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Formulation and Evaluation of Acyclovir Capsules

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Abstract

Hydrodynamic Balanced Systems (HBS) can remain in stomach for long periods and hence can release the drug over a prolonged period of time. The aim of the present study was to develop a hydrodynamically balanced system of acyclovir as single-unit floating capsules. Low-density polymers were used for formulation and development of these floating capsules. The capsules were prepared by physical blending of acyclovir and various polymers in different ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in 0.1 N HCl. HPMC K4M gave the best in vitro percentage release and was found as the optimized formulation. By fitting the data into zero-order, first-order, and Higuchi models, we concluded that the release followed zero-order kinetics, as the correlation coefficient (R value) was higher for zero-order release.

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Introduction

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, 2, 3]. Gastro retentive dosage forms significantly extend

the period of time over which drugs may be released, prolong dosing intervals and increase patient compliance. Such retention systems are much important for drugs that are degraded in intestine or for drugs like antacids or certain antibiotics, enzymes that act locally in the stomach such systems are more advantageous in improving gastrointestinal absorption of drugs with narrow absorption windows as well as for controlling release of the drugs having site-specific absorption limitation [4,5,6]. Retention of drug delivery systems in the stomach prolongs overall GIT transit time, thereby resulting in improved bioavailability for some drugs [7]. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying [8, 9]. 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 [12]. Acyclovir [9-(2-hydroxyethoxymethyl) guanine] is an acyclic nucleoside analogue of guanosine that is a potent and selective antiviral agent. Acyclovir has a relatively short plasma half-life (3 hr). When orally administered, 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 [13]. And acyclovir has a short half life (2.5-3.3 hours) and low bioavailability (15-30%) in the upper part of GIT.

Material and Method

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

2.1 Preparation of Capsules

Single-unit capsules were formulated with the help of different low-density polymers, which upon administration would attain a density of less than that of the gastric fluids and therefore would float [14]. Exactly 200 mg of acyclovir was weighed and physically blended with polymers in a glass mortar and pestle and filled in a hard gelatin capsule # 0. The drug and polymer blend was transferred into the empty capsule shells manually. The polymer and drug mixture was blended for 10 minutes in a double cone blender. The composition of the HBS capsules is given in Table 1.

Table 1: Formulae of Acyclovir capsules

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200	200
HPMC K4M	60	120	180	240	300	360	420	480	—	—	—	—	—
Compritol 888 ATO	—	—	—	—	—	—	—	—	60	120	180	240	300
Sodium bicarbonate	10	10	20	20	20	30	30	30	20	30	40	50	60
Succinic acid	10	15	20	25	30	35	30	30	—	—	—	—	—

2.2 Evaluation of capsules

The capsules were evaluated for various parameters as follows

2.2.1 Appearance and Shape

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

2.2.2 Weight Variation/uniformity of weight

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

2.2.3 Uniformity of content

Five capsules 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.

2.2.4 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. Capsules 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. The polymer that showed the best floating behavior was used for in vitro release studies

2.2.5 Dissolution Studies

The release rate of acyclovir from floating matrix capsules (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±0.5°c 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.

2.2.6 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, and the model with the higher correlation coefficient was considered to be the best fit model. (Table 1)

Table 1: Models for analysis of *in vitro* dissolution data

S. No.	Model	Equation	Ref
1	Zero Order	F=kxt (where F is the fraction of drug release, k is the release constant and t is the time)	Chen and Hao, 1998 [15]
2	First Order	ln F= kxt (where F is the fraction of drug release, k is the release constant and t is the time)	Shah et al., 1987 [16]
3	Higuchi	$F=k\sqrt{t}$	Higuchi, 1961 [17]
4	Hixson and Crowell Powder Dissolution Method	$F=100(1-(1-kt)^3)$	Hixson and Crowell, 1931 [18]
5	Korsmeyer and Peppas Model	$F=kt^{n*}$	Korsmeyer et al., 1983: Ritger and Peppas, 1987 [19]

*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.

3 Result and discussion

3.1 Weight variation

The average weight of capsules within each formulation was found to be uniform. This indicates uniform filling of powder blend during capsule filling. 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.

3.2 Drug content

In all the ten formulations, the values for drug content were found to be uniform among different batches of the FDDS and ranged between 98.3 and 102.7% of the theoretical value. The value ensures good uniformity of the drug content in the capsules.

3.3 In vitro buoyancy study of the capsules

The initial batches of A1 and A2 prepared with less amount of sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the capsule. The sodium bicarbonate generates Carbondioxide in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the capsule below 1 gm/mL, and the capsule becomes buoyant. Succinic acid was incorporated in the formulation batches A1 to A8 to nullify the effect of the acidic dissolution media on the drug release. No formulation from batches B1 to B5 containing Compritol 888 ATO showed floating because the formulation did not swell and hence failed to form a gel.

