Current Pharma Research
ISSN: 2230-7842
CPR 1(3), 2011, 245-249.

Preparation and *In Vitro* Evaluation of Gastroretentive Tablets of Anti Retroviral Drug Using Different Polymers.

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Abstract

The objective of this research was to prepare a gastroretentive drug delivery system of Stavudine. Gastric residence time can be increased by various approaches like high density dosage forms, swelling systems, expandable systems, mucoadhesive systems, and floating drug delivery systems etc. Effervescent floating drug delivery system of this class contains a highly swellable polymer and an effervescent agent. Guar gum, xanthan gum, and hydroxypropyl methylcellulose were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. Tablets were prepared by the dry granulation (slugging). Tablets were evaluated for their physical characteristics, *in vitro* buoyancy & drug release studies using United State Pharmacopoeia (USP) 24 paddle type dissolution type apparatus using 0.1N HCl as a dissolution medium 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. The best formulation (F7) was selected based on floating characteristics.

Key Words

Colchicine; ampicillin; paracetamol**;** ion chromatography**;** dilute and shoot approach; urine sample.

Introduction

Stavudine is commonly used as a part of highly active antiretroviral therapy as a nucleotide analogue reverse transcriptase inhibitor, which is administered two times a day. Short elimination half life (0.8-1.5 hours) of stavudine following oral administration favors the development of gastroretentive dosage form. After oral administration, GRDF would be retained in stomach and release the drug in a sustainable manner, so that the drug would be supplied continuously in stomach and upper GIT. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of sustained release dosage forms for these types of drugs. Several approaches are used for the formulation of gastroretentive systems such as mucoadhesion (bioadhesion to stomach mucosa)[1,2], floatation (low density form of dosage form that causes buoyancy on gastric fluid in the stomach)[3], sedimentation (high density dosage form that is retained in the bottom of stomach)[4], expansion which limits emptying of dosage form through, pyloric sphincter)[5], by passage delaying excipients (lowered motility to the GIT by concomitant administration of drugs or pharmaceutical excipients)[6,7]. FDDS offers the most effective and rationale protection against early and random gastric emptying FDDS. This system also prolongs the gastric residence time to produce an acceptable drug bioavailability[8, 9]. Both single-unit systems (tablets or capsules) and multiple-unit systems (multiparticulate systems) have been reported in the literature[10,11,12]. These systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Drugs with an absorption window in the stomach or the upper small intestine[13], which act locally in the stomach[14] and drugs that are poorly soluble or unstable in the intestinal fluid are suitable candidates for the formulation of FDDS. Based on the mechanism of buoyancy, two different technologies i.e. non-effervescent and effervescent systems have been used[15]. The purpose of this work was to develop sustained release effervescent floating tablets with different polymers which prolongs the gastric residence time of Stavudine. Xanthan gum and guar

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gum were selected as because of their excellent solubility and stability under acidic and alkaline conditions. Guar gum hydrates and swells in cold water forming viscous colloidal dispersions or sols. This gelling property retards the drug release and makes it a flexible carrier for extended release dosage forms[16,17]. HPMC is a hydrophilic polymer that swells and forms a gel when comes in contact with water.

Materials and Methods

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

Preparation of Floating tablets

Stavudine 40mg was mixed with varying quantities of different polymers like xanthan gum, guar gum and HPMC & sifted through different mesh sieves. Other 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 3-4 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.) with flat-faced die punches of 8mm diameter. The tablet weights were 200±2 mg with average diameter of 8.0±0.2 mm. (Table 1)

(a) Evaluation of granules

Pre-compression parameters of granules

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

(b) Evaluation of tablets

The prepared tablets were evaluated for quality control tests like weight variation, hardness[18], thickness, friability[19], and content uniformity.

Assay of tablets

Ten tablets were selected randomly & crushed in motor with pestle. An accurately weighed quantity of powdered tablets (20mg) was transferred to 50ml volumetric flask containing approximately 20ml of 0.1N HCl and was allowed to stand for 1 h with intermittent sonication to ensure complete solubility of the drug. Then the volume was made up to 50ml with the buffer, and then 1ml of the solution was taken and filtered through 0.45 µm filter, diluted suitably and the absorbance of the resultant solution was measured spectrophotometrically at 266nm using 0.1N HCl as blank.

