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Formulation and Evaluation of Vaginal Bioadhesive Drug Delivery System of Acyclovir

Bhaskar Mohite[1*], Rakesh Patel[1] and Nandu Kayande[2]

[1]School of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore (M. P), India.
[2]Thakur Shiv Kumar Singh Memorial Pharmacy College, Burhanpur, (M. P), India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Acyclovir is an anti-viral, which has been used in the treatment of vaginal disorder. Acyclovir is almost completely absorbed after oral administration but has low bioavailability of about 10-15% because of first pass metabolism. As first pass metabolism removes approximately 85-90% of the drug, so for clinical efficacy of the drug it should be frequently administered. Hence an attempt has been made to produce sustained release dosage form of the acyclovir which can be specifically employed for the treatment of vaginal disordered by Herpes simplex virus. The Mucoadhesive tablets of acyclovir has been prepared by direct compression methods and evaluated for various parameter such as thickness, friability, hardness, drug content, weight variation, swelling index, surface pH, bioadhesive force, bioadhesive time, drug release etc. The kinetic data was applied to the optimized formulations. So formulation of acyclovir in a vaginal mucoadhesive tablet dosage form will decrease the frequency of administration, which can lead to an improvement in patient adherence and thereby improving its clinical efficacy.

Keywords: Mucoadhesive tablet; acyclovir; mucoadhesive force; dissolution.

**Corresponding author: E-mail: bhaskarmohitepatil@gmail.com;*

1. INTRODUCTION

The vagina, as a site for drug delivery, offers certain unique features that can be exploited in order to achieve desirable therapeutic effects. The vagina has been studied as a favorable site for the local and systemic delivery of drugs, specifically for female-related disorders. Traditionally, the vaginal cavity has been used for the delivery of locally acting drugs such as antibacterial, antifungal, antiprotozoal, antiviral, labor-inducing and spermicidal agents, prostaglandins and steroids [1]. The effectiveness of the vagina as a site of drug administration for local effects has been well established [2]. It is an important route for local treatment of several gynecological conditions, such as infections and in hormonal therapy. This route provides advantages such as reducing or eliminating the incidence and severity of side effects, being a non-invasive route of administration and accessibility. These benefits could contribute to a better adherence, thus achieving improved therapeutic out come. Furthermore, the vagina possesses properties which include: large surface area of the vaginal wall, permeability, a rich blood supply and importantly, the ability to bypass first-pass liver metabolism. These properties are considered to be advantageous in relation to drug absorption [3]. Currently; there is a variety of pharmaceutical products available on the market designed for intravaginal therapy (tablets, creams, suppositories, pessaries, foams, solutions, ointments and gels) [4]. However, their efficacy is often limited by a poor retention at the site of action due to the self-cleansing action of the vaginal tract. Furthermore, the vagina has unique features in terms of microflora, pH and cyclic changes, and these factors influence the performance of the formulations and must be considered during the development and evaluation of vaginal delivery systems. Therefore, a successful delivery of drugs through the vagina represents a pharmaceutical challenge [5].

Acyclovir is an antiviral agent that is used for treating herpes simplex virus infections (type-I/II). Generally, for years, it has been administered through oral routes or to some extent by cream. The low bioavailability (~20%), high volume of distribution (32-61 L), rapid metabolism by viral thymidine kinase, plasma elimination half-life of 2.5 hr, and rapid urinary excretion have resulted in reduced effectiveness at the site of action [6]. Acyclovir suffers from the problem of solubility under both hydrophilic and lipophilic conditions which lead to high variability in therapy. Therefore, in order to amplify the therapeutic effectiveness by elevating the bioavailability the Mucoadhesive vaginal drug delivery system of acyclovir was prepared and evaluated [7].

2. MATERIALS AND METHODS

Acyclovir obtained as a gift sample from Matrix Labs, Aurangabad, India. Polymer such as Carbopol 934, Hydroxy Propyl Methyl Cellulose, Guar gum and Xanthan gum were purchased from SD Fine Chemical Mumbai. All the solvents used were purchased from Qualigen, Mumbai and of analytical grade.

