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Development and Evaluation of Floating Matrix Tablets of Acyclovir

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ABSTRACT

Acyclovir [9-(2-hydroxyethoxymethyl) guanine] is an acyclic nucleoside analogue of guanosine that is a potent and selective antiviral agent. It 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 short biological half life of drug favors the development of a sustained release formulation which retain in the stomach for a prolonged period of time.. The present work emphasis on the study of dissolution studies and in vitro buoyancy of acyclovir floating system.

Key words: Acyclovir, floating matrix tablets.

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INTRODUCTION

Acyclovir is a potent antiviral drug with low toxicity. It is used in treatment of herpes simplex infection, varicella zoster infection, chicken pox and shingles [1]. Recently, acyclovir has been used in combination with AZT to treat AIDS patients. Acyclovir [9-(2-hydroxyethoxymethy) guanine] is an acyclic nucleoside analogue of guanosine. It has a relatively short plasma half-life (3 hr). It is slowly and scarcely absorbed from the gastrointestinal tract when administered orally and has maximum absorption in stomach and upper part of small intestine [2]. As a result of low gastric retention time, the bioavailability of drug is low as large portion of drug misses the absorption window. The plasma concentration reaches its therapeutic level in 1.5 to 2 hour. The total bioavailability of acyclovir is estimated between 15% and 30% and decreases with increasing dose [7, 8]. The drug is almost completely unionized and has the maximum solubility (2.5 mg/ml) at pH 7.0[2].

Due to the ease of administration, patient compliance and flexibility in formulation, etc oral delivery of drug is the most preferable route of drug delivery [3]. A traditional oral sustained release formulation releases most of the drug at the colon. Therefore the drug must have an absorption window either in the colon or throughout the gastrointestinal tract [4]. Conventional drug delivery systems achieve as well as maintain the therapeutically effective range of drug concentration needed for treatment only when taken several times a day. This results significant fluctuations in drug levels and side effects [5].Acyclovir has 30% absolute bioavailability and is absorbed only in stomach and the initial part of the small intestine. Hence the success of clinically acceptable sustained release dosage forms of acyclovir prepared with conventional technology is doubtful. The oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract can be improved by the floating drug delivery systems that can be retained in the stomach [6]. Thus a single dose for the whole duration of treatment can be considered. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

MATERIALS AND METHODS

Materials

The following chemicals were used. Acyclovir, hydroxypropyl methyl cellulose K4M, Compritol 888 ATO, Sodium bicarbonate, Succinic acid, talc, Magnesium stearate.

Tablet Preparation

The direct compression technique was used to prepare different tablet formulation. The powders were passed though an 80 mesh sieve (180 micrometer size). Drug and matrix polymers (HPMC K4M and compritol 888 ATO) were mixed thoroughly in required quantities as shown in Table 1. As glidant and lubricant, talc and magnesium stearate were added respectively. Using a multipunch tablet compression machine the blend was compressed.

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Table 1: Formulae of acyclovir tablets

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9	B1	B2	B3	B4	B5
Acyclovir	200	200	200	200	200	200	200	200	200	200	200	200	200	200
HPMC k4M	50	100	150	200	250	300	350	400	450	—	—	—	—	—
Compritol 888 ATO	—	—	—	—	—	—	—	—	---	50	100	200	250	300
Sodium bicarbonate	--	--	20	20	20	30	30	30	30	20	30	40	50	60
Succinic acid	10	15	20	25	30	35	30	30	30	—	—	—	—	—
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total weight	280	345	410	465	520	585	630	680	730	290	350	460	520	580

Floating Behaviour of the Tablets

Time period between placing the tablet in the medium and the tablet floating is the floating lag time which was determined by the in vitro buoyancy method [9]. The tablets were placed in a 100 ml beaker containing 0.1 mol/l HCl. The time required for the tablets to rise to the surface and float was taken as the floating lag time.

Swelling Index

The swelling index of the tablets was determined in 0.1 mol /l HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals and the swelling index was calculated by the following equation:

Where, W0 is the initial weight of the tablet, and Wt is the weight of the tablet at time t. Tablets composed of polymeric matrices form a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. The kinetics of swelling is important because the gel barrier is formed by water penetration. Swelling is also vital to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored [24-25].

In Vitro Studies

The release rate of acyclovir from floating tablets (n = 3) was determined. The dissolution test was performed using United States Pharmacopeia (USP) type II (paddle) apparatus, 900 mL of 0.1 N HCl, at 37°C ± 0.5°C and 100 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 24 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 254 nm using a Shimadzu UV-1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan). Cumulative percentage drug release was

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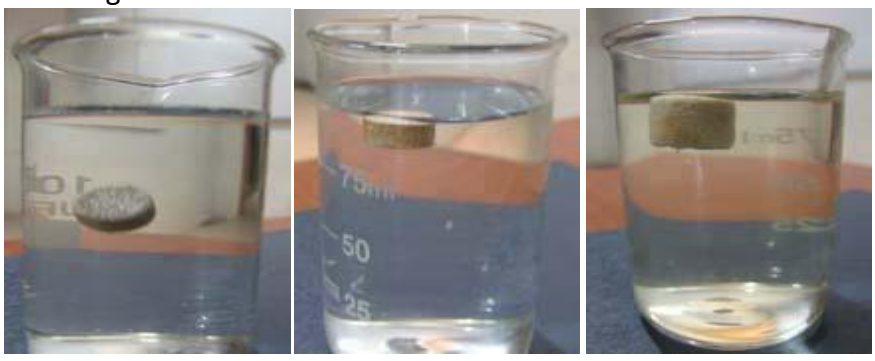
calculated using a PCP Disso Version 2.08 software (Poona College of Pharmacy, Pune, India), the time required for 50% and 85% drug release was calculated based on the Korsmeyer and Peppas model.

