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Original Article

Design and Development of Mucoadhesive Acyclovir Tablet

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Abstract

The purpose of this study was to design and optimize an oral controlled release acyclovir mucoadhesive tablet, in term of its drug release and mucoadhesive strength. A 3^2 full factorial design was employed to study the effect of independent variables like Carbopol-934P and hydroxypropyl methylcellulose K100M, which significantly influence characteristics like swelling index, ex-vivo mucoadhesive strength and in-vitro drug release. Tablets were prepared by direct compression and evaluated for mucoadhesive strength and in-vitro dissolution parameters. In all the nine formulations studied, the exponent (n) varied between 0.5266 and 0.7110, showing non-fickian release behavior corresponding to coupled diffusion or polymer relaxation, resulting in a controlled and complete drug release up to 12 h. Both these polymers had a significant effect on the mucoadhesive strength of the prepared tablets, measured as the force of detachment against sheep gastric mucosa. Besides unraveling the effect of the two factors on the various response variables, this study helped in finding the optimized formulation with excellent mucoadhesive strength and controlled drug release. It can be concluded that by formulating mucoadhesive tablets of acyclovir, its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption could be solved by increasing the retention of drug in GIT for a longer duration.

Keywords: Drug release; Acyclovir; Carbopol-934P; HPMC K100M; Mucoadhesion; Mucoadhesive tablet.

Introduction

For systemic delivery, the oral route has been the preferred route of administration for many systemically active drugs due to the ease of administration, patient compliance and flexibility of formulation. Oral delivery systems have been developed to act as drug reservoir, from which active substances can be released over a defined period of time at a predetermined and controlled rate. The progress in the field of oral dosage forms is immense and presently immediate release, to site-specific delivery systems are available. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid oral controlled release dosage forms. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract (GIT) is to control the gastric residence time. Dosage forms with a prolonged gastric residence, commonly known as gastro- retentive dosage forms (GRDFs); provide new and important therapeutic options (1).

GRDF's extend significantly the period of time over which the drug may be released. Thus,

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Table 1. Composition of the acyclovir tablets.

Ingredients	Amount (mg)
Acyclovir	200
Carbopol-934P (CP)	50-55
HPMC K100M	45-135
Dibasic calcium phosphate (DCP) (5%)	22.5
Talc (1%)	4.5
Spray dried lactose (SPD)	qs* to 450

*qs indicate quantity sufficient.

they prolong dosing intervals and improve patient compliance. This is especially applicable to delivery of sparingly soluble and insoluble drugs, and preferentially those absorbed in the upper part of small intestine. The placement of a drug delivery system in a specific region of the GIT offers numerous advantages, especially for drugs exhibiting an absorption window and solubility problems. They can help in optimizing the oral controlled delivery of drugs having 'absorption window' by continuously releasing drug prior to absorption window, over a prolonged period of time, thus ensuring optimal bioavailability (2).

Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analog 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 (3). The pharmacokinetic parameters of acyclovir, following oral administration, are generally highly variable. It has an everage plasma half-life of about 3 hours on average in adults with normal renal function (4). 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; being 200 mg five times a day up to 400 mg five times a day depending upon the type of infection (5).

In the present work, attempts are made in order to increase the rate and extent of absorption of Acyclovir by retention of drug in GIT for a longer duration. The objective of this study is to formulate a mucoadhesive acyclovir tablet and investigate the effect of different polymer concentrations of on the mucoadhesion strength and percent age of drug release.

Experimental

Materials

Acyclovir was provided exgratis by Biochem Laboratories Ltd; (Mumbai, India). Carbopol-934P (CP) was a gift from Ind-Swift Laboratories (Chandigarh, india). Hydroxypropyl methylcellulose (HPMC) K100M was gifted by Flamingo Pharmaceuticals (Mumbai, India). All other chemicals employed were of analytical grade.

Preparation of mucoadhesive tablets

Table 1 enlists the composition of different mucoadhesive formulations prepared using varying amounts of polymers (i.e. CP and HPMC K100M). Dibasic calcium phosphate (DCP) was added as the pore forming agent, while spray dried lactose (SDL) acted as the diluent, with a fixed quantity of talc as lubricant. Drug and the excipients were homogeneously blended and subsequently compressed into flat-faced tablets (450 mg, 10 mm diameter), using a single punch tablet compression machine.

