEVELOPMENT AND OPTIMIZATION

A 3^2 full factorial design by Design Expert software (Design Expert Software Version 8.0.1) was used for the development of floating sustained release tablet in which the composition of release retardant polymer and effervescent agent were incorporated as two independent variables or factors [7]. In the constructed design the independent variables selected are HPMC K 4M (X1) and NaHCO3 (X2). The three levels of the two factors were preferred on the basis of the preliminary studies which carried out before implementing the experimental design with suitable support of literature survey [8]. All other formulation and processing variables were kept invariant throughout the study. The dependent variables studied were the buoyancy lag time (Y1) and percent cumulative drug release (Y2). Accurate quantity of drug and release retarding polymer HPMC K4M were weighed and mixed well. Sodium bicarbonate was added as gas generating agent. Finally lubricant was added and blend was mixed properly. Accurately weighed 500 mg powder was fed manually at the 10 station of tablet machine and compressed by using 9 mm flat faced punch. Compression force was kept constant for all formulations. (Table 1)

FORMULATION OF FLOATING SUSTAINED RELEASE TABLETS

Various formulation batches were tried out to finalize the concentration of release retardant polymer and effervescent agent. Finally on the basis of trial and error with literature support the various levels were set. Accurate quantity of drug and release retarding polymers were weighed and mixed well. Sodium bicarbonate was added as effervescent agent. Finally lubricant was added and blend was mixed properly. Accurately weighed 500 mg powder was fed manually in to 10 station tablet machine (Rimek minipress-1) and compressed by using 9 mm flat faced punch. Compression force was kept constant for all formulations. (Table 2)

EVALUATION OF FLOATING SUSTAINED RELEASE TABLETS

Prepared sustained release tablets were evaluated for post compression parameters like thickness, hardness, friability, drug content, weight variation, swelling study, floating lag time, total floating time and in vitro drug release study [9,10].

Swelling Study of Floating Sustained Release Tablet

The hydration ability of the formula is important because it influences: (i) tablet buoyancy, (ii) adhesion ability of swellable polymers in contact with the test fluid and (iii) drug release kinetics. The ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains [11].

The swelling behaviour of the tablet was determined, according the method described. A tablet was weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5oC. The tablet was taken out and the excess surface liquid was carefully removed by a filter paper. The swelling index was calculated at the end of 8 h. The swollen tablet was then reweighed (W2). The % swelling was calculated using following formula.

$$\% \text{ Swelling} = \{(W2-W1)/W1)\} \times 100$$

Determination of Floating Lag Time (FLT) and Total Floating Time

Floating lag time is the time required for the tablet to rise towards surface and float. The floating of tablets was studied at 37 ± 0.5^{O}C in 200 mL of 1.2 pH buffer (simulated gastric fluid without pepsin). The floating lag time was measured by using stop watch and total floating time was observed visually [12].

In Vitro Drug Release Study

In vitro drug release study was performed using type II (paddle) apparatus (Electrolab TDT08L plus, dissolution tester USP Mumbai, India) at 50 rpm in 900 mL simulated gastric fluid of 1.2 pH for 12 h [13]. Temperature was maintained at 37 ± 0.5^{0}C. The 5 mL sample was withdrawn at predetermined time intervals and replaced with same fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45 µm, suitably diluted and analyzed by using UV spectrophotometer (UV Shimadzu 1700) at λmax 282.9 nm.

RESULT AND DISCUSSION

The drug-excipients interaction study of Nevirapine with different excipients was carried out satisfactorily using FTIR. Overlay Infrared spectra of NVP, HPMC K4M, Lactose and physical mixture of lipids with NVP mentioned in Figure 1. All the spectra of all compounds were found within shift, no overlapping was observed hence conclude that all are compatible with each other.

Development and Optimization

Multiple regression and mathematical model was used to develop a floating sustained release system with release retardant polymer and effervescent agent. The polymer compositions with effervescent agent level are important parameters affecting the drug release profile as well as buoyancy of dosage form, regardless of the core composition. A multivariate optimization approach was approved with the aim of finding the optimum polymers and effervescent agent composition to achieve a gastro retentive release pattern from a floating sustained release tablet. Figure 2 shows the release profiles of the 9 experimental runs performed in accordance with Table 3. The consequences obtained from the research were statistically analysed for response variables by using Design Expert 8.0.1 version (Stat-Ease Inc., Minneapolis, Minnesota). The design was evaluated by a 3-level two factorial design [14]. The regression coefficients for each term in the regression model (equations) are summarized in Table 3, and the analysis of variance (ANOVA) information is exposed in Table 4.

