DESIGN AND DEVELOPMENT OF MUCOADHESIVE DRUG DELIVERY SYSTEM FOR ANTIVIRAL DRUG

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ABSTRACT:
Tenofovir disoproxil fumarate , a hyperlipedemic agