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Formulation and evaluation of floating gastroretentive capsules of acyclovir with piperine as a bioenhancer

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Abstract
The aim of the present investigation was to develop and evaluate the sustained release hydrodynamic balanced systems for acyclovir using hydrocolloid polymers such as hydroxy propyl methylcellulose (HPMC) and ethyl cellulose (EC). Floating was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The best formulation was selected based on *in vitro* characteristics and further *in vivo* studies were carried out on Sprague Dawley strain rats to evaluate the bioavailability of the drug. Nearly two times higher Area under the curve (AUC) was observed as compared to the drug solution. In addition, Acyclovir formulation showed the ability to maintain the acyclovir plasma concentration through 24 hr as compared to the drug solution that could maintain this level of drug only for 4 hr.

Keywords: Acyclovir, Hydroxyl propyl methyl cellulose, Piperine, Floating Drug Delivery System

1. Introduction
Bioenhancers` are the agents, which, when combined with an active drug lead to the potentiation of the pharmacological effect due to increase in the bioavailability of the drug. One such example is piperine, an alkaloid obtained from *Piper nigrum.* Piperine has the ability to increase drug bioavailability by increasing the blood supply to the gastrointestinal tract, decreasing hydrochloric acid secretion which prevents breakdown of some drugs, increasing emulsifying content of the gut, increasing enzymes like gamma-glutamyl transpeptidase which participate in active and passive transport of nutrients to the intestinal cells, and inhibiting enzymes participating in biotransformation of drugs, preventing their inactivation and elimination [1]. Another rationale approach to enhance bioavailability and improve pharmacokinetics 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. Thus, one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile is to control the gastric residence time in GIT [2, 3]. Gastro retentive dosage forms significantly extend the period of time over which drugs may be released and prolong dosing intervals which may increase patient compliance. Such systems are more advantageous in improving gastrointestinal absorption of drugs with narrow absorption windows as well as for controlling the release of the drugs having site-specific absorption limitation [4-6]. Retention of drug delivery systems in the stomach prolongs the overall GI 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, 13]. 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 of 3 hrs. The aim of the present study was to develop a hydro-dynamically balanced system of acyclovir with piperine [14] as single-unit floating capsules.

2. Material and Method

Acyclovir and Hydroxypropyl Methylcellulose (HPMC) K4M were obtained as a gift sample from M/s Ranbaxy Research Laboratories (Gurgaon, India). Piperine was purchased from Sigma Chem. Ltd., New Delhi. All other chemicals and reagents used were of analytical grade.

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. 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 with Piperine

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Acyclovir	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
HPMCK4M	150	200	250	300	350	400				
Ethyl Cellulose							50	100	150	200
Sodium bicarbonate	10	20	30	40	50	50	50	50	50	50
Piperine	40	40	40	40	40	40	40	40	40	40
Succinic Acid	10	15	20	25	30	30	30	30	30	30

2.2 Evaluation of capsules [15-18]

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 (100 ml). The content was dissolved in 0.1 N HCl and the volume made up to 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 [19]

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 II. 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 ºC and the study was carried out for 12 hrs. Aliquot of 5 ml was withdrawn at an interval of 30 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr and 12 hr respectively. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper (No. 41) and the volume made up to 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 was 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 highest correlation coefficient was considered to be the best fit model.

2.2.7 Pharmacokinetic study of acyclovir floating capsules with piperine [20]

Rats (Sprague Dawley strain), 6 to 8 months old, weighing 200–220 g were divided into four groups, each consisting of six animals. The protocols for these investigations were approved by the Institutional Animal ethics committee in accordance with the disciplinary principles and guidelines of CPCSEA (registration no 723/02/a/CPCSEA). Rats were kept on fasting 12 h before drug administration and until 24 h post dosing. Water was provided ad libitum throughout the study. The first group received an oral administration of 0.1 % sodium CMC suspension (normal control). The second group received an oral administration of 4 % drug solution in sodium CMC suspension. An accurately weighed sample of floating capsules equivalent to 40 mg of acyclovir were suspended in 0.1 % sodium CMC suspension and administered orally using a feeder tube under non-anesthetic condition. At 1, 2, 4, 8, 12 and 24 h time intervals, blood samples were collected from the jugular vein in Eppendorf tubes and centrifuged at 3000 rpm for 10 min (REMI Equipment, Mumbai, India). Supernatant was collected and filtered through a 0.45 μm filter into volumetric flask and drug concentration was determined by LCMS method.

