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Research Article

DESIGN & IN-VITRO EVALUATION OF GASTRORETENTIVE, SUSTAINED RELEASE TABLET FORMULATION OF ACYCLOVIR USING HYDROPHILIC POLYMERS

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ABSTRACT

The purpose of this research was to develop a gastroretentive sustained release delivery system with swellable and mucoadhesive properties for a drug like acyclovir. Hydrophilic polymers like poly ethylene oxide, and Hydroxypropyl methylcellulose were tried in combinations and statistically optimized. A 3^2 factorial design was used to optimize the formulation to get the release profile for up to 12 h. Concentrations of HPMC K15 and Polyox WSR301 was used as independent variables and in vitro drug release profile, swelling characteristics and in vitro mucoadhesive strength as dependent variables. The optimized formulation (F_3) showed the maximum drug release (95.2 ± 4.5%), highest swelling index (182.47) and maximum mucoadhesive strength in 12 h. The in vitro drug release mechanism was found to be of anomalous or non-Fickian type. The high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of acyclovir. A formulation developed using swellable mucoadhesive polymers, show excellent adhesion and gastroretention and desired release profiles thus providing absolute control.

Keywords: Acyclovir, Gastroretentive, Mucoadhesion, Polyethylene oxide, Hydroxypropyl methylcellulose.

INTRODUCTION

The absorption of drug from the gastrointestinal tract is a complex procedure. A number of variables are directly or indirectly affecting the drug absorption. It has been reported that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa [1]. Gastro retentive systems can remain in the gastric region for several hours and therefore significantly prolong the gastric residence time of drugs. Many approaches have been reported in the literature for the formulation of such systems viz. mucoadhesion [2], floatation [3], swellable/expansion [3,4], sedimentation [5], modified shape systems [6,7] or by the simultaneous administration of pharmacological agents [8,9] which delay gastric emptying. Both single unit systems (tablets or capsules) [3] and multiple unit systems (multi particulate systems) have been reported in the literature [10,11]. Swellable and mucoadhesive drug delivery offers a number of applications for drugs having absorption window in the upper part of gastrointestinal tract and also for localized action. It retains the dosage form at the site of absorption and thus enhances the bioavailability [12].

Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analogue derived from guanine is the most widely used antiviral agent. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2 and varicella zoster virus. According to the biopharmaceutical classification system acyclovir is categorized as a class- III drug i.e. having high solubility and less permeability [13]. The pharmacokinetic parameters of acyclovir, following oral administration, are generally highly variable. It has an average plasma half-life of about 3 hours on average in adults with normal renal function. Its absorption in the GIT is slow, variable and incomplete. The bioavailability of acyclovir after oral administration ranges from 10-30%. Approximately 80% of an oral dose is never absorbed and excreted through feces. Also the frequency of administration of acyclovir is high, depending upon the type of infection [14].Among a variety of hydrophilic polymers, Polyethylene oxide (Polyox), and Hydroxypropyl methylcellulose (HPMC) are frequently used candidates in pharmaceutical formulation, mainly because of its non-toxicity, high water-solubility and swellability, mucoadhesive strength, insensitivity to the pH of the biological medium and ease of production [15-16]. The aim of the present study was to prepare a swellable, mucoadhesive type of formulation giving sustained delivery of acyclovir using hydrophilic polymers. Swelling, mucoadhesive properties and drug release of the tablets with different proportions of polymers in formulations was conducted applying experimental design.

MATERIALS AND METHODS

Acyclovir was received as gift sample from Glen mark Pharmaceuticals Ltd. (Mumbai, India). Hydroxypropyl methylcellulose (HPMC) K15M, Poly (ethylene oxide) WSR - 301(Polyox) and all other chemicals and ingredients used were either of analytical or pharmaceutical grades.

Compatibility studies

Sample of pure drug, physical mixture of polymers and drug in (1:1) ratio was placed at accelerated stability condition 40±2 °C and 75±5% relative humidity for a period of 3 month. At the end of 3 month samples were evaluated for drug-Excipients compatibility using Differential scanning calorimeter (DSC) (Mettler Toledo DSC 822e, Japan) and Fourier transformed infrared spectroscopy (FT-IR) (Shimadzu Corporation, Japan, 8400s).