Factorial design

A 3^2 full factorial design was constructed, where the amounts of CP (X_1) and HPMC K100M (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. Table 2 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

Physical evaluation

Ten tablets from each formulation were evaluated for uniformity in tablet weight and thickness (6). Since the tablet weight is 450 mg, 13 tablets from each formulation were examined for friability (7), using the Roche friabilator

Table 2. Factor combinations as per the chosen experimental design.

Trail no.	Coded factor levels		
	X_1		X_2
1	-1		-1
2	-1		0
3	-1		+1
4	0		-1
5	0		0
6	0		+1
7	+1		-1
8	+1		0
9	+1		+1
Translation of code levels in actual units			
Coded level	-1	0	+1
X_1 Carbopol-934P (mg)	50	52.5	55
X_2 HPMC K100M (mg)	45	90	135

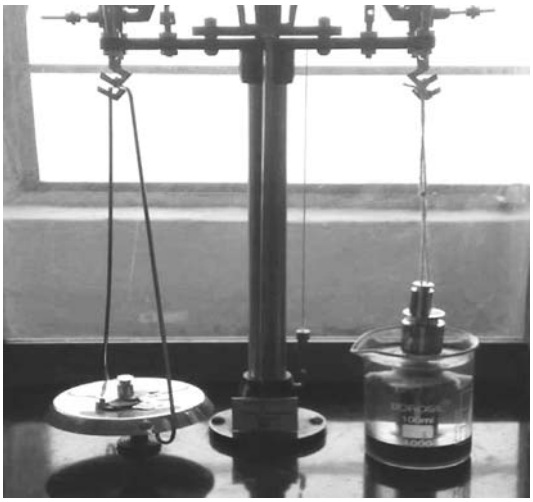


Figure 1. Modified analytical balance used for the Mucoadhesion test.

(Lab Hosp.) and hardness using a Monsanto type hardness tester.

Content uniformity

Five 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 254 nm (6).

In vitro drug release studies

Dissolution studies were performed on all the formulations prepared, in triplicate, employing United States Pharmacopoeia (USP)-23 paddle methods (Electrolab, TDT-06P Mumbai) and 0.1 N HCl as the dissolution medium at 50 rpm and 37°C ± 0.5°C. A 0.5-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 254 nm (7).

Ex-Vivo mucoadhesion studies

The working of a double beam physical balance formed the basis of the bio-adhesion test apparatus fabricated (Figure 1). The right pan of a physical balance was removed and replaced with a steel cylinder hanged with a lightweight thread. The height of this total set-up was adjusted to accommodate a glass container below it, leaving a head space of about 0.5 cm in between, A steel block was fabricated with an upward protrusion on one of its face. This was kept inside the glass container, which was then placed below the right hand set-up of the balance. The two sides were then balanced.

The sheep mucus membrane was excised and washed (equilibrated at 37°C ± 1°C for 30 min in phosphate buffer saline medium before the mucoadhesion evaluation study) and tied tightly with the mucosal side upwards, using a thread over the protrusion in the steel block. The block was then lowered into the glass container, which was then filled with isotonic phosphate buffer kept at 37°C ± 1°C, such that the buffer just reaching the surface of mucosal membrane and keeping it moist. This was then kept below the right hand set-up of the balance. The tablet was then stuck to the cylinder, using cyanoacrylate glue and the balance beam raised, A constant weight of 10 g was then placed over the steel block for the total contact period of 5 min. Mucoadhesive strength was then assessed by adding weights on the left pan till the tablet separated from the mucosal surface, in terms of the weight (in g) required to detach tablet from the membrane (8, 9).

All nine formulations were statistically

Table 3. Dissolution parameters of the nine formulations (n=3) prepared as per the 32 factorial designs.