2.1 Preparation of Mucoadhesive Acyclovir Tablets

Mucoadhesive controlled acyclovir matrix tablets were prepared by direct compression method. Acyclovir and various concentrations of HPMC, guar gum and xanthan gum were used as a release retardant polymer. Carbopol-934 was used as bioadhesive polymer. All the ingredients were sieved and then blended in mortar with pestle to obtain uniform mixing. Finally talc was added as lubricants which was then compressed by multi-station punch machine using 12 mm flat faced punch. The weight of tablet was adjusted to 600 mg and each tablet contained 200 mg Acyclovir [8].

2.2 Fourier Transform Infrared Spectroscopy (FTIR) Interpretation

To analyse the compatibility of drug and polymer the infrared spectrum of pure acyclovir sample and combination of drug, with Carbpol 934, HPMC Xanthun gum and Gaur gum were recorded by using Fourier Transform Infrared Spectroscopy. Also the spectrum analysis was conducted.

2.3 Micromeritic Properties of Drug and Polymers [9]

The micromeritic characteristic of the drug and polymers were evaluated.

2.4 Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

Table 1. Formulation of acyclovir mucoadhesive vaginal tablet

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	200	200	200	200	200	200	200	200	200
Carbapol 934	200	200	200	200	200	200	200	200	200
HPMC	150	100	50	---	---	---	---	---	---
Guar gum	---	---	---	150	100	50	---	---	---
Xanthan Gum	---	---	---	---	---	---	150	100	50
MCC	45	95	145	45	95	145	45	95	145
Talc	5	5	5	5	5	5	5	5	5
Total	600	600	600	600	600	600	600	600	600

$$D_b=M/V_0$$

Where, M is the mass of powder, $\mathbf{V_0}$ is the Bulk volume of the powder.

2.5 Tapped Density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by,

$$D_b=M/V_t$$

Where, M is the mass of powder, V_t is the tapped volume of the powder.

2.6 Angle of Repose

The frictional forces in a loose powder can be measured by the angle of repose, (θ). This is the maximum angle possible between the surface of a pile of powder and the horizontal plane and it is given as,

$$\tan \theta=h/r \quad \theta=\tan^{-1}h/r$$

Where, θ is the angle of repose, h is the height in cm, r is the radius.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

2.7 Carr's Index (I)

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I= D_t-D_b/D_t\times100$$

D_t is the tapped density of the powder. D_b is the bulk density of the powder.

2.8 Thickness

The thickness of vaginal acyclovir tablets were determine using vernier calipers[10].

2.9 Hardness and Friability

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw, the body of Monsanto hardness tester carries an adjustable scale which was set at zero against an index mark fixed to the compression plunger. When the tablet was held between the jaws, the load was gradually increased until the tablet fractured. The value of the load at the point gave a measure of the tablet hardness [10].

Friability was evaluated by means of friability test apparatus known as Roaches friabilator (Electrolab, Mumbai, India). Twenty weighed tablet were placed in the friabilator and then operated at 25 rpm for 4 minutes[10]. The tablets were then removed and weighed again. The difference in the two weights was used to calculate friability.

$$F= 100 [1-W/W_0]$$

Where, W_O = Initial weight, W= Final weight

2.10 Weight Variation Test

Twenty tablets were weighed individually and the average weight was calculated. The individual weights were then compared with the average weight. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablets differ by more than double the percentage limit given [10].

2.11 Drug Content Uniformity

Weighed 20 tabltes and power it. Weighed accurately a quantity of the powder containing about 0.2 g of Aciclovir, Then it was dissolved in the acetate buffer pH 4.6. The absorbance of the solution was then measured at the maximum at about 255 nm, using acetate buffer pH 4.6 as the blank [10].