Preparation of tablet

Oral gastroretentive sustained release tablets containing acyclovir were prepared by direct compression technology. The composition of different formulations prepared using varying amounts of polymers (i.e. Polyethylene oxide and HPMC K15M). Microcrystalline cellulose was added as the compressing agent with a fixed quantity of magnesium stearate (1%) as lubricant. Drug and the Excipients were homogeneously blended and subsequently compressed into tablet (12 mm Punch) using 12 station multi tooling rotary tablet punching machine.

Table 1: It shows factor combinations as per the chosen experimental design

Formulations	X_1	X_2
F_1	0	0
F_2	-1	0
F_3	-1	+1
F_4	+1	0
F_5	-1	-1
F_6	0	-1
F_7	0	+1
F_8	+1	-1
F_9	+1	+1

Coded level	-1	0	+1
X_1 HPMC 15K (mg)	50	100	150
X_2 Polyox (mg)	50	100	150

Factorial design

A 3^2 full factorial design was constructed, where the independent variables were concentration of HPMC K15M (X_1) and Polyox (X_2) respectively selected as the factors. The levels of the two factors were selected on the basis of preliminary studies carried out before implementing the experimental design. The dependent variable were Y_1 (Swelling index), Y_2 (mucoadhesive strength) and Y_3 (% Drug release). Table 1 summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

Evaluation of formulations

Thickness

The thickness of the tablet was measured using Vernier caliper. Thickness of five tablets from each batch was measured and mean was calculated.

Friability and Hardness

Twenty tablets from each formulation were examined for friability [18], using the Veego friabilator and hardness using a Monsanto type hardness tester.

Drug Content

Ten tablets from each formulation were powdered individually and a quantity equivalent to 100 mg of acyclovir was accurately weighed and extracted with a suitable volume of 0.1 N HCl. Each extract was suitably diluted and analyzed spectrophotometrically at 255 nm [19].

Weight variation test

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average USP weight variation test.

Swelling study

The Swelling studies were carried out by determining the swelling index using USP Type- II Apparatus (Paddle). Tablets were initially weighed (W_0) and then placed in the basket and revolved at 50 rpm for 12 hrs. At intervals of 1 hr., tablets were removed from basket and weighed (Wt). Then swelling index was calculated by using the formula given in equation:

$$SI = \frac{W_t - W_0}{W_0} \times 100$$

Where,

SI =Swelling index

Wt = Weight of swollen tablet at each time interval

W_0 = Initial weight of tablet.

In-vitro mucoadhesion studies [23]

The mucoadhesive forces of tablets were determined by means of modified analytical two pan balance (Fig.1). The pieces of stomach (Fundus) tissue of sheep were taken in saline solution to 37 ^{0}C before use. At the time of testing a section of tissue was attached, keeping the mucosal side out, on to upper glass vial using a rubber band. Then, the vial with a section of tissue was connected to the balance and the other vial was fixed on a height-adjustable pan. To the lower vial, a tablet was applied with the help of double-sided adhesive tape. The height of the vial was adjusted so that the tablet could adhere to the mucosal tissues of upper vial. After which the upper vial was then connected to the balance. On the other side of the modified balance an empty beaker was placed on pan and then water was added at a constant rate to the beaker until the tablet gets detached from tissue. The mucoadhesive force in dyne/cm^2 was determined from the minimal weights required for the detachment using the following equation:

$$\text{Mucoadhesive Force} = \frac{mg}{A}$$

Where,

m = the weight added to the balance in gm

g = acceleration due to gravity taken as 980 cm/sec^2

A = area of tissue exposed and is equal to 'r'

(r-the radius of the tablet attached to tissue).

