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Designing, Development & Evaluation of Floating Acyclovir Tablets

Smriti Khatri[1*], Farhan Jalees Ahmed[2], Sushma Drabu[2], Babita Sarangi[1]

[1] *Dr. K. N. Modi Institute of Pharmaceutical Education & Research, Modinagar- 201201, U.P., India*

[2] *Jamia Hamdard, New Delhi, India*

Address for Correspondance: Smriti Khatri; smritidua3@gmail.com

ABSTRACT: Floating Drug delivery system helps the drug to remain in stomach for longer periodof time and hence can release the drug. The aim of the present study was to develop a hydrodynamically balanced system of acyclovir as single-unit floating tablets. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), alone or in combination, Drug release of optimized formulation was fitted in to zero order, first order and higuchi models. It was found that the release followed Zero order kinetics. Good stability was observed for 6 months during stability studies. Thus, results of the current study clearly indicate, a promising potential of the Acyclovir floating system as an alternative to the conventional dosage form.

KEYWORDS: Acyclovir; Floating Drug Delivery System; Higuchi Model.

INTRODUCTION

The important point in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract until all the drug is released for desire period of time. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose1. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamic profiles is to retain the drug reservoir above its absorption area, i.e. In the stomach and to release the drug in a controlled manner, so as to achieve zero order kinetics for a prolonged period of time, one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile is to control the gastric residence time in GIT [1-3]. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release [4-6]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract [10, 11]. It retains the dosage form at the site of absorption and thus enhances the bioavailability [7-9].

Acyclovir is an antiviral drug (deoxiguanosine). It is widely used in the treatment of Herpes simplex virus infections, as well as in the treatment of Herpes zoster (shingles). Bioavailability of acyclovir is 10–20% when given orally owing to an important first pass metabolism. It has an elimination half-life of 2-3 hours and has an absorption zone from the upper intestinal tract. The recommended adult oral dosage of acyclovir is 200 mg twice daily or 400 mg once daily. The effective treatment of genital herpes simplex requires administration of 1000 mg of acyclovir in 5 divided doses per day. it is slowly and scarcely absorbed from the gastrointestinal tract. The plasma concentration reaches its therapeutic level in 1.5 to 2 hr. The estimated total bioavailability of acyclovir is between 15% and 30% and decreases with increasing dose. Acyclovir is almost completely unionized and has the maximum solubility (2.5 mg/ml) at ph 7.0 And acyclovir has a short half life (2.5-3.3 hours) and low bioavailability (15-30%) in the upper part of

GIT. Floating matrix tablets of acyclovir were developed to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, thickness, and weight variation. Further, tablets were evaluated for in vitro release characteristics for 8 hr. The effect of effervescent on buoyancy and drug release pattern was also studied. In vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC-based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

MATERIALS & METHODS

Acyclovir and hydroxypropyl methylcellulose (HPMC) K4M were obtained as a gift sample from M/s Ranbaxy Research Laboratories (Gurgaon, India).

Preparation of acyclovir tablets

Direct compression technique

The composition of different formulation of Acyclovir floating tablets shown in Table 1.

Floating tablets were prepared by direct compression technique. hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), sodium bicarbonate, and acyclovir were mixed homogeneously. Magnesium stearate, talc and Aerosil were added as a lubricant and the powder was compressed into tablets using multi punch tablet machine.

Evaluation of tablets

(i) Precompression parameters of Acyclovir blend

The flow properties of blend (before compression) were characterized in terms of angle of repose6, tapped density, bulk density7, Carr's index8, and Hausner ratio.

The tablets were evaluated for various parameters as follows

(ii) Appearance and Shape

The general appearance of the tablets includes the morphological characteristics like size, shape, colour, etc.

(iii) Weight Variation/uniformity

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed as per I.P.

(iv) Uniformity of content

Five tablets were weighed and their contents were removed. An accurately weighed sample equivalent to 100 mg of Acyclovir was taken in a stoppered volumetric flask (100ml). The content was dissolved in 0.1N HCl and the volume made upto 100 ml. This solution was filtered through Whatman filter paper No.41. The solution was diluted and the absorbance was measured at 254 nm. The drug content was calculated.

(v) In Vitro Buoyancy Study

All formulations were subjected to buoyancy test. Buoyancy test was done using USP type II apparatus at 50 rpm maintained at 37±0.5°C. tablets were placed in 900 ml jar containing 0.1N HCl as dissolution medium. The amount of time during which the capsules remained buoyant was the floating time(Table 2).

