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Research Article

DEVELOPMENT AND IN VITRO EVALUATION OF FLOATING MATRIX TABLETS OF ANTI RETROVIRAL DRUG

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ABSTRACT

The objective of this study was to develop a gastroretentive floating drug delivery system using gas-forming agent like sodium bicarbonate and polymer like hydroxypropyl methylcellulose. Floating tablets were prepared for minimizing the side effects of drug which are produced due to the accumulation in the body and also increases the patient compliance. Tablets were prepared by the dry granulation (slugging) technique, using polymers such as hydroxypropyl methylcellulose (HPMC K100M) and sodium carboxy methyl cellulose. Tablets were evaluated for their physical characteristics, *viz*., hardness, thickness, friability, weight variation, assay and floating properties. Further, tablets were evaluated for *in vitro* drug release characteristics for 12 hours. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium. Non-Fickian diffusion was confirmed as the drug release mechanism from these tablets, indicating that water diffusion and polymer rearrangement played an essential role in drug release. The best formulation (F2) was selected based on *in vitro* characteristics. The accelerated stability studies, at 40^0C/75% RH, of the optimized formulation were carried out for three months and no significant change was observed.

Keywords: Floating drug delivery system, Matrix tablets, Hydroxypropyl methylcellulose, Gastric residence time

INTRODUCTION

Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties i.e. single dosed or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.[1]

Sustained release (SR)-gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to stomach and upper parts of the gastrointestinal (GI) tract. These systems are designed to be retained in the stomach for longer period of time and hence significantly prolong the gastric residence time of drugs. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems, swelling and expanding systems, floating systems and delayed gastric emptying devices. [2, 3, 4]

Among these, the floating dosage form has been used most commonly. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, [5] drugs acting locally in the stomach, [6] and for drugs that are poorly soluble or unstable in the intestinal fluid.[7] The floating systems include single, multiple and raft forming systems. The principle of these systems offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

The present investigation is concerned about the development of effervescent floating drug delivery systems that generate CO_2, thus reduces the density of the system in the stomach for prolonged period of time and releases the drug slowly at desired rate. Stavudine is used as a part of highly active anti retroviral therapy. Formulation of extended release effervescent floating tablets of stavudine improves patient compliance and minimizes the dose related side effects. Therefore, this study aims at formulating once-a-day floating hydrophilic matrix tablets using hydroxypropyl methylcellulose (HPMC) as a release rate modifying polymer, $NaHCO_3$ and lactose were used as floating aid and release modifier.

MATERIALS AND METHOD

Stavudine and all the polymers were procured from Ranbaxy Laboratories Limited, Gurgaon. All other chemicals and ingredients for study were of analytical grade.

Preparation

Effervescent floating tablets containing drug (20%) were prepared by dry granulation technique (slugging) using varying concentrations of polymers i.e. hydroxy propylmethyl cellulose and sodium carboxymethyl cellulose and sodium bicarbonate as effervescent component. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except magnesium stearate and talc all other ingredients were blended uniformly in polyethylene bag for 5-6 min. Slugging the powder blend and sifted through sieve no. # 22. Granules were lubricated with magnesium stearate and talc (1%) for additional 3 min., compressed in to tablets using a 16 station rotary tablet machine (Cadmach, Ahmedabad, India.) using 8mm standard flat face punch, compression force was adjusted to obtain tablets with hardness in range of 5.1 ± 0.51- 5.8 ± 0.23 kp. The tablet weights were 200±2 mg with average diameter of 8.0±0.2 mm.