RESULTS AND DISCUSSIONS

Floating behavior of the tablets

Matrix tablets densities are made lower than the density of the release medium by incorporation of the highly porous powder in them. With the low density copolymer powder (based on the mass of the tablet), it was possible to achieve proper *in vitro* floating behavior for at least 10 h [9,10]. These tablets floated immediately upon contact with the release medium, in contrast to most conventional floating systems (including gas-generating ones), with no lag-times in floating behavior because the low density was provided from the beginning (t = 0). Air entrapped within the low density powder particles leads to extended floating time and this is only slowly removed from the system upon contact with the release medium [11, 12, 13].

The initial batches of A1 and A2 prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO_2 generation 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 tablet below 1 gm/mL, and the tablet becomes buoyant. To study the effect of sodium bicarbonate concentration on floating lag time, batches A3 to A8 were selected. It was found that as the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate 10% was essential to achieve optimum in vitro buoyancy (ie, floating lag time of 4 to 5 minutes and floating duration of 24 hours). Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus 10% concentration of sodium bicarbonate was kept constant for batches A6 to A9, which showed floating lag time between 4 and 6 minutes and remained floating for 24 hours. Succinic acid was incorporated in the formulation batches A1 to A8 to keep the tablet weight constant and 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.



At initial time **after 3 s** **after 8 h**

Figure 1: Floating behavior of the tablets at different time intervals

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Swelling index

The swelling index of the best batch after 8 h was 1.622, which may be because of the high viscosity and high water retention of HPMC K4M.

In vitro release test

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.

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

Formulation No.	Floating Lag Time (minutes)	Floating Time (hours)	T_{50} (Time for 50% of drug release) ±SD	T_{85} (Time for 85% of drug release) ±SD
A1		6	—	—
A2	10	24	6.5	12.3
A3	30	12	7.0	12.7
A4	4.2	24	7.1	12.9
A5	4.1	24	7.1	13.2
A6	4.4	24	8.5	20.4
A7	4.6	24	9.8	23.5
A8	4.5	24	9.8	23.9
A9	4.4	24	9.6	22.1
B1	—	—	0.9	4.0
B2	—	—	2.8	7.9
B3	—	—	3.6	11.2
B4	—	—	5.4	13.1
B5	—	—	4.2	12.1

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

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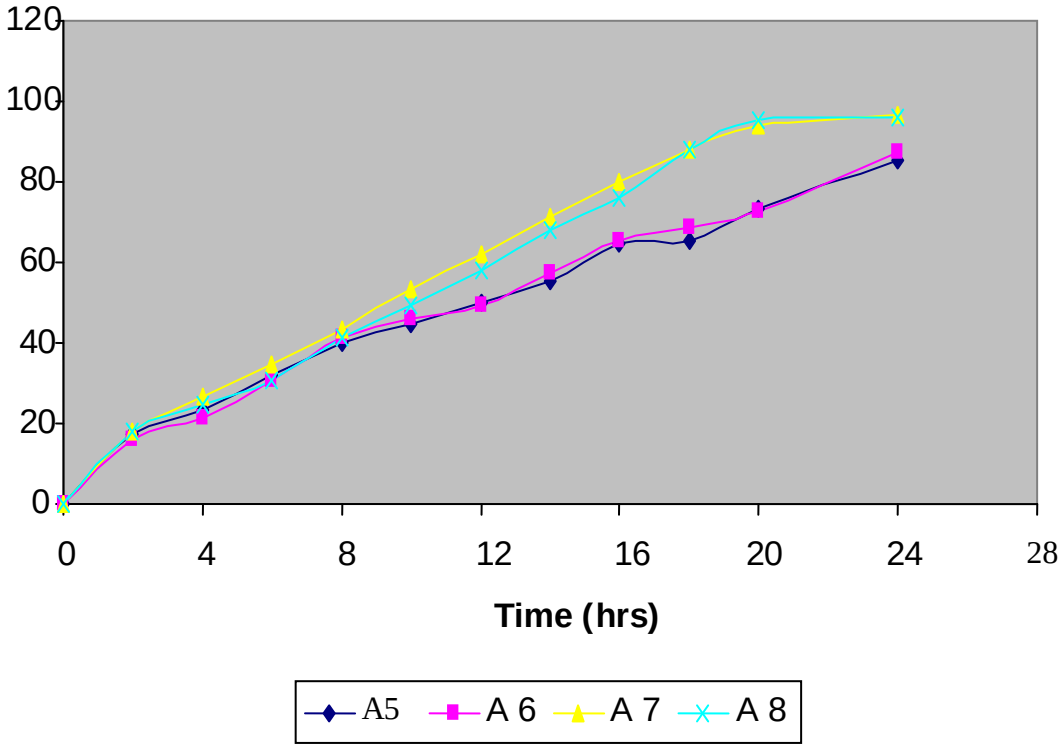

Figure 1: *in-vitro* release profile for Acyclovir tablets

CONCLUSION

The tablets were prepared by using various polymers such as HPMC K4M, HPMC and Comprito 888 ATO. Formulations were evaluated for floating behaviour, which showed floating lag time [A8] in the range of 4.5 minutes, and total 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 [A1-9] 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 required floating lag time, swelling index and drug release. Thus the above studies indicate a promising potential for acyclovir floating drug delivery system.

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