Where, Y1 = Floating lag time
Y2= % Cumulative drug release
A = HPMC K4M
B = NaHCO3

Effect of formulation variables on release properties in the case of Y1 (FLT) coefficients X1 and X2 were found to be significant, with an interaction of X1X2. While the highest polymer content to formulation (X1) increased, drug release decreased. Similar results were reported earlier as the polymer concentration increases the %CDR decreases. Effect of factors on 3^2 full factorial design model and connected p-values for the responses Y1 and Y2 are offered in table 4. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In this case X1, X2 are significant model terms for Y1 and X2 is significant in the case of Y2 (% CDR) [15]. Values greater than 0.1000 indicate the model terms are not significant. A factor is considered to influence the response if the effects significantly differ from zero and the p-value is less than 0.05.

Response Surface Analysis

The relationship between variables was further elucidated using response surface methodology. The effects of X1 and X2 on Y1 are specified in Figure 2 A. Y1 did not illustrate any significant changes at low as well as high level of X2. But the same when the release retardant polymer concentration (HPMC K 4M as X1) was increased Y2 (% CDR) decreased from 97.99 % to 57.48 % at the end of 12 h. The effects on Y1 by factors X1 and X2 expressed in Figure 2. X2 (effervescent system i.e. $NaHCO_3$) showed the increase and decreased in floating lag time. As the concentration of $NaHCO_3$ increased the FLT was decreased whereas concentration of (HPMC K 4M) (X1) decreases the Y2 get increased [16].

Evaluation of Floating Sustained Release Tablets

Table 5 indicated the post compression data. Almost all the batches showed uniform thickness. Hardness range was in between 5.1-5.4 and drug content was in the range of 96.14-98.75%. All batches passed weight variation test and found to be within range (500 ± 5%) and friability was less than 1%, it indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage, transportation and until they are consumed. Percentage swelling for all batches was observed in the range of 158±25 to 174±39. Floating lag time was observed lees than 78 sec for all batches and total floating time was observed more than 12 h [17].

Swelling study, Floating Lag Time (FLT) and Total Floating Time (TFT)

It was observed that as the concentration of the HPMC K4M increased the percentage of swelling also increased. The tablets were removed and the excess surface liquid was carefully removed by a filter paper. As the water continues to enter the tablet, a highly concentrated polymer solution is formed, denoted as a gel layer. The solvent continues to penetrate the tablet, the gel layer and the dimensions of the swollen tablet increase, a process normally referred to as the swelling process. Complete swelling was achieved by the end of seven hrs. Thus, the percentage of swelling was determined at the end of 8 h for all the developed formulations. The buoyancy of floating sustained release tablet was studied at 37 ± 0.5oC in 200 mL of 1.2 pH buffer (Simulated gastric fluid without pepsin). The buoyancy lag time was measured by using stop watch and total floating time was observed visually. Floating lag time was observed less than 78 sec for all batches. Total floating time was observed more than 12 h [18]. Results were reported in Table 6.

The in vitro Dissolution Study of Floating Sustained Release Tablets

The *in vitro* dissolution study of Nevirapine floating sustained release tablets were carried out by using USP dissolution type II (Paddle) apparatus (Electro lab TDT- 08L plus, Dissolution tester USP Mumbai, India). *In vitro* dissolution study carried using polymer such as HPMC K4M, $NaHCO_3$ and lactose. Comparative *in vitro* dissolution of floating sustained release tablets using 3^2 full factorial design in 1.2 pH buffer shown in Figure 3.

Effect of HPMC K4M: The varying percent cumulative drug release (%CDR) after 12 h for formulation F1 to F9 were obtained with different concentration of HPMC K4M. Highest concentration of HPMC K 4M, decrease the % CDR and low concentration of HPMC K 4M, increase the % CDR. The percent cumulative drug release for formulation F3, F4 and F7 was 92.72±4.1%, 76.45±5.1% and 61.08±5.2%, respectively. These variations were observed in drug release because of change in concentration of HPMC K 4M. Thus one can conclude that HPMC K 4M is a major variable to regulate the release rate of Nevirapine from tablet. The percent cumulative drug release after 12 h for formulation F1 was found 97.99±6.5% hence considered as optimized by considering all other parameters [19].

Effect of Effervescent system: Nevirapine (NVP) floating sustained release tablets containing effervescent (NaHCO3) showed much less floating lag time. If the concentration of effervescent ($NaHCO_3$) increase then the FLT was decrease, and if the concentration effervescent ($NaHCO_3$) decrease then FLT was increase. NVP tablets of batch F1, F2, F4, and F6 started floating immediately. NVP Tablets showed floating lag time was 11, 18, 42 and 25 Sec respectively. Sodium bicarbonate acts as a gas generating agent; it generates CO_2 gas when it comes into contact with an acidic environment of the stomach [20]. This gas entraps into the matrix of water-soluble polymers and the formulation floats in an acidic environment of the stomach. All above batches contain same concentration of $NaHCO_3$, the variation in FLT is only because of concentration of HPMC K4M. As the concentration of sodium bicarbonate increase, the drug release was increase at the end of 12 h. The duration of floating for all formulations was found to be >12 h in pH 1.2 buffer with the short floating lag time showed optimum batch F1 NVP floating sustained release tablet was 11 Sec [21].

Table 1: Selection of independent and dependent variables for 3^2 full factorial design

Coded Values	Independent Variables		Dependent Variables	
	HPMC K4M Concentration (X1)	$NaHCO_3$ Concentration (X2)	Floating Lag Time (Y1)	Cumulative Drug Release (Y2)
-1	**70**	**40**	Sec	%
0	**82.5**	**50**	Sec	%
+1	**95**	**60**	Sec	%

Table 2: Composition of floating sustained release tablets using 3^2 full factorial design

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	200	200	200	200	200	200	200	200	200
HPMC K 4M	70	82.5	70	82.5	70	95	95	95	82.5
NaHCO3	40	40	50	60	60	40	50	60	50
Lactose	187.5	175	177.5	155	167.5	162.5	152.5	142.5	165
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table 3: Multiple regression and mathematical model building

Final Equation in Terms of Coded Factors
Y1 = +42.00-7.67*A[1] -1.00*A[2]+23.67*B[1]-0.33*B[2]
Y2 = +77.16+16.22*A[1]-0.39*A[2]-3.87*B[1]-0.41*B[2]

Table 4: Analysis of variance for 3^2 full factorial design

Y1: (Sec) Floating Lag Time					
Source	**Sum square**	**DF**	**Mean square**	**F value**	**p- value Prob > F**
Model	3813.33	4	953.33	124.35	0.0002 Significant
X1- HPMC K4M	404.67	2	202.33	26.39	0.0050
X2- NaHCO3	34.8.67	2	1704.33	222.30	< 0.00012
Residual	30.67	4	7.67		
Cor Total	3844.00	8			
Y2: (%) CDR					
Model	1641.09	4	410.27	6020.63	0.0001 Significant
X1- HPMC K 4M	1540.86	2	770.43	11305.80	0.0001
X2- NaHCO3	100.24	2	50.12	735.46	0.0001
Residual	0.27	4	0.068		
Cor Total	1641.36	8			

Table 5: Evaluation of Post Compression Parameters for floating sustained release tablets

Formulation	Hardness (kg/cm2) Mean ± S.D.	Friability (%) Mean ± S.D.	Thickness (mm) Mean ± S.D.	Weight variation (mg) Mean ± S.D.	Drug content (%) Mean ± S.D.
F1	5.2±0.3	0.3 ± 0.1	4.34 ± 0.2	500±2.3	96.95±1.3
F2	5.1±0.2	0.5 ± 0.2	4.84 ± 0.7	500±4.4	96.45±1.4
F3	5.4±0.2	0.2 ± 0.05	4.06 ± 0.3	500±2.1	97.15±1.5
F4	5.2±0.4	0.4 ± 0.08	3.98 ± 0.6	500±1.2	96.14±1.2
F5	5.4±0.3	0.3 ± 0.1	4.21 ± 0.8	500±3.5	96.95±1.7
F6	5.3±0.4	0.2 ± 0.09	4.57 ± 0.5	500±2.2	96.95±1.5
F7	5.1±0.1	0.5 ± 0.2	4.259 ± 0.1	500±3.1	97.05±1.7
F8	5.2±0.2	0.3 ± 0.07	4.87 ± 0.5	500±1.3	98.75±1.3
F9	5.3±0.3	0.4 ± 0.1	4.61 ± 0.8	500±2.5	97.95±1.2

(n = 3) mean value ± S.D.

Table 6: Swelling study of tablet in 1.2 pH at 37 ± 0.5 °C

Formulation Code	% Swelling (8 h) Mean± S.D.	Floating lag time (Sec^{-1}) Mean ± S.D.	Total floating time (h)	In vitro release (12 h) Mean ± S.D.
F1	162±20	11±2	> 12	97.99±6.5
F2	168±29	18±3	> 12	80.88±5.5
F3	158±25	36±4	> 12	92.72±4.1
F4	164±35	42±5	> 12	76.45±5.1
F5	161±34	56±6	> 12	89.43±5.3
F6	174±39	25±3	> 12	65.45±5.4
F7	168±20	49±5	> 12	61.08±5.2
F8	171±30	78±9	> 12	57.48±5.1
F9	164±35	63±8	> 12	72.98±5.6

(n = 3) mean value ± S.D.