Table 1: Formulation batches of effervescent floating tablets of stavudine

Ingredients	Formulation code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Stavudine	40	40	40	40	40	40	40	40	40	40	40
HPMC K100M	30	40	50	60	70	80	40	40	40	40	40
SCMC	5	5	5	5	5	5	-	10	5	5	5
$NaHCo_3$	15	15	15	15	15	15	15	15	15	10	20
CSD	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Magnesium stearate	1	1	1	1	1	1	1	1	1.5	1	1
Lactose	107.95	97.95	87.95	77.95	67.95	57.95	102.95	92.95	97.45	102.95	92.95
Talc	1	1	1	1	1	1	1	1	1	1	1

*All the quantities are in mg

Evaluation of granules

Pre-compression parameters of granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, [2] tapped density, bulk density, [8] and Carr's index. [9]

Evaluation of tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods[10]. The weight variation was determined by taking 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to average of tablet. Tablet hardness was determined for 10 tablets using a Monsanto tablet hardness tester (MHT-20, Campbell Electronics, Mumbai, India). Friability was determined by testing 10 tablets in a friability tester (FTA-20, Campbell Electronics) for 4 minutes at 25 rpm. Acceptance criteria are not more than 1 % of their weight.

***In Vitro* drug release study**

The release rate of the drug from floating tablets was determined using USP testing apparatus II (Paddle Type). The dissolution test was performed using 900ml of 0.1N HCl at 37±0.5^{o}C and 50 rpm. 5ml of aliquots were withdrawn at specific time intervals and the level of the dissolution media was maintained by replacing the same which was already maintained at sink conditions. The samples were filtered through a 0.45 µm membrane filter. Absorbances of these samples were taken at 266nm using UV visible spectrophotometer (Shimadzu UV 1700) against 0.1N HCl as blank. Cumulative percent drug release was calculated.

Assay of tablets

The drug content in each formulation was determined by triturating 10 tablets and a quantity of powder equivalent to the mass of one tablet was extracted with pH 1.2 buffer and the solution was filtered through 0.45 µ membranes. The absorbance was measured at 266 nm after suitable dilution.

Floating lag time and total floating time

The time between the introduction of a floating tablet of the drug in to the medium and its buoyancy to the upper one third of the dissolution vessel was measured as floating lag time which is a part of dissolution studies. The time for which FDDS constantly float on the water surface is total floating time. It is performed by visual observations during the dissolution studies[11, 12].

Kinetics of drug release

A gel layer is formed around the tablet core when the tablet containing a polymeric matrix comes in contact with water, which governs the drug release. Drug release from HPMC matrix tablets is controlled by diffusion through the gel layer in case of water soluble drug or by erosion of the outer polymer chains for water insoluble drugs. Hence, the kinetics of swelling is important because the gel barrier is formed with water penetration. The drug release rate kinetics was calculated for zero order, first order and Higuchi models. [13, 14, 15]

Mechanism of drug release

The mechanism of drug release was determined by fitting the drug release data of drug release to Korsmeyer et al's equation and graphs were plotted as log cumulative percentage of drug release vs. log time and the exponent *n* was calculated through the slope of the straight line and finding the R^2 values of the release profile corresponding to each model

$Mt/M_\infty = at^n$

Where Mt/M_∞ is the fractional solute release, t is the release time, a is constant incorporating structural and geometrical characteristics of the drug dosage form and n is the release exponent indicative of drug release mechanism and function of time, t. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion, and if 0.45 < n <0.89, then it is non-Fickian or anomalous diffusion. An exponent's value of 0.89 is indicative of case-II Transport or typical Zero-order release.[15]

Stability studies

The stability studies were carried out on optimized formulation i.e. F2. The formulations were stored at 40^{o}C/ 75 RH for three months to assess their long term stability. Samples were withdrawn after 1, 2 & 3 months and retested for physical properties, drug content, floating lag time and *in vitro* drug release.

RESULTS AND DISCUSSION

The present study was aimed to prepare and evaluate effervescent floating matrix tablets of stavudine with HPMC as polymer using dry granulation technique. HPMC was chosen because it is widely used as a low density hydrocolloid system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in intestinal pH. Sodium CMC acts as buoyancy increasing agent and also improves the gelling property of polymer. Sodium CMC was used in combination with HPMC to slow the drug release; Sodium CMC's ability to do this is due to low solubility at pH 1.2 to 3.

The granules prepared for compression of floating tablet were evaluated for their flow properties (Table-2). Angle of repose (□) was in the range of 23.21 ± 1.2 to 26.25 ± 1.8^{0}. Bulk density ranged between 0.328 ± 0.05 to 0.427 ± 0.06 gm/cm^3. Tapped density ranged between 0.401 ± 0.02 to 0.522 ± 0.02 gm/cm^3. Carr Index was found to be 21.17 ± 0.41 to 25.01 ± 0.10. These values indicate that the prepared granules exhibited good flow properties.