Formulation code	X1	X2	C-934P (gm)	HPMC K100M (gm)	SI ± SD (%)	MS ± SD (g)
F1	-1	-1	50	45	6.94±0.59	14±0.25
F2	-1	0	50	90	8.30±0.48	15±0.20
F3	-1	+1	50	135	9.30±0.28	16±0.20
F4	0	-1	52.5	45	6.93±0.05	14.5±0.15
F5	0	0	52.5	90	9.14±0.69	15.5±0.1
F6	0	+1	52.5	135	10.17±0.70	16.5±0.57
F7	+1	-1	55	45	6.25±1.00	16±0.25
F8	+1	0	55	90	8.71±0.44	17±0.45
F9	+1	+1	55	135	9.30±0.47	19±0.57

compared in terms of the mucoadhesive strength, using the one way ANOVA.

Swelling studies

The Swelling studies were carried out by determining the swelling index using USP Type-I Apparatus (Basket). Tablets were initially weighed (W_0) and then placed in the basket and revolved at 50 rpm for 12 h. At intervals of 1 h, tablets were removed from basket and weighed (W_t). Then swelling index was calculated by using the formula given in equation (10):

$$\text{Swelling index} = (W_t - W_0 / W_0) \times 100 \quad \text{Eq. (1)}$$

W_t = weight of swollen tablet at each time interval

W_0 = initial weight of tablet

Data analysis

Various Response Surface Methodology (RSM) computations for the current optimization study were performed employing the Design Expert software (Version 7.1.3, Stat-Ease). The parameters studied, using RSM, were the percentage of drug released ($rel_{12}h$), mucoadhesive strength (f) and the time required to release 50% of the drug content ($t_{50\%}$). Polynomial models, including interaction and quadratic terms, were generated for all the response variables using the multiple linear regression analysis (MLRA) approach. The general form of the MLRA model has been represented in equation 2. The data obtained from dissolution studies were analyzed using PCP Disso version 3. The general form of the model is shown in equation 2:

$$Y = \beta_0 + \beta_1 X_1 + \beta_1 X_2 + \beta_1^2 X_1 X_2 + \beta_1^2 X_1^2 + \beta_2^2 X_2^2 \quad \text{Eq. (2)}$$

where β_0, the intercept, is the arithmetic average of all quantitative outcomes of nine runs, β_1 and β_2 are the coefficients computed from the observed experimental values of Y, Y is the response variables ($rel_{12}h$, f and $t_{50\%}$) and X_1 and X_2 are the coded levels of the independent variables, where X_1 is Carbopol-934P and X_2 is HPMC K100M. The terms X_1X_2, X_1^2 and X_2^2 are the interaction and polynomial terms, respectively. Also, the 3-D response surface graphs and 2-D contour plots were drawn in PCP Disso version 3, using the output files generated by the Design Expert software.

Results and Discussion

Tablet assay

The assayed content of drug in various formulations varied between 96.01% to 104.6%. The results showed no interference of the formulation excipients, i.e. Carbopol-934P, HPMC K100M, DCP and SDL.

Physical evaluation

The weights of all tablets were within ± 5% of the average weight, thickness between 4 and 4.6 mm, and hardness between 12 and 12.5 kg/cm^2. Friability ranged between 0.3 and 0.6%. Thus,

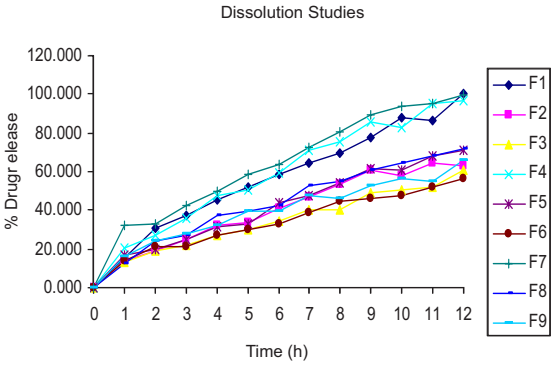


Figure 2. The plot showing in-vitro dissolution profiles of the nine formulations prepared as per 3^2 factorial design.

all the physical parameters of the compressed tablets prepared were practically within the acceptable limits.