***In Vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time and total floating time. It is performed by visual observations during the dissolution studies[20].

***In vitro* drug release study**

The release rate of the stavudine from floating tablets (n=6) was determined using United States Pharmacopoeia 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. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hr, the samples were replaced with the same which was already maintained at sink conditions. After filtration through a 0.45 µm membrane filter, absorbance of these solutions was measured at 266nm using UV visible spectrophotometer (Shimadzu UV 1700) against 0.1N HCl as blank.

Weight gain and Water uptake (WU)

The study is done by immersing the dosage form in simulated gastric fluid at 37^{o}C ±0.5^{o}C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in the terms of percent weight gain, as given by equation

$$\mathbf{WU = (Wt - Wo)\ X\ 100\ /\ Wo}$$

In which Wt and Wo are the weights of the dosage form at time t and initially, respectively.

Kinetics of drug release

The release of drug from a polymeric matrix tablet depends on the gel layer around the tablet core. The dissolution profiles of all the batches were fitted to various kinetic models: zero order as cumulative amount of drug release vs time, first order as log cumulative percentage of drug remaining vs time and Higuchi's model as cumulative percentage of drug release vs square root of time to ascertain the kinetics of drug release.

Mechanism of drug release

Drug release data was fitted to Korsmeyer–Peppas 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.

$$\mathbf{Mt/M_\infty = at^n}$$

Where Mt/M_∞ is the fractional solute release, t is the release time, a, is constant incorporating structural and geometrical characteristics of the dosage form and n is the release exponent indicative of drug release mechanism and function of time, t.

Results and Discussion

The present study was aimed to prepare and evaluate floating tablets of stavudine with polymers like xanthan gum, guar gum and HPMC using dry granulation technique. Both the gums have excellent solubility and stability under acidic and alkaline conditions. As HPMC forms low density hydrocolloid system and 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 stomach pH. Sodium CMC was used in combination with HPMC to slow the drug release because of its 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 (θ) was in the range of 23.23 ± 1.3 to 26.10 ± 1.6^0. Bulk density ranged between 0.298 ± 0.02 to 0.432 ± 0.05 gm/cm^3. Tapped density ranged between 0.334 ± 0.01 to 0.569 ± 0.08 gm/cm^3. Carr Index was found to be 21.12 ± 0.21 to 25.01 ± 0.12. These values indicate that the prepared granules exhibited good flow properties. The thicknesses and hardness of the tablets were found in the range of 3.12 ± 0.05 - 3.24± 0.21 mm and 4.8 ± 0.13- 5.8 ± 0.13 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. The cumulative percent drug release was found to be in the range of 71.12± 0.65 to 97.12 ± 0.12 %. Among all the formulations F7 was found to be the optimized in terms of floating properties at the end of 12 hr as shown by results in table 3. The dissolution profiles of all the formulations are shown in figure 1, 2, 3 &4. The assays of tablets of all the formulations were found within the range as per the requirement of pharmacopoeia. Water uptake and lag time was increased with the increase in polymer concentration but total drug release was decreased. The data clearly indicate the drug release can be effectively controlled by varying the polymer and its ratio. On immersion in 0.1 N HCl, at 37 ± 0.5^0C, all floating tablets floats immediately and remain buoyant up to 24 h without disintegration only in case of HPMC containing tablets. It was observed that the gas generated by sodium bicarbonate is trapped and protected within the gel, formed by hydration of polymers, thus decreasing the density of the tablet below 1 and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies in case of HPMC and xanthan gum containing tablets. The penetration of water into tablets prepared with guar gum was rather slow, causing delayed gel formation and subsequent increase in the floating lag time compared to tablets prepared with xanthan gum. The data obtained from *in vitro* dissolution studies were fitted in different models (shown in Table-4). The Higuchi plots were found to be followed as indicated by their high regression value. To confirm the exact mechanism of drug release from these tablets, the data were fitted to Higuchi and Korsmeyer Peppa's equation. The formulation F7 with HPMC K 100 M (20%) shows maximum release of 93.25 ± 0.25 % at a time period of 12 h 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 (0.981) and Peppa's (n = 0.581) plot respectively, the drug release was confirmed to follow diffusion mediated non-fickian transport mechanism.