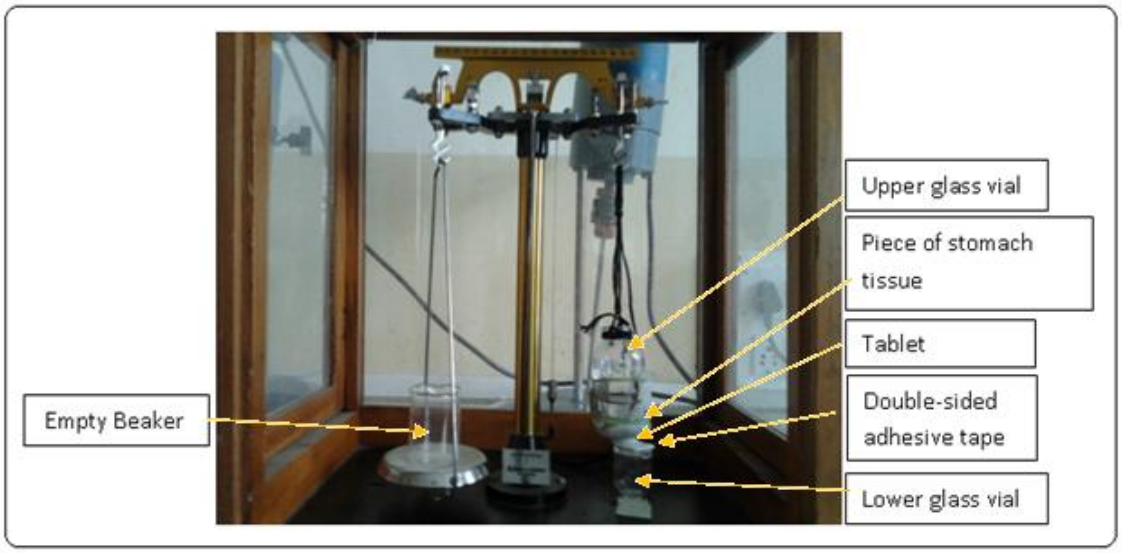

Fig. 1: Modified analytical two pan balance for Mucoadhesion Test

In vitro drug release studies

Dissolution studies were performed on all the formulations prepared, in triplicate, employing Tablet dissolution test apparatus (VEEGO-VDA-6D USP Standards) and 0.1 N HCl as the dissolution medium at 50 rpm and 37°C ± 0.5°C. 0.1 ml aliquots of each test sample were withdrawn periodically at suitable time intervals and the volume was replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 255 nm.

Kinetic data analysis

To analyze the in vitro release data various kinetic models were used to describe the release kinetics, the dissolution profiles were analyzed according to the zero-order, first-order[20], Higuchi's square root equations[21] and Korsmeyer - Peppas Model[22]. A high value of correlation coefficient suggested good correlation between *in vitro-in vivo* data. In case of tablets a value of n<0.45 indicates Fickian or Case I release; 0.45<n<0.89 for non-Fickian or anomalous release; n=0.89 for Case II release; and n>0.89 indicates Super Case II release[23].

RESULTS AND DISCUSSION

Compatibility study

1) FTIR spectra

The FTIR spectra of Acyclovir and optimized formulation of Acyclovir tablet are shown in Figure 2. It suggested that there was no interaction between the drug and polymers because principle peaks of optimized formulation were nearly similar to that of pure drug.