Table 2: Granule properties of formulation F1 to F13 of stavudine matrix tablets

Parameters	Formulation code										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Angle of Repose (□)	25.13 ± 1.6	26.25 ±1.8	24.15 ±1.2	25.45 ±1.3	26.15 ±1.0	25.67 ±1.1	23.78 ±1.6	26.15 ±1.5	24.30 ±1.1	24.15 ±1.0	23.21 ±1.2
Bulk Density (gm/cm^3)	0.351 ±0.08	0.452 ± 0.02	0.328 ± 0.05	0.427 ± 0.08	0.331 ± 0.03	0.382 ± 0.04	0.427 ± 0.06	0.346 ± 0.02	0.418 ± 0.06	0.373 ± 0.03	0.384 ± 0.02
Tapped Density (gm/cm^3)	0.422 ±0.01	0.602 ± 0.02	0.361 ± 0.04	0.481 ± 0.02	0.389 ± 0.05	0.411 ± 0.07	0.459 ± 0.08	0.380 ± 0.01	0.461 ± 0.06	0.401 ± 0.02	0.412 ± 0.03
C.I. (%)	23.12 ± 0.21	25.01 ± 0.10	22.17 ± 0.41	22.20 ± 0.12	21.18 ± 0.21	21.21 ± 0.31	22.31 ± 0.45	21.79 ± 0.22	21.62 ± 0.34	23.98 ± 0.12	22.95 ± 0.33

*Each reading is an average of three determinations (Avg.± S.D)

The thicknesses and hardness of the tablets were found in the range of 3.09 ± 0.08 to 3.24 ± 0.03 mm and 5.1 ± 0.51- 5.8 ± 0.23 kp respectively as shown in table 3. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

On immersion in 0.1 N HCl, pH 1.2 solution at 37 ± 0.5^{0}C all effervescent floating tablets floats immediately and remain buoyant up to 24 h without disintegration. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (HPMC K 100 M), thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. The cumulative percent drug release was found to be in the range of 63.26 ± 0.35 to 96.08 ± 0.21 %. Among all the formulations F2 was found to be the optimized one in terms of floating lag time and drug release at the end of 12 hr as shown by results in table 3. The dissolution profiles of all the formulations are shown in figure1 and figure 2.

The assays of tablets of all the formulations were found with in the range as per the requirement of pharmacopoeia. When the concentration of polymer was increased, the lag time was increased but total drug release was decreased. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio. Incorporated sodium bicarbonate into the HPMC matrix could increase the drug release rate. It was found that the drug release rate was extended as the content of Na-CMC increased. The increase in the quantity of sodium bicarbonate decreases the lag time but increases the drug release. As magnesium stearate is hydrophobic in nature and when it was increased extra granularly then floating lag time was increased slightly but no effect on initial drug release from the matrix tablets.

Table 3: Different properties of tablets of batch F1 to F10

Parameters	Formulation code										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Thickness (mm)	3.21 ± 0.02	3.17 ± 0.01	3.24 ± 0.03	3.22 ±0.01	3.21 ± 0.02	3.19 ±0.01	3.11 ± 0.07	3.09 ± 0.08	3.23 ± 0.04	3.17 ± 0.06	3.20 ± 0.05
Hardness (kp)	5.6 ± 0.11	5.5 ± 0.18	5.5 ± 0.31	5.4 ± 0.12	5.5 ± 0.17	5.8 ± 0.23	5.5 ± 0.14	5.1 ± 0.51	5. 2 ± 0.22	5.4 ± 0.31	5.5 ± 0.35
Friability (%)	0.15	0.13	0.21	0.08	0.09	0.26	0.29	0.31	0.29	0.32	0.18
Floating lag time (sec.)	18	25	30	36	42	49	19	22	24	28	16
Cumulative % drug Release	96.08 ± 0.21	91.02 ± 0.17	78.84 ± 0.13	75.43 ± 0.26	71.74 ± 0.11	63.26 ± 0.35	93.25 ± 0.25	88.86 ± 0.21	72.34 ± 0.11	77.73 ± 0.44	84.22 ± 0.31