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

Hydrodynamic Balance System and ranged between 98.3 and 102.7% of the theoretical value. The value ensured the uniformity of the drug content in the capsules.

3.3 *In vitro* buoyancy study of the capsules [21-24]

The initial batches of M1 and M2 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 carbon dioxide in the presence of dissolution medium (0.1 N HCl).

The gas generated was 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 became buoyant. Succinic acid was incorporated in the formulation batches to nullify the effect of the acidic dissolution media on the drug release. No formulation from batches M7 to M10 containing Ethyl Cellulose showed floating because the formulation did not swell and hence failed to form a gel. The formulation M6 containing drug and polymers in the ratio of 50:50 remained buoyant in 0.1 N HCl for more than 12 h and maintained the shape as shown in figure 1. So this combination was selected for further study

Fig 1: The formulation M6 containing drug and polymers remained buoyant for more than 12 h

3.4 Dissolution studies [25-27]

In vitro release test was performed in 900 ml 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 200 mg of acyclovir) was placed and 1 ml 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 was diluted with 3 ml of simulated gastric fluid containing 0.5% Tween 80 and analyzed for the drug content by using UV-spectrophotometer at 254 nm. The cumulative percentage of drug release was calculated as shown in Figure 2.

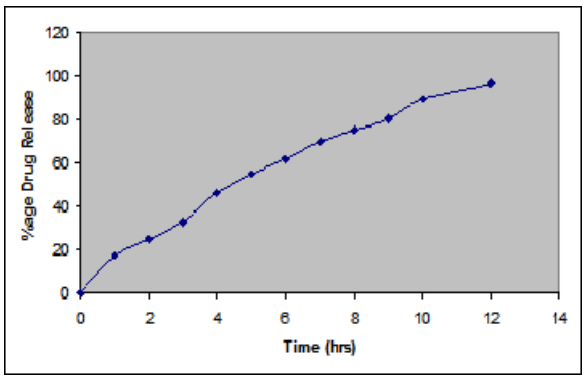

Fig 2: *In vitro* release profile from optimized Capsules of Acyclovir with pipeline

3.5 Kinetics of drug release

The *in vitro* release from the optimized formulation was fitted to kinetic release models (PCP Disso v3) and it was concluded that the drug release from the formulation followed a zero order, as the R^2 value for zero order was 0.995 as compared to the R^2 value for first order release was 0.959. Further the zero order release was supported by good R^2 value by fitting the *in vitro* release into Higuchi model i.e. 0.932. Thus, it could be concluded that the drug release from the formulation is diffusion controlled.

3.6 Pharmacokinetic parameters of different formulations containing acyclovir after oral administration.

The formulation of acyclovir with piperine showed superiority over the other formulations. Nearly two times higher AUC0–24 value of acyclovir for these capsules (14614.13±6953.13 ng h/ml) as compared to drug solution (7552.33±3219.09 ng h/ml) was observed. In addition, Acyclovir formulation showed the ability to maintain the acyclovir plasma concentration through 24 h as compared to the drug solution that could maintain this level of drug only for 4 h.

4. Conclusion

The results obtained, confirmed the sustained release potential of floating capsules of acyclovir with piperine prepared from HPMC K4M polymer. Hence, the overall better pharmacokinetics performance of the floating Hydrodynamically balanced system of acyclovir with piperine in comparison to drug solution is due to increased residence time within the upper GI tract as evident by the GI distribution study as well as due to piperine as a bioenhancer.

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