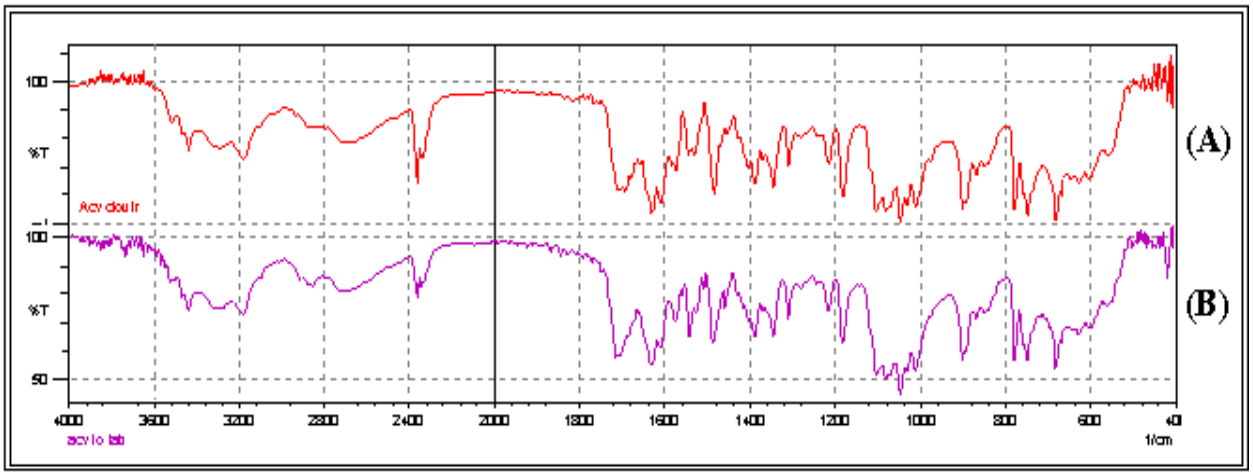

Fig. 2: It shows FTIR spectra (A - Acyclovir Drug, B- Optimized Formulation).

2) DSC Thermo grams

DSC thermo grams of the pure Acyclovir and the optimized formulation of Acyclovir tablet (Fig.3). The DSC analysis of pure Acyclovir showed a sharp endothermic peak at 251.47^{0}C, corresponding to drug's melting point. The DSC analysis of the optimized formulation showed a negligible change in melting point of Acyclovir in the presence of polymer mixture studied.

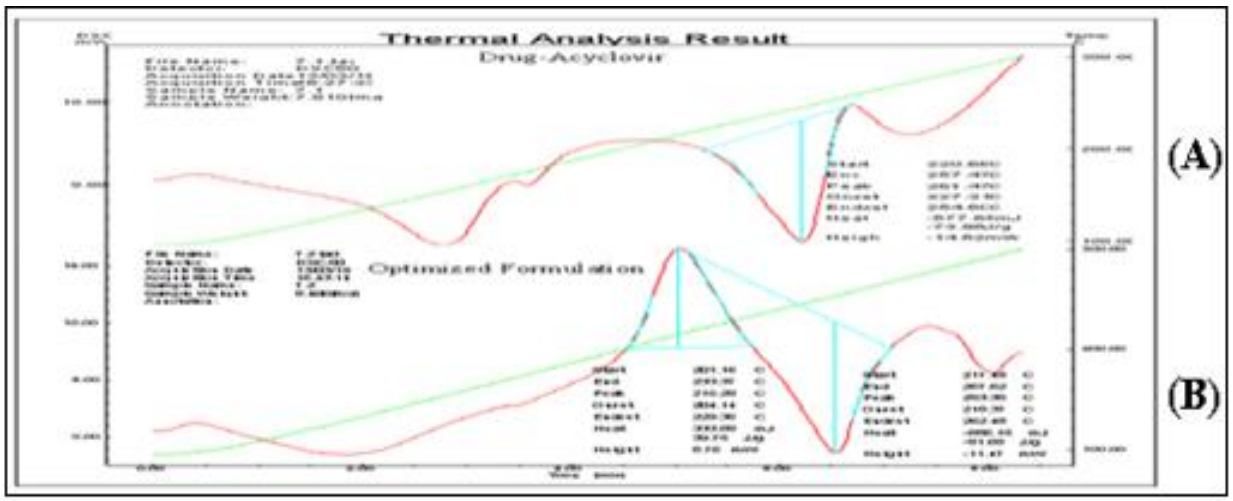

Fig. 3: It shows DSC thermo grams (A - Acyclovir Drug, B - Optimized Formulation)

Factorial Design

A 3^2 full factorial design was constructed, where the amounts of HPMC K15M (X_1) and Polyox (X_2) selected as the factors. The levels of the two factors were selected on the basis of preliminary studies carried out before implementing the experimental design.

The design was evaluated by following interactive model.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1 X_2$) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. The responses swelling index (Y_1), mucoadhesive strength (Y_2), and % drug release (Y_3) for nine formulations (F_1-F_9) prepared according to 3^2 factorial designs are as follows (Table 2).