Ingredients	**AT1**	**AT2**	**AT3**	**AT4**	**AT5**	**AT6**	**AT7**
Acyclovir	200mg	200mg	200mg	200mg	200mg	200mg	200mg
HPMC K4M:HPMC K15M	0.5:1.5	1:1	1.5:0.5	2:0	2:0	-	-
GUAR GUM	20 mg	20 mg	30 mg	30mg	40mg	40mg	50 mg
SCMC	-	-	-	-	100mg	150mg	200mg
SODIUM BICARBONATE	20	20	30	30	40	40	50

Table 1: Formula of acyclovir tablets

Formulation	Floating lag time (min)	Floating Time (hrs)
AT1	5	12
AT2	5	14
AT3	4.5	15
AT4	4.5	22
AT5	3.5	23
AT6	3.5	21
AT7	3	20

Table 2. Results of In Vitro Buoyancy Study

Dissolution Studies

The release rate of acyclovir from floating matrix tablets(n=3) was determined using USP dissolution test apparatus Type I. The dissolution test was performed using 900 ml of 0.1N HCl at 50 rpm. The temperature of the medium was maintained at 37±0.5ºc and the study was carried out for 12 hrs. Aliquot of 5 ml were withdrawn at an interval of 30 min, 1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr respectively. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper (No.41) and the volume made upto 10 ml with 0.1N HCl. The samples were analyzed at 254 nm.

Kinetics of Drug Release

The dissolution profile of all the batches were fitted to zero order kinetics, first order kinetics, Higuchi, Hixon-Crowell, Korsmeyer and Peppas equation to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, Different n values of Korsmeyer and Peppas equation indicate different mechanism of drug release. If the n value is around 0.5 then fickian diffusion is apparent, if the n value ranges from 0.5 to 1.0 it represents anomalous diffusion transport and if the n value reaches 1 and above then case II and Super case II transport is indicated which shows that the release is following Zero order.

RESULTS & DISCUSSION

Compatibility studies of Acyclovir

Acyclovir was subjected to Drug – Excipients compatibility studies with various excipients The mixtures have shown no colour change and lumping.

Precompression parameters of Acyclovir granules

The formulations showed good flow property and Carr's index. Angle of repose ranged from 24.10 ±0.7 to 25.10 ±0.1 and the Carr's index ranged from 15.50±0.32 to 32.39±0.27. The Bulk Density and Tapped Bulk Density of the prepared granules ranged from 0.465±0.012 to 0.551±0.015 and 0.598±0.058 to 0.710±0.036 respectively. The results of angle of repose indicates good flow property of the granules and the value of carr's compressibility index further showed support for the flow property.

Post compression parameters of Acyclovir floating Tablets

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The hardness of the tablets was measured by Pfizer tester (Biological museum, Mumbai, India) and was in between 4.8 kg/cm2. The friability was measured by Friabilator (Roche Type Friabilator) and was found to be 0.499 which is an indication of satisfactory mechanical resistance of the tablets.

The drug content

The drug content estimations showed values in the range of 99.12 with 0.04% variation which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±7.5% of the weight.

Weight variation

The average weight of tablets within each formulation was found to be uniform. Not more than two of the individual weights deviated from the average weight by more than 7.5% and none deviated by more than twice that percentage, which provided good weight uniformity.

Dissolution studies

In vitro release test was performed in 900ml of simulated gastric fluid (pH 1.2) containing 0.5% Tween 80, which was based on USP XXII method (Dissolution apparatus at 50 rpm and 37±0.5°C). The tablet formulation (containing 200mg of acyclovir) was placed and 1ml sample was withdrawn at regular time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24

hours) and the same amount of simulated gastric fluid was replaced. The withdrawn 1ml sample were diluted with 3ml of simulated gastric fluid containing 0.5% Tween 80 and analyzed for the drug content by using UV-spectrophotometer at 254nm. The cumulative percentage of drug release was calculated using an equation obtained from a standard curve.
Thus, results of the current study clearly indicate, a promising potential of the Acyclovir floating system as an alternative to the conventional dosage form.

CONCLUSION

Hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG), and sodium carboxymethylcellulose (SCMC), sodium bicarbonate, and the acyclovir (AT 5) showed controlled drug release for 16hrs, emerging as best formulation. Mechanism of drug release of optimized formulation AT 5) found to be Zero order non fickian diffusion. Good stability was observed for 6 months during stability studies. Thus, results of the current study clearly indicate, a promising potential of the Acyclovir floating system as an alternative to the conventional dosage form.

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