2.12 Swelling Index

From each formulation, single tablet was taken and weighed, individually (W1)and placed separately in petridish containing 5 ml of acetate buffer PH 4.6. The petridishes were kept at room temperature for 30 minutes, then vaginal tablets were removed from the petridish and excess of water was removed carefully by using filter paper. The swollen vaginal tablets were weighed (W_2). Percentage swelling index was calculated, each experiment was performed in triplicate, and average reading was taken [11].

$$\% \text{ Swelling index} = W_2\text{-}W_1/W_1 \times 100$$

Where, W_1 = Initial weight, W_2 = Final weight

2.13 Surface p^H Study

The surface pH of the vaginal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As more acidic or alkaline pH may cause discomfort to the vaginal mucosa, the pH was maintained to weak acid as closely as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of acetate buffer (pH 4.4 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 ml acetae buffer (pH 4.4 ± 0.05) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min [12].

2.14 Matrix Erosion Test

After swelling study, the swollen tablets were dried at 60°C for 24 h in an oven and kept in descicator for 48 h and reweighed (W3). Matrix erosion was calculated using following formula.

$$\% \text{ Matrix erosion} = [(W1\text{-}W3) \div W3] \times 100$$

2.15 Bioadhesion Strength

Bioadhesive strength of the vaginal tablets was measured on the “Modified Physical Balance method”. The method used ship vaginal membrane as the model mucosal membrane. The fresh ship vaginal mucosa was cut into pieces and washed with acetate buffer pH 4.6. A piece of mucosa was tied to the glass slide which was moistened with acetate buffer pH 4.6. The tablet was stuck to the lower side of another glass slide with glue. Both pans were balanced by adding an appropriate weight on the left- hand pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. Previously weighed beaker was placed on the right hand pan and powder (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated. Bioadhesive strength was assessed in terms of weight (gm) required to detach from membrane. Bioadhesion strength which was measured as force of adhesion in Newton by using formula [13].

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} / 100 \times 9.81$$

2.16 Bioadhesion Time

The ex-vivo mucoadhesion time was examined after application of the vaginal tablet on freshly cut ship vaginal mucosa (Collected from slaughter house). The fresh ship vaginal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of acetate buffer pH 4.6 and pasted to the sheep vaginal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 4.6 and kept at 37 ± 1°C. After 2 minutes, stirring was applied slowly to simulate the vaginal cavity environment, and tablet adhesion was monitored for 12 hr. The time for the tablet to detach from the sheep vaginal mucosa was recorded as the mucoadhesion time [13].

2.17 *In-vitro* Dissolution Study

The release rate of Acyclovir from Bioadhesive tablets was determined using USP dissolution testing apparatus II (Paddle type, Electrolab, Mumbai, India). The dissolution test was

performed using 900 ml pH 4.6 acetate buffer, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The absorbance of these solutions was measured at 241 nm [14].

2.18 Data Treatment

In order to investigate the mode of release from the tablets the release data were analyzed with the following mathematical models. The application of kinetic to the release data was conducted by using PCP disso.

a) Zero- order kinetic: Q0 = Qt + K0t

Where Qt is the amount of drug release at time t and K0 is the zero order release rate constant. Q0 is the amount of drug present initially at t = 0.

b) First- order kinetic: ln (100 - Q) = *ln*Q0 + K_1t

Where Q is the amount of drug release at time t, Q0 is the amount of drug present initially and K0 is the First order release rate constant.

c) Higuchi equation: Q = KHt1/2

where Q is the amount of drug release at time t and KH is the Higuchi dissolution constant.

d) Hixson-Crowell equation: $W_0^{1/3}$-$W_t^{1/3}$=K_st

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time *t* and K_s is a constant incorporating the surface–volume relation.

e) Peppas equation: Q =$K_P t^n$

In the above equation Q is the percent of drug released at time t and K_P is the constant incorporating structural and geometric characteristics of the release device and n is the release exponent indicative of the mechanism of drug release [15].

2.19 Stability Study

The best batch was subjected to stability study at elevated temperature (60 0C/ humidity)for six week. The sample of stability study were withdrawn at the end of six weeks and evaluated for the changes in the physical character and drug released pattern [16].