The fitted equation relating the response Y_1, Y_2, Y_3, are shown below,

$$Y_1 = 181.80 - 4.56 X_1 + 0.37 X_2 - 4.66 X_1 X_2 - 7.61 X_1^2 - 4.07 X_2^2 \ldots\ldots\ldots (1)$$

$$Y_2 = 5591.82 - 37.07 X_1 + 1201.64 X_2 - 8.99 X_1 X_2 + 74.05 X_1^2 + 192.56 X_2^2 \ldots\ldots\ldots (2)$$

$Y_3 = 89.54 - 5.01\ X_1 + 3.12\ X_2 - 3.32\ X_1 X_2 - 3.77\ X_1^2 - 3.41\ X_2^2$.....(3)

Effect of formulation variables on swelling index

The swelling index values of all the formulations were increased with increasing amounts of polymer concentration. Maximum swelling index value was observed with the formulation F_3. The mucoadhesion and drug release profile are dependent upon swelling behavior of the tablets. As the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer supported the anomalous release mechanism of acyclovir. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. The result of regression analysis and ANOVA clearly shows that the coefficient of X_1, X_2 and X_1X_2 were found to be significant at $P < 0.05$ hence they were retained in polynomial equation(1).

Table 2: It shows Summary of Results of Regression Analysis for Response Y_1, Y_2, Y_3

Response	Models	F value	Prob > F	R^2	Adjusted R^2	Predicted R^2	S.D	Remarks
Y_1	Quadratic	12.80	0.0021	0.9014	0.8310	0.2990	3.36	Suggested
Y_2	Quadratic	281.33	0.0001	0.9950	0.9915	0.9648	91.74	Suggested
Y_3	Quadratic	24.36	0.0003	0.9457	0.9060	0.6135	1.94	Suggested

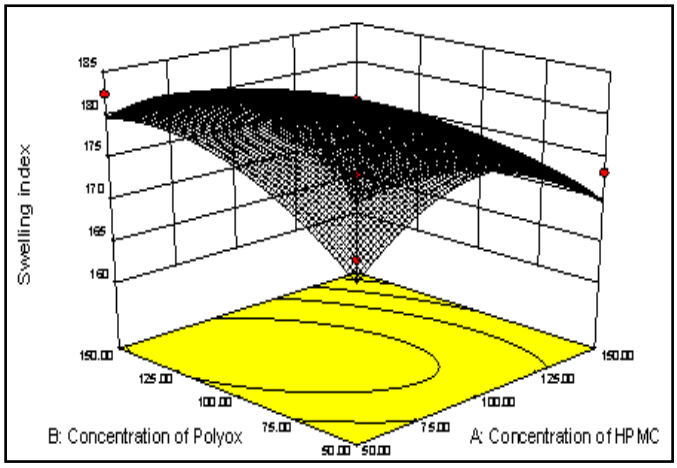

Fig. 4: Response surface plot of swelling index

Effect of formulation variables on Mucoadhesive strength

The Polynomial equation(2) and the figure 5 obtained using Design Expert software DX8 shows an increasing trend in mucoadhesive strength, with an increase in the amount of single polymer. The maximum mucoadhesive strength was exhibited by formulation F_3 that contains polymer (i.e. Polyox) at their highest concentrations. However, formulation F_5 containing the least amount of the Polyox showed the lowest mucoadhesive strength.