3.4 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 capsule 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 as shown in table 2.

Table 2: Floating time, Time for 50% of drug release and Time for 85% of drug release profile for acyclovir capsules

Formulation No.	Floating Time (hours)	T_{50} (Time for 50% of drug release) ±SD	T_{85} (Time for 85% of drug release) ±SD
A1	5	—	—
A2	23	5.5	11.3
A3	13	6.0	11.7
A4	23	6.5	11.9
A5	23.5	6.9	12.2
A6	24	7.5	18.4
A7	24	8.8	20.5
A8	24	9.8	24.0
B1	—	0.9	5.0
B2	—	2.8	7.8
B3	—	3.6	10.2
B4	—	5.4	11.1
B5	—	4.2	13.1

The effect of the polymer concentration from preliminary trials on release profile of acyclovir shown in Figure 1.

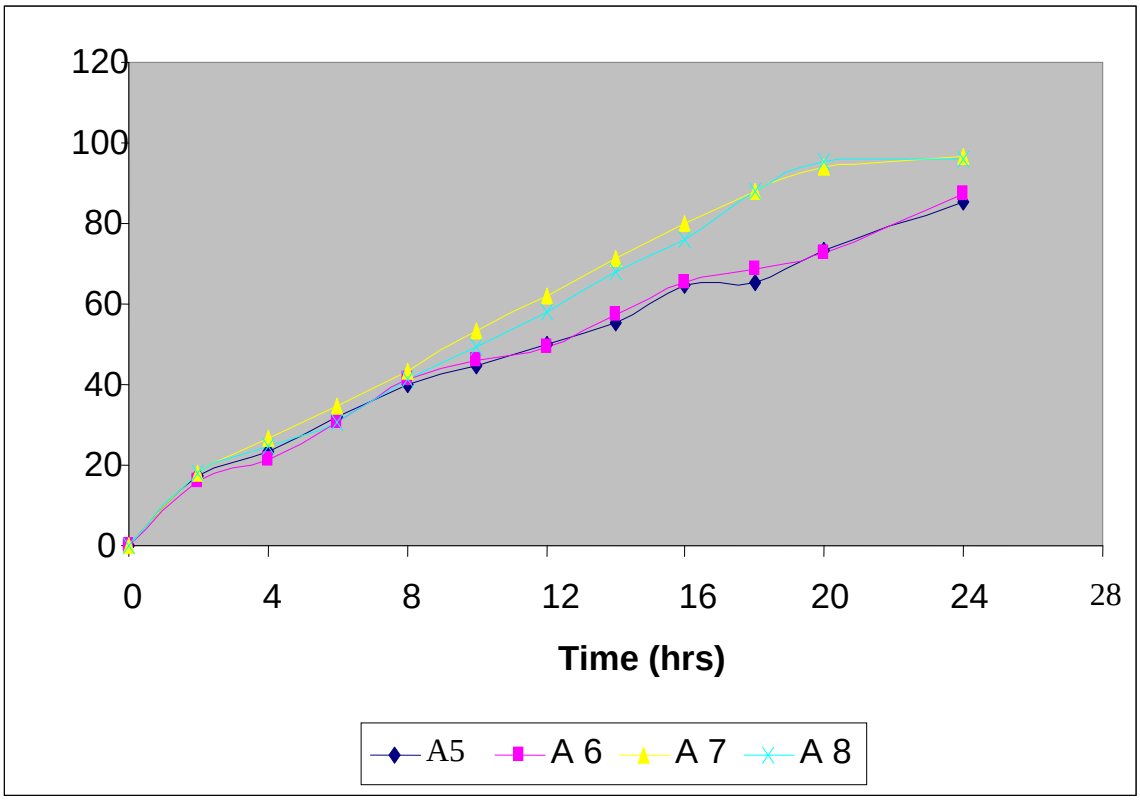

Figure 1: Release profile of acyclovir drug

Conclusion

The capsules were prepared by using various polymers such as HPMC K4M, and Compritol 888 ATO. Formulations were evaluated for floating behaviour, which showed floating time in the range of 20-24 hr. *In-vitro* drug release study was performed in simulated gastric fluid (1.2 pH), which shows that all formulations [A1-8] follow zero order drug release pattern and non-fickian as a drug release mechanism. The optimized formulation A8 gives the best results in term of the floating behavior, swelling index and drug release. Thus the above studies indicate a promising potential for acyclovir floating drug delivery system.

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