3. RESULTS AND DISCUSSION

The Mucoadhesive tablets of acyclovir were prepared using direct compression methods. The bioadhesive polymer carbopol 934 was used along with the rate retardant polymer such as HPMc, gaur gum and Xanthan gum. The compatibility of drug and polymer was determined by using FT-IR. Pure drug show the characteristic peaks 3528.3, 3445.45, 1685.55, 1192.25 of O-H stretching, N-H stretching, C=O stretching, C-O stretching respectively when this spectrum compare with formulation it shows no significance changes in the shifting of peaks. This indicates that drug and polymer are compatible to each other.

3.1 Micromeritic Properties

The flow property of study such as the bulk density, tapped density,carr's index,hausners ratio and angle of repose for pure drug, carbapol 934P, HPMC, Xanthan gum and gaur gum was found to be good and all parameters obtained were within range as per official standard.

All the formulations evaluated for the important parameters, result obtained were shown in Table 3. The average weight from all the formulation were found to be in the range 585-628, indicates that all the batches have the average weight as per the official standards. The drug content in all the batches were in the range of 98.05±0.55-101.52±0.22. All the batches have good hardness and friability as per standards. The surface P^H of the tablet should be check because it can irritate the mucosal surface if the surface P^H changes. The thickness of the tablet was in the range of 4.5±0.02 – 4.61±0.2.

3.2 *Ex vivo* Mucoadhesion Time and Mucoadhesion Force

The Fig. 3 and Fig. 4 indicate that the bioadhesive time as well as bioadhesive force increased significantly with carbopol-934 and other polymers. The time for the tablet to detach from ship vaginal mucosa was recorded as the mucoadhesion time. The formulation F2 containing more carbopol 934 and HPMC showed higher mucoadhesion time(12.8 hour) and mucoadhesion force compare to other formulation which consist of carbopol 934 and

gaur gum, carbopol 934 and xanthan gum. However the remaining formulations show optimum mucoadhesion time. Bioadhesion is a surface phenomenon in which a material of natural or synthetic origin adheres or sticks to a biological surface, usually mucus membrane. Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adhering to the epithelial surface and more force require breaks tablet and mucus membrane [17].

3.3 Swelling Index and Erosion Study

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. The swelling index profile of all formulation, prepared as per the experimental design, is shown in Fig. 5. The two polymers used, namely Carbopol-934 and HPMC, showed an increase in the values of swelling index as their concentration was increased, formulation F2 consist of HPMC and carbapol 934 showed the high swelling similarly F4< F7< F2. The swelling behavior of the Carbopol-934 is attributed to the uncharged COOH group which become hydrated by forming hydrogen bonds with the imbibing water and therefore, extending the polymer chain on the other hand, HPMC 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 via diffusion through the gel and erosion of gel barrier in Fig. 6. On comparing the swelling indices of all formulations, it was observed that HPMC swelled more than gaur gum and xanthan gum formulations [18].

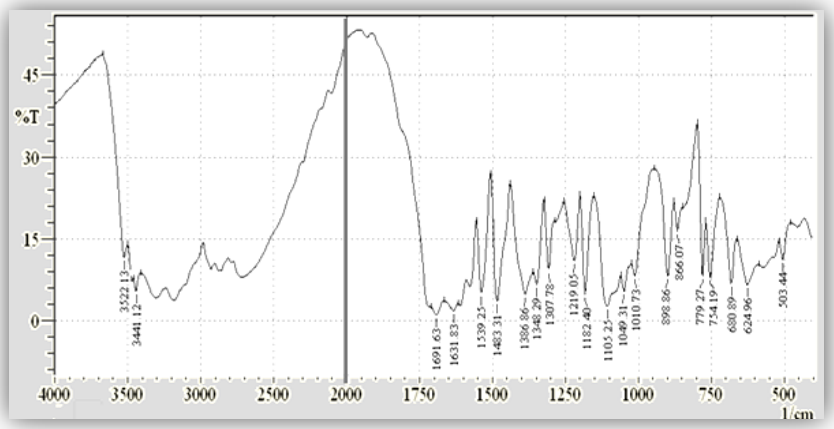

Fig. 1. FTIR spectrum of pure Acyclovir

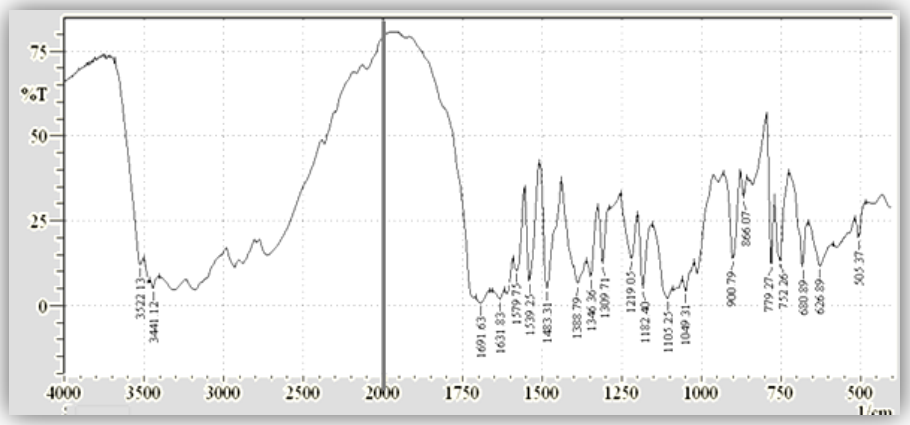

Fig. 2. FTIR Spectra of physical mixture (Pure drug and polymers)

Table 2. Micromeritic characterization of drug and polymers

Parameters/ Polymers	Acyclovir	Carbopol 934	HPMC	Xanthan Gum	Gaur Gum
Loose bulk density(g/cm3)	0.42± 0.02	0.224± 0.011	0.340±0.011	0.320±0.011	0.312±0.021
Tapped density(g/cm3)	0.49± 0.23	0.322± 0.012	0.480± 0.012	0.488±0.028	0.451±0.022
Carr's Index	16.50± 0.024	31.22±0.05	36.40±0.012	34.420.012	30.820.04
Hausner's ratio	1.16±0.1	1.43±0.022	1.41±0.012	1.52±0.012	1.44±0.011
Angle of repose	21.25±0.4	18.2±0.6	17.4±0.3	17.1±0.2	18.25±0.2

Table 3. Evaluation of acyclovir mucoadhesive vaginal tablet

Formulation	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Average weight (mg)	Drug content (%)	Surface P^H
F1	4.81±0.01	5.2±0.3	0.53± 0.06	585±0.5	100.15	4.5±0.02
F2	4.82±0.04	5.6±0.3	0.54 ±0.03	586±0.5	98.05	4.61±0.4
F3	4.92±0.02	5.5.±0.2	0.54 ±0.08	620±0.5	99.62	4.59±0.2
F4	4.95±0.01	5.2±0.3	0.56 ±0.02	590±0.5	99.83	4.6±0.01
F5	4.81±0.01	5.6±0.3	0.56±0.05	595±0.5	99.81	4.5±0.04
F6	5.06±0.03	5.7±0.1	0.53 ±0.06	610±0.5	100.57	4.4±0.02
F7	5.10±0.05	5.1±0.2	0.59 ±0.05	615±0.5	101.52	4.45±0.3
F8	4.85±0.01	5.3±0.1	0.58 ±0.02	589±0.5	98.41	4.57±0.1
F9	5.1±0.04	5.4±0.2	0.55 ±0.06	628±0.5	99.22	4.6±0.01

Table 4. *Ex vivo* mucoadhesion time and mucoadhesion force

Formulation	*Ex vivo* Mucoadhesion time (hr)	Mucoadhesive force
F1	12.8±0.03	0.21±0.04
F2	12.2±0.23	0.15±0.02
F3	11.5±0.01	0.15±0.01
F4	12.4±0.02	0.18±0.01
F5	12.3±0.01	0.15±0.23
F6	12.4±0.01	0.17±0.12
F7	12.2±0.12	0.16±0.20
F8	12.5±0.20	0.15±0.01
F9	12.5±0.03	0.17±0.02