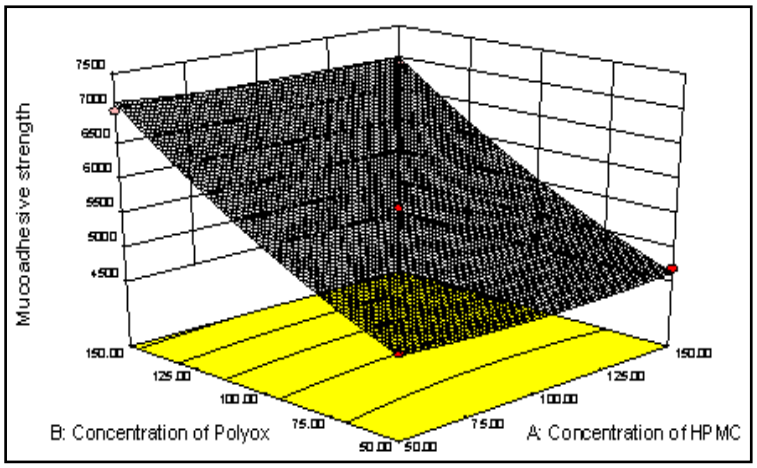

Fig. 5: Response surface plot of Mucoadhesive strength

Effect of formulation variables on % Drug release

According to polynomial equation 3, Increasing the amount of HPMC K15M (X_1) resulted in retardation of drug release of tablet as suggested by the negative sign of the coefficient of X_1, however Increasing the amount of Polyox (X_2) resulted in increases the drug release of tablet. The optimized formulation (F_3) showed the maximum drug release (95.2 ± 4.5%) in 12 h whereas the formulation F_4 showed lowest drug release (73.3 ± 1.5%) in 12 h. The in vitro drug release mechanism was found to be of anomalous or non-Fickian type. The high water uptake leading to higher swelling of the tablet supported the anomalous release mechanism of acyclovir.

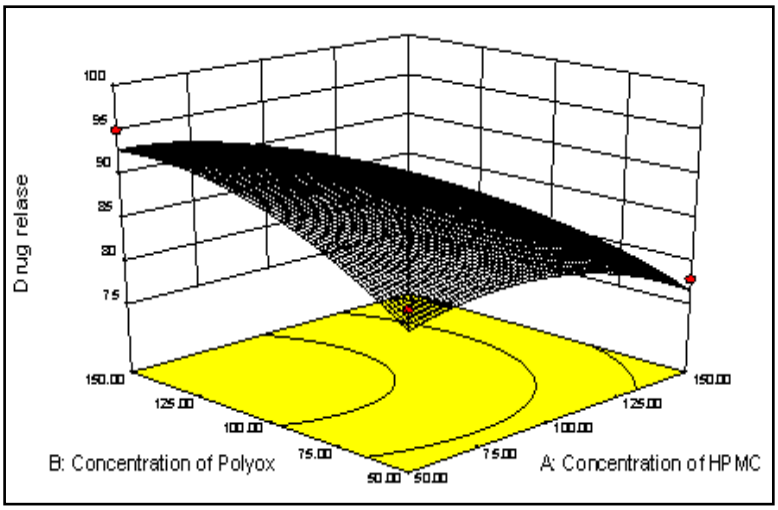

Fig. 6: Response surface plot of % Drug release

Kinetic data analysis

The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release is shown in Table 3. Results of *in-vitro* drug release kinetics study suggests that, all formulations follows Higuchi model with r^2 value in range of 0.99 and fitting the release data to Korsmeyer equation release exponent (n) ranged from 0.788 to 0.883 this indicated that the nature of drug release from the tablets followed non-Fickian diffusion mechanism (anomalous transport)[24].

Table 3: It shows Release Kinetic Parameters of Sustained Release Tablet.

Formulation No.	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Korsmeyer-Peppas(r^2)	Korsmeyer-Peppas (n)
F_1	0.986	0.971	0.990	0.995	0.871
F_2	0.982	0.982	0.991	0.996	0.866
F_3	0.989	0.933	0.992	0.998	0.790
F_4	0.982	0.996	0.995	0.990	0.872
F_5	0.984	0.984	0.989	0.991	0.851
F_6	0.982	0.994	0.995	0.995	0.788
F_7	0.986	0.984	0.995	0.990	0.883
F_8	0.982	0.990	0.991	0.995	0.856
F_9	0.987	0.983	0.991	0.998	0.877

CONCLUSION

This study suggests that the polymers Polyox and HPMC K 15M can produce a controlled pattern of drug release in the prepared acyclovir tablets. The high mucoadhesive strength of this formulation is likely to increase its residence time in the gastrointestinal tract, which eventually improves the extent of bioavailability. However, an appropriate balance between various levels of the two polymers is needed to acquire proper release and mucoadhesion. In this formulation the amount of Polyox mainly affects on the Mucoadhesion and Swelling of tablets. It can be concluded that by formulating gastroretentive sustained release tablets of acyclovir, its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption can be solved by increasing the retention time of drug in GIT for a longer duration of time.

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