In vitro drug release studies

All the tablets belonging to the nine formulations examined, showed a controlled pattern of drug release up to 12 h. The results showed that as the concentration of polymer present within the formulation increased, the amount of drug released was retarded (Table 3). The comparison of drug release profile of all formulations, prepared as per the experimental design, showed that formulation F1 that contains the least amount of Carbopol-934P and HPMC K100M showed maximum drug release (Figure 2). The overall rate of drug release at 12 h ($rel_{12}h$) tended to decrease with an increase in the amount of polymer. The comparison of the mechanism of drug release from swellable matrices could be determined by several physicochemical phenomena. Among them, polymer water uptake, gel layer formation and polymeric chain relaxation are primarily involved in the modulation of drug release (11). In case of carbopol-934P, the carboxyl groups highly dissociate repulsion between the negatively charged carboxyl groups causing uncoiling and expansion of molecules and thus result in gel formation. The gel thus formed consists of closely packed swollen particles (12-14). Carbopol-934P is a cross-linked polymer with high molecular weight (~2×10^6 Da) and viscosity, and when it comes in contact with water, it would swell and hold water inside its microgel network (13-15). This particular property may partially be responsible for the retarded drug release from Acyclovir tablets. Also, the presence of DCP as a water insoluble excipient might have decreased the swelling of the particles in the gel layer, leading to a slow diffusion of drug and thus decreasing the drug release rate.

In the case of HPMC K100M, which is also a hydrophilic swellable polymer, a retarded drug release pattern was observed. A high HPMC K100M content results in a greater amount of gel being formed (16). This gel layer increases the diffusion pathlength of the drug, hence controlling drug release via diffusion through the gel and erosion of the gel barrier. Its viscous nature also affects the diffusion coefficient of the drug (13, 16-18). As a result, drug release was found to be decreased as the amount of HPMC K100M was increased. Consequently, the values of $t_{50\%}$ significantly enhanced from 3.2 to 10.2 h with a rise in the content of polymer present in the formulation. Formulation F5 was found to follow the Hixson Crowell model (R value of 0.9857). Formulation F7 was found to follow the Matrix model, while formulations F1-F6 and F8-F9 showed Korsemeyer Peppas model (R values of 0.9760 to 0.9876). In all the nine formulations studied, the exponent (n) varied between 0.5266 and 0.7110, showing non-fickian release behavior corresponding to coupled diffusion or polymer relaxation (11, 19).

Swelling studies

All the tablet matrices were stable throughout the period of swelling, without any disintegration being observed. The swelling index of all formulations was found to be more or less superimposable, due to the low invariance amongst their chosen polymer compositions (Table 4). The swelling index profile of all formulations, prepared as per the experimental design, is shown in Figure 3. The two polymers used, namely Carbopol-934P and HPMC K100M, showed an increase in the values of swelling index as their concentration was increased. The swelling behavior of the Carbopol-934P is attributed to the uncharged –COOH groups which become hydrated by

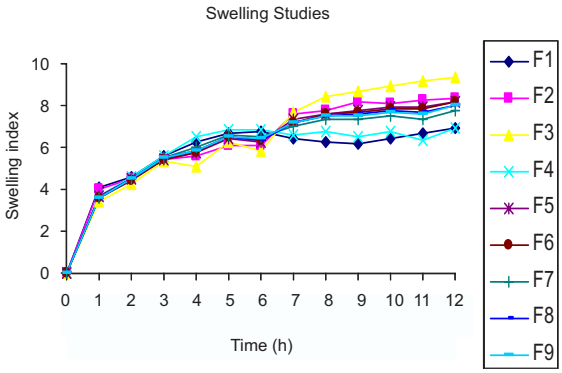


Figure 3. The plot showing swelling index of the nine formulations prepared as per 3^2 factorial design.

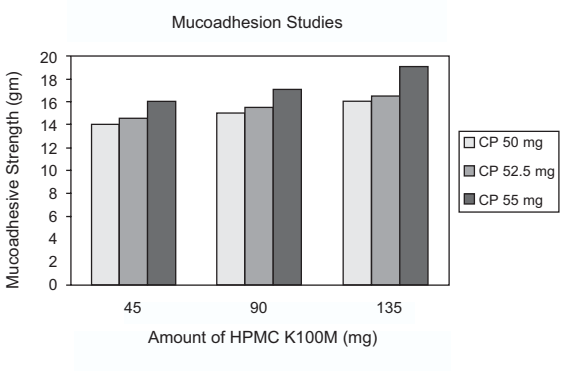


Figure 4. Bar chart showing the values of mucoadhesive strength obtained at various levels of Carbopol-934P and HPMC K100M.