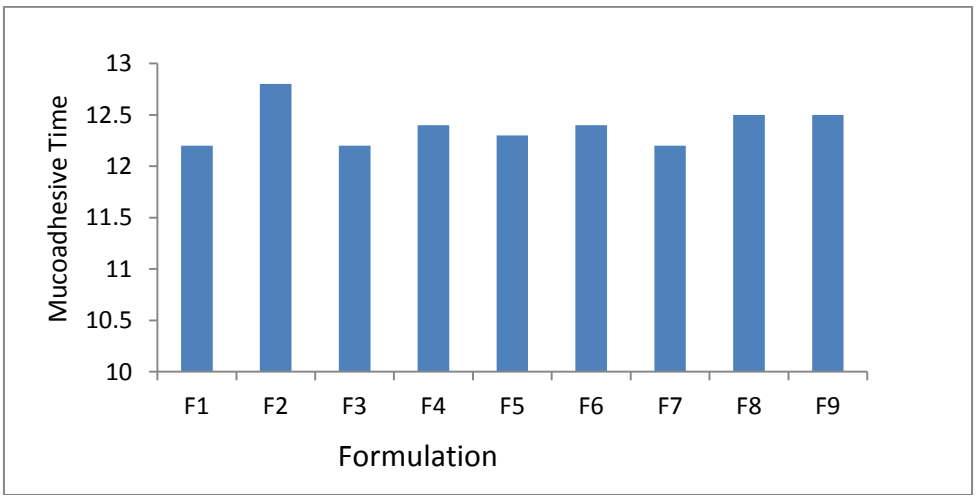

Fig. 3. *In vitro* bioadhesion time study of optimization formulations

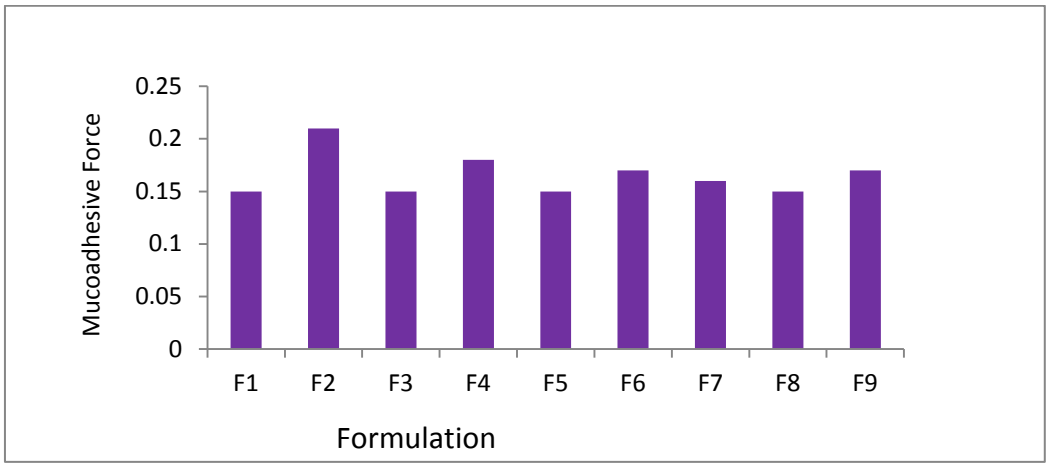

Fig. 4. *In vitro* bioadhesion force study of optimization formulations

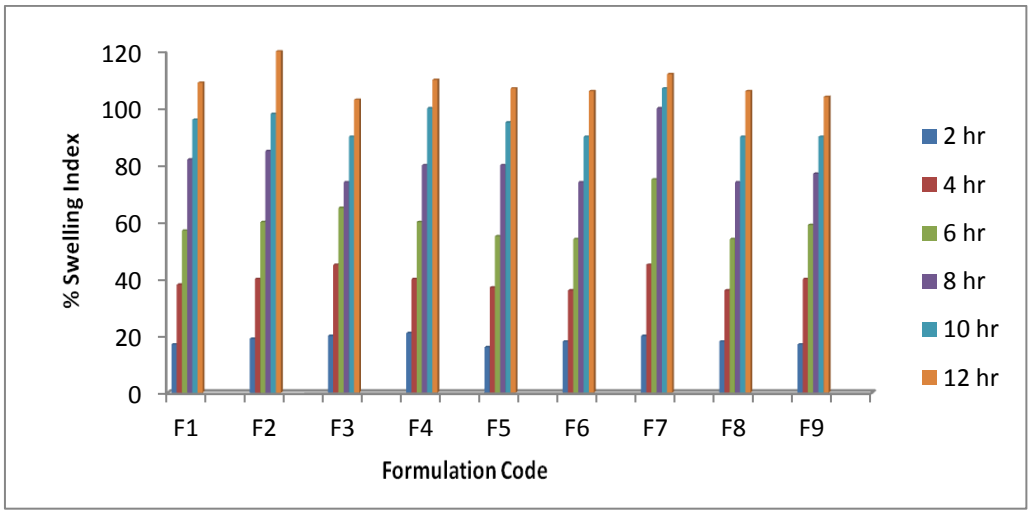

Fig. 5. % Swelling index of optimization formulations

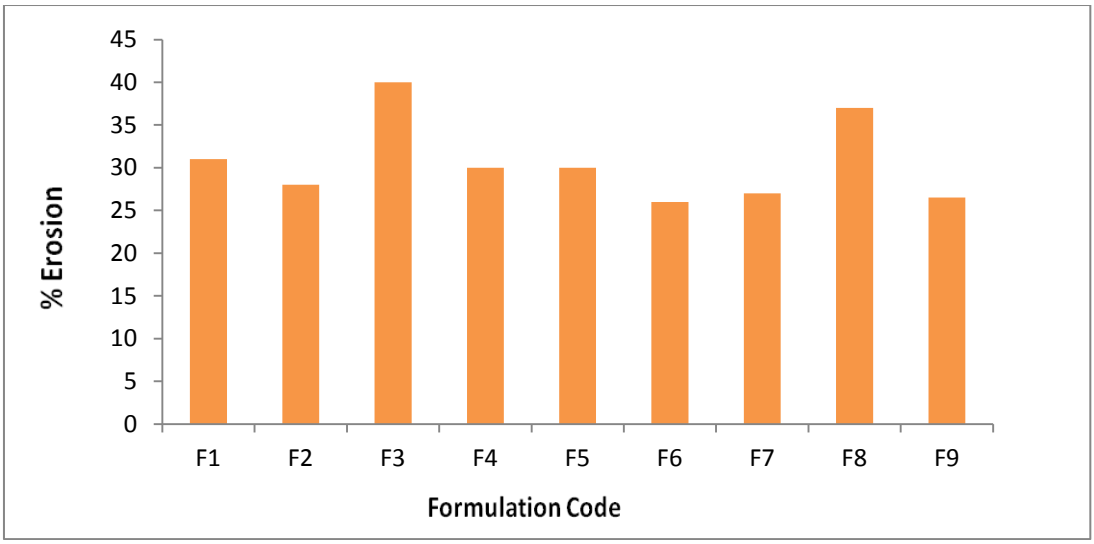

Fig. 6. % Erosion of optimization formulation

3.4 Dissolution

All the tablets showed a sustain release pattern of drug release up to 12 hr. The results showed that as the concentration of polymer present within the formulation increased, the amount of drug released was retarded. This revealed that formulation F1 that contains the amount of Carbopol- 934 and HPMC showed maximum drug release but up to 12 hr. The overall rate of drug release at 12 hr tended to decrease with an increase in the amount of polymer in the formulations such as F1 < F2 < F7 < F8 < F9. The formulation F1 maximum released 96% drug up to 12 hr at optimum ratio of carbapol 934 and HPMC. 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. In case of carbopol-934, 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. Carbopol-934 is a cross-linked polymer with high molecular weight and viscosity, and when it comes in contact with water, it would swell and hold water inside its microgel network. This particular property may partially be responsible for the retarded drug release from acyclovir tablets. In the case of HPMC, which is also a hydrophilic swellable polymer, a retarded drug release pattern was observed. A high HPMC content results in a greater amount of gel being formed. This gel layer increases the diffusion path length 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. As a result, drug release was found to be decreased as the amount of HPMC was increased [19].