Conclusion

Floating drug delivery has become the most popular method for controlling the drug release. Stavudine floating tablets were prepared by blending the drug, polymers (xanthan gum, guar gum, HPMC), gas generating agent, and diluent followed by slugging. These tablets swelled while coming in contact with the aqueous medium. The formulations containing xanthan gum and guar gum exhibited good drug retaining capabilities but floating abilities were found to be poor when compared with HPMC containing tablets. It was concluded that formulation F7 gave the best *in vitro* release of 93.25 ± 0.25% in 12 hrs.

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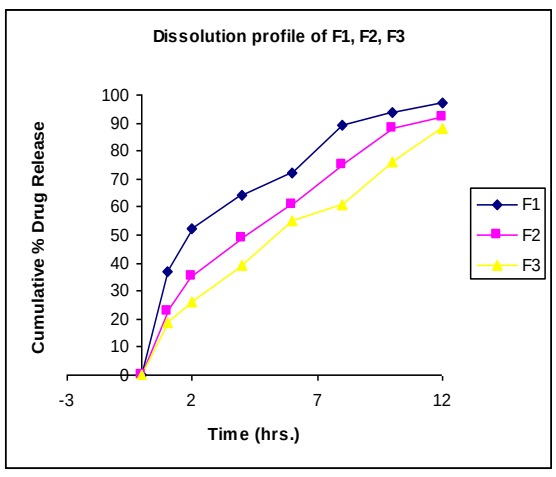