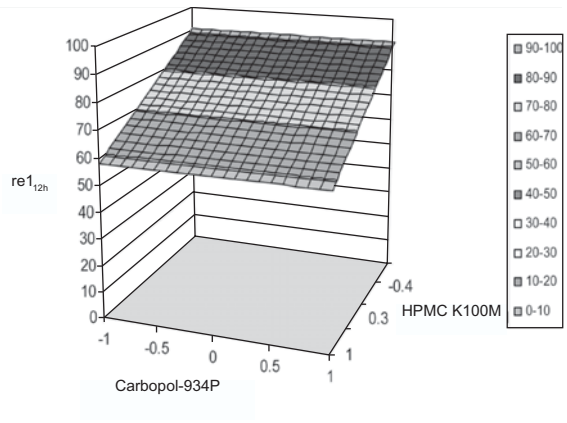
forming hydrogen bonds with the imbibing water and therefore, extending the polymer chain (15). On the other hand, HPMC K100M is a hydrophilic polymer that swells to a significant extent upon contact with water. A high HPMC content results in a greater gel formation and forms a gelatinous barrier which retards drug release (10, 12). On comparing the swelling indices of all formulations, it was observed that HPMC K100M swelled more than Carbopol - 934P.

Ex-vivo mucoadhesion studies

The mucoadhesive strength of all formulations has been shown in Table 4, while Figure 4 shows the bar chart depicting the significant variation in the values of mucoadhesive strength, obtained using different ratios of polymers. This figure depicts an increasing trend in mucoadhesive strength, with an increase in the amount of either polymer. The maximum mucoadhesive strength was exhibited by formulation F9 (i.e. 19 g), that contains both polymers at their highest concentrations. However, formulation F1 containing the least amount of the two polymers showed the lowest mucoadhesive strength (i.e. 14 g). The hydrogels are known to swell readily when they come in contact with a hydrated mucus membrane. The water sorption reduces the glass transition temperature below ambient conditions, and hydrogels become progressively rubbery due to uncoiling, increased mobility of the polymer chains. This glass rubbery transition provides an adhesive surface for maximum contact with the mucin, as well as flexibility to the polymer chains for interpenetration within the mucin. Increasing the amount of polymer may provide more adhesive sites and polymer chains for interpenetration into the mucin, consequently resulting in the aggrandization of the mucoadhesive strength (12).

Formulation F9 with the highest concentration of Carbopol-934P and HPMC K100M, showed the highest mucoadhesive strength, while formulation F1 with the least Carbopol-934P and HPMC K100M concentration, showed the least mucoadhesive strength. When the mucoadhesive strength the data obtained from all nine formulations were subjected to ANOVA, it was found that no significant difference ($P > 0.05$) exists in mucoadhesive strength between formulations F1 & F4, F2 & F5 and F3 & F6. This could be due to the fact that Carbopol-934P has increased marginally in these formulations. However, in formulations other than those mentioned above, and F3 & F6, the increase in Carbopol-934P significantly increased the mucoadhesive strength. When formulations F1 to F3, F4 to F6 and F7 to F9, with the same Carbopol-934P concentration were compared using ANOVA, it was found that a significant difference ($P < 0.001$) exists between these formulations showing that an increase in HPMC K100M concentration can significantly increase the mucoadhesive strength. This observation is in contrast with previous earlier studies (15). This could be

(a)



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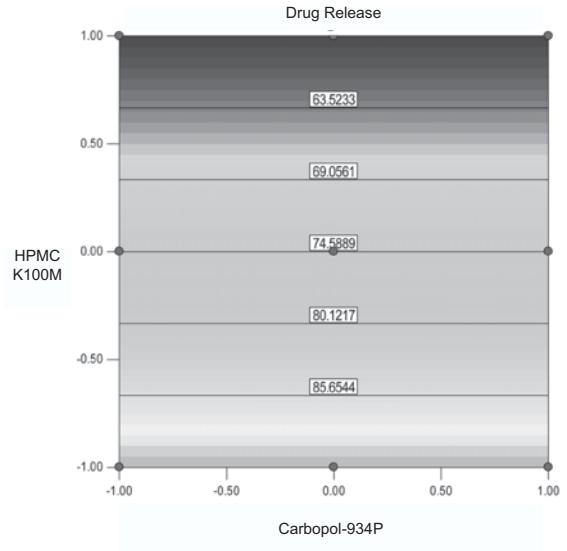