*Each reading is an average of three determinations (Avg.± S.D)

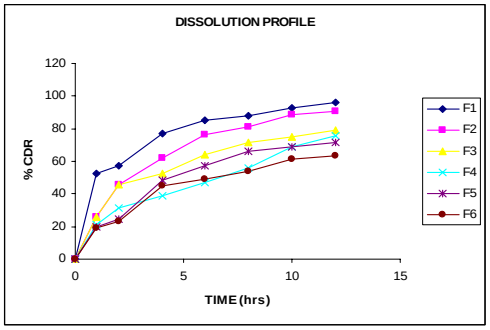

Fig. 1: *In- vitro* dissolution profile of F1 to F6

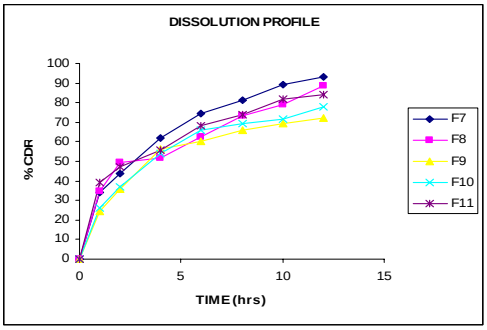

Fig. 2: *In- vitro* dissolution profile of F7 to F11

The data obtained from *in vitro* dissolution studies were fitted in different models viz. Zero order, First order, Higuchi and Korsmeyer Peppa's equation (shown in Table-4). The Higuchi plots were found to be followed as indicated by their high regression values (r^2 = 0.958 to 0.978). To confirm the exact mechanism of drug release from these tablets, the data was fitted to Higuchi and Korsmeyer Peppa's equation. The formulation F2 with HPMC K 100 M (20%) shows maximum release of 91.02 ± 0.17 % at a time period of 12 hours in a controlled manner. The *in-vitro* release plot has shown drug release followed by Higuchi plot, which was also confirmed from the regression value in table 4. From the regression and slope value of Higuchi's (0.978) and Peppa's (n = 0.5819) plot respectively, the drug release was confirmed to followed by diffusion mediated non-Fickian transport mechanism.

Table 4: Release kinetic parameters of tablets of Batch F1 to F10

Formulation code	Zero order plots	First order plots	Higuchi plots	Korsmeyer et al's plots
F1	0.919	0.949	0.967	0.921
F2	0.912	0.956	0.978	0.928
F3	0.922	0.934	0.971	0.919
F4	0.942	0.932	0.962	0.915
F5	0.916	0.947	0.959	0.924
F6	0.952	0.956	0.968	0.921
F7	0.911	0.960	0.969	0.918
F8	0.923	0.933	0.974	0.923
F9	0.956	0.955	0.962	0.919
F10	0.932	0.951	0.958	0.910
F11	0.910	0.958	0.973	0.937

The optimized F2 formulation was subjected to stability studies for 3 months. At the interval of 30 days the tablets were withdrawn and evaluated for hardness, thickness, weight variation, friability. All the parameters have not shown much variation when compared to the initial data. The *in-vitro* dissolution was also carried out for specified time intervals. Based on the results, we observed that, drug release profiles were not affected by exposing to temperature and the specified humidity conditions.

CONCLUSION

Nowadays, controlling the drug release by gastroretentive drug delivery system has become the most popular method. A Gastroretentive system means retention of the drug in the GIT for long period of time and sustaining the effect of drug. There are various approaches to increase the gastric retention time of dosage form and floating system is one of the approaches for delivery of drugs which are absorbed from stomach and upper small intestine.

Stavudine has high solubility in stomach pH and is formulated as effervescent floating drug delivery system. For anti-retroviral therapy, the drug has to administer for long period of time and due to this more drug will be accumulated in the body, which ultimately increases the side effects. This targeted delivery of the drug through FDDS reduces the dose, duration of therapy and also the side effects.

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