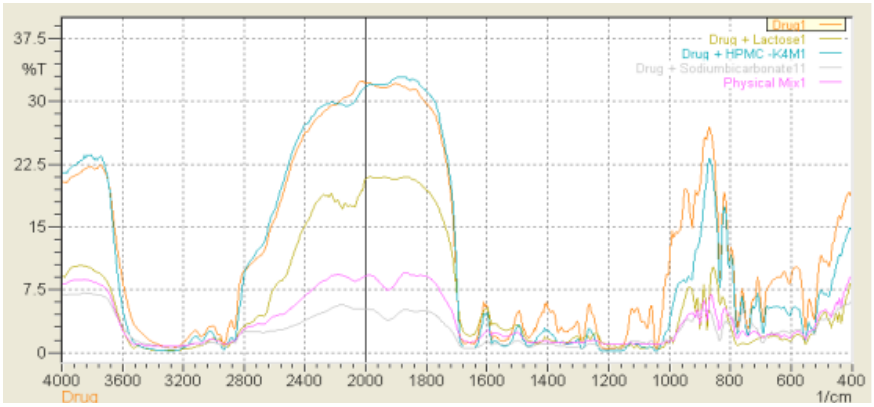

Figure 1: Overlay spectra of Nevirapine, HPMC K4M, lactose and physical mixture

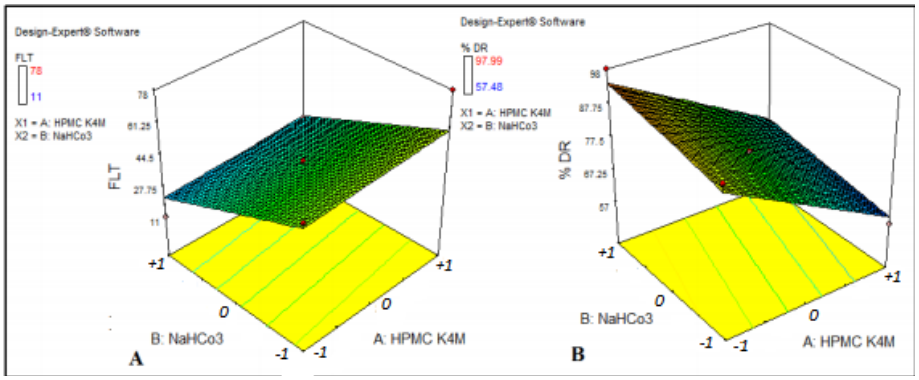

Figure 2: 3D diagram A- Effect of X1 and X2 on Y1. B- Effect of X1 and X2 on Y2

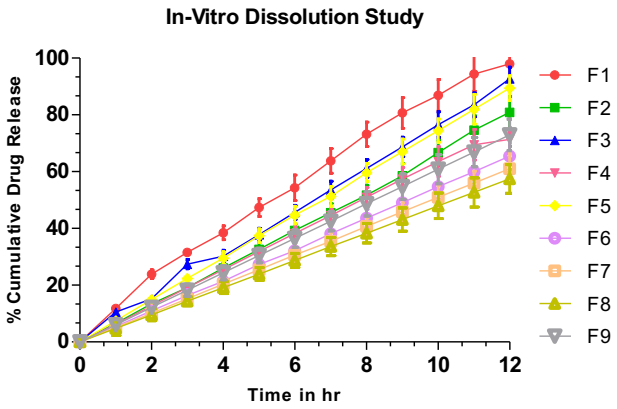

Figure 3: Percent drug released up to 12 hrs

CONCLUSION

This study discussed a positive application of a computer optimization technique for the development of a gastro-retentive delivery. It was concluded on the basis of *in vitro* release study, that optimized F1 formulation containing 200 mg of NVP is suitable as floating sustained release tablet. This study showed that there is potential for this novel intragastric, floating sustained tablet to remain in the stomach for a longer time and to have a better *in vitro* drug release for 12 h. The dosage form can control the release; extend the duration of action of a drug with prolonged floating time and gives proper utilization of drug. Hence, this new type of floating sustained release tablet which can transfer to industry scale production with high output rates by considering the need of nevirapine.

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