Figure 5. (a) Response surface plot showing the influence of HPMC K100M and Carbopol-934P on $rel_{12}h$.
(b) Corresponding contour plot showing the relationship between various levels of the two polymers.

due to the minute changes in concentration of Carbopol-934P (from 50 mg to 55 mg), as compared to HPMC K100M concentration (from 45 mg to 135 mg). Thus, both Carbopol-934P and HPMC K100M can influence the mucoadhesive strength.

Data analysis

The mathematical relationships constructed for the studied response variables are expressed as equations 3 to 5.

$$rel_{12}h = 68.51\text{-}18.86\ X_2 \qquad \text{Eq. (3)}$$

$$f = 15.944+1.16\ X_1+1.16X_2 \qquad \text{Eq. (4)}$$

$$t_{50\%} = 7.11+2.866\ X_2 \qquad \text{Eq. (5)}$$

All the polynomial equations were found to be statistically significant ($P < 0.01$), as determined using ANOVA, as per the provision of Design Expert software. The polynomial equations comprise the coefficients for intercept, first-order main effects, interaction terms, and the higher order effects. The sign and magnitude of the main effects signify the relative influence of each factor on the response.

From equation 3, it can be concluded that, HPMC K100M has a predominant effect on drug release, as compared to Carbopol-934P. HPMC K100M has a negative effect on the amount of drug release (i.e. as the concentration of HPMC K100M increases drug release decreases). Whereas, Carbopol-934P insignificantly affects the drug release (i.e. change in concentration of Carbopol-934P has no significant effect on drug release). This may be due to the narrow range of Carbopol-934P concentration (from 50 to 55 mg) used in the study. Figure 5 (a) depicts the response surface plot, showing the influence of HPMC K100M and Carbopol-934P on $rel_{12}h$. The surface plot shows that $rel_{12}h$ varies as the concentration of the two polymers changes. It can be seen from the plot that as the concentration of HPMC K100M increases, drug release decreases in a nearly linear fashion. Whereas, a change in concentration of Carbopol-934P has no significant effect on drug release. Figure 5 (b) represents the corresponding contour plot, showing the relationship between various levels of the tow polymers. The contour plot shows that HPMC K100M has a comparatively greater influence on the response variable than Carbopol-934P.

From equation 4, it can be concluded that both polymers (i.e. Carbopol-934P and HPMC K100M) significantly affect the mucoadhesive strength. As the concentration of Carbopol-934P is increased, mucoadhesive strength also increases. Figure 6 (a) shows the response surface plot, representing the influence of