3.5 Drug release Kinetics

In case of most of the formulations the R^2 values were higher for First order model than Zero order model indicating that the drug release from the formulation followed First order kinetics. Higuchi model, indicating that the drug release mechanism from the tablets was diffusion controlled. Obtained values of n lies between 0.5168 - 0.5877, indicating non-Fickian release kinetics, which is indicative of drug release mechanisms involving - diffusion mechanisms. Therefore, the release of drug from the prepared tablets is controlled by swelling of the polymers, followed by drug diffusion through the swelled polymer

3.6 Stability Study

The batch A was selected as the best batch among the all different formulations. Accelerated stability study on the selected batch was carried out to determine the rate of degradation of the formulation. There were no physical changes in the tablets after six weeks. All the parameters of the tablets are having no changes and also the drug release is similar after six weeks.

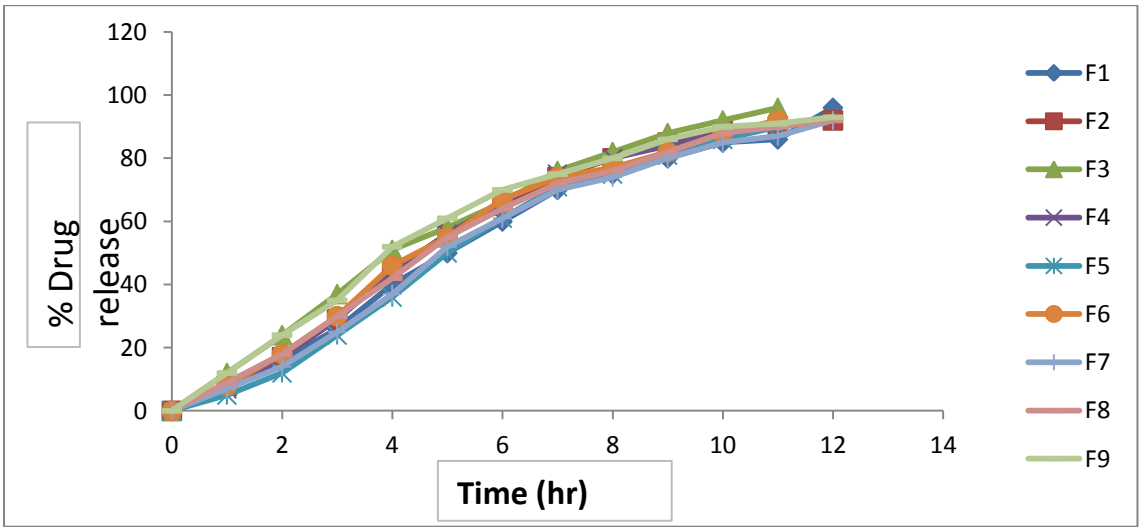

Fig. 7. Dissolution profiles of acyclovir mucoadhesive vaginal tablet

4. CONCLUSION

The present study was an attempt to develop a mucoadhesive vaginal drug delivery system for acyclovir. The main advantage achieved by this tablet dosage form resulted from its ability to prolong the local release of the drug in the vaginal cavity. The results suggest that acyclovir containing mucoadhesive vaginal tablets would be useful as alternative routes of administration with reduced dosing intervals, lower systemic side effects and hence, improved patient adherence. The bioadhesive polymers along with the rate retardants were successfully employed for the bioadhesion and drug release for the period of 12 hrs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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