Figure 1

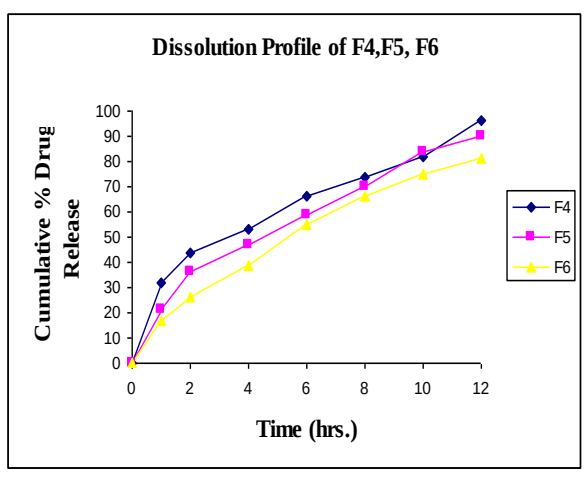

Figure 2

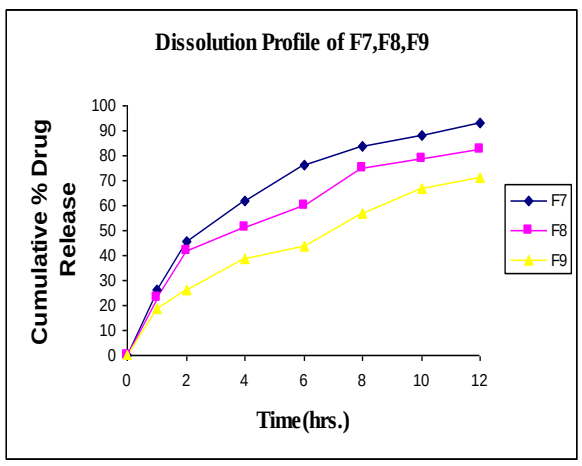

Figure 3

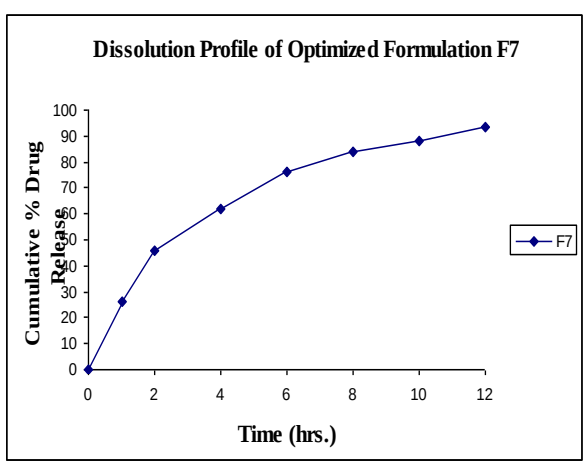

Figure 4

Table 1: Tablet Formulation for Preliminary Trials.

Ingredients	Formulation Code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Stavudine	40	40	40	40	40	40	40	40	40
Xanthan gum	40	60	80	-	-	-	-	-	-
Guar Gum	-	-	-	40	60	80	-	-	-
HPMC K100	-	-	-	-	-	-	40	60	80
Na CMC	-	-	-	-	-	-	5	5	5
Lactose	102.95	82.95	62.95	102.95	82.95	62.95	97.95	77.95	57.95
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1
CSD	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
NaHCO3	15	15	15	15	15	15	15	15	15

Table 2: Granule properties of formulation F1 to F9 of stavudine matrix tablets.

Parameters	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Angle of Repose (θ)	24.11 ± 1.2	25.15 ±1.5	25.35 ±1.0	23.23 ±1.3	25.10 ±1.2	25.67 ±1.1	23.78 ±1.6	24.19 ±1.4	26.10 ±1.6
Bulk Density (gm/cm^3)	0.298 ±0.02	0.365 ± 0.05	0.331 ± 0.03	0.432 ± 0.05	0.387 ± 0.04	0.391 ± 0.07	0.427 ± 0.05	0.346 ± 0.03	0.418 ± 0.07
Tapped Density (gm/cm^3)	0.334 ±0.01	0.410 ± 0.02	0.382 ± 0.04	0.511 ± 0.01	0.541 ± 0.06	0.538 ± 0.07	0.569 ± 0.08	0.478 ± 0.02	0.569 ± 0.01
C.I. (%)	22.22 ± 0.11	25.01 ± 0.12	22.17 ± 0.21	23.19 ± 0.12	23.51 ± 0.23	21.12 ± 0.21	22.31 ± 0.31	22.67 ± 0.14	22.42 ± 0.24

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

Table 3: Tablet properties of the different formulations of stavudine floating tablets.

Parameters	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Thickness (mm)	3.12 ± 0.12	3.14 ± 0.06	3.24 ± 0.04	3.19 ±0.05	3.17 ± 0.22	3.22 ±0.11	3.12 ± 0.05	3.23 ± 0.11	3.24 ± 0.21
Hardness (kp)	4.8 ± 0.13	5.1 ± 0.11	5.2 ± 0.24	4.9 ± 0.12	5.3 ± 0.21	5.4 ± 0.23	5.4 ± 0.67	5.6 ± 0.42	5. 8 ± 0.13
Friability (%)	0.21	0.14	0.18	0.11	0.17	0.15	0.29	0.08	0.06
Floating lag time (sec.)	23	33	55	19	37	65	21	43	79
Cumulative % drug Release	97.12 ± 0.12	92.04 ± 0.22	88.33 ± 0.46	96.21 ± 0.66	89.73 ± 0.76	81.25 ± 0.62	93.25 ± 0.25	82.66 ± 0.81	71.12 ± 0.65

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

Table 4- Release kinetics parameters of designed controlled release matrix tablets of Stavudine

Formulation code	Zero order plots	First Order plots	Higuchi plots	Korsmeyer et al's plots
F1	0.593	0.946	0.971	0.921
F2	0.868	0.959	0.991	0.928
F3	0.937	0.943	0.966	0.919
F4	0.719	0.924	0.987	0.915
F5	0.866	0.916	0.990	0.924
F6	0.917	0.949	0.978	0.921
F7	0.677	0.960	0.981	0.918
F8	0.718	0.923	0.985	0.923
F9	0.865	0.948	0.988	0.919