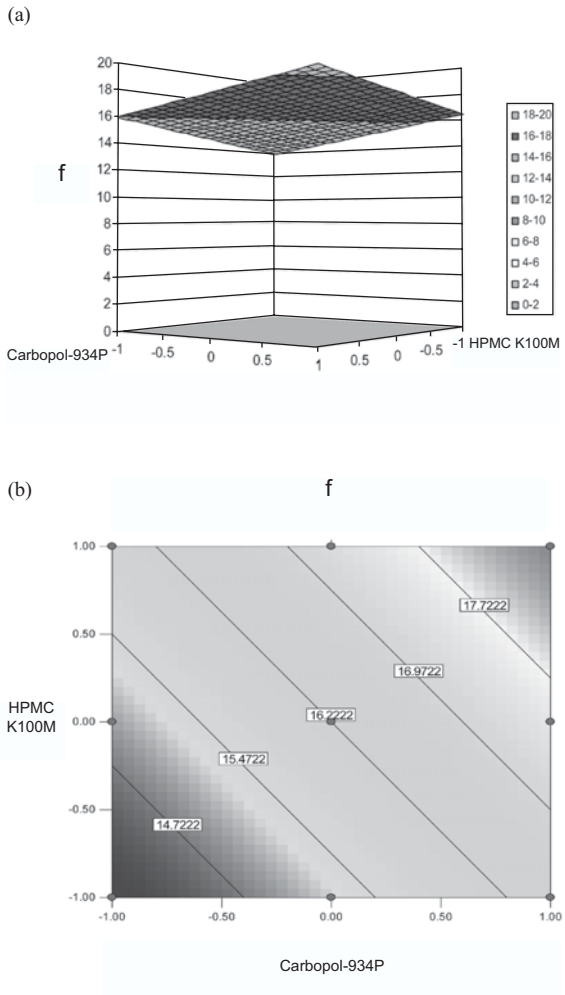

Figure 6. (a) Response surface plot showing the influence of HPMC K100M and Carbopol-934P on mucoadhesive strength (f). **(b)** Corresponding contour plot showing the relationship between various levels of the two polymers.

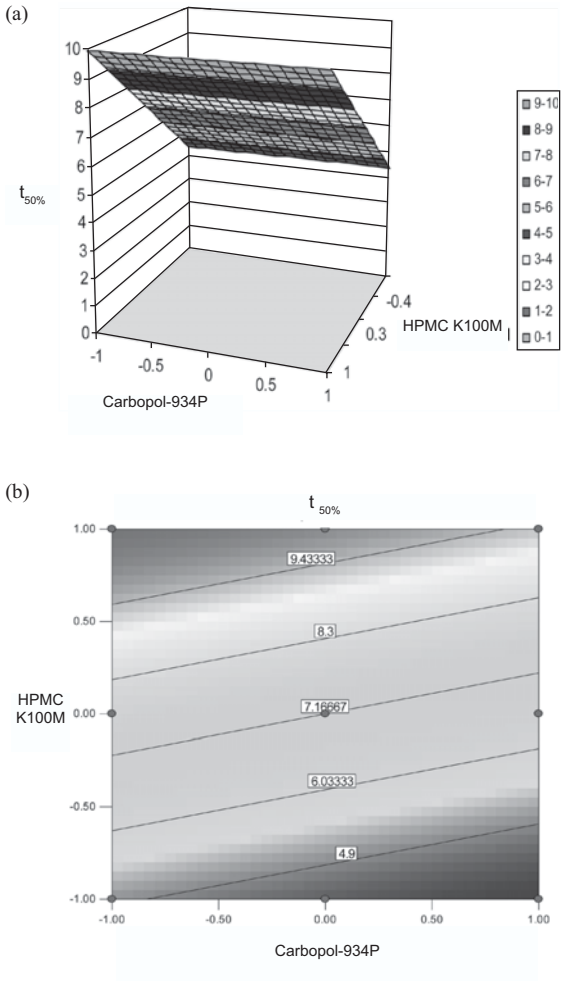

Figure 7. (a) Response surface plot showing the influence of HPMC K100M and Carbopol-934P on $t_{50\%}$ **(b)** Corresponding contour plot showing the relationship between various levels of the two polymers.

HPMC K100M and Carbopol-934P on the mucoadhesive strength (f). From the plot, it can be seen that both polymers significantly affect the mucoadhesive strength. Figure 6 (b) presents the corresponding contour plot, showing the relationship between various levels of the tow polymers.

From equation 5, it can be concluded that, HPMC K100M has a predominant effect on the $t_{50\%}$ value, whereas Carbopol-934P has no significant effect on this value. Figure 7 (a) depicts the response surface plot, showing the influence of HPMC K100M and Carbopol-934P on $t_{50\%}$. From the plot, it can be seen that as the concentration of HPMC K100M is increased, $t_{50\%}$ also increases, whereas an increase in the concentration of Carbopol-934P has no significant effect on the $t_{50\%}$ value. Finally figure 7 (b) shows the corresponding contour plot, representing the relationship between various levels of 2 polymers.

Conclusion

This study suggests that the polymers Carbopol-934P and HPMC K 100M 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 tow polymers is needed to acquire proper release and mucoadhesion. It can be concluded that by formulating mucoadhesive 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.

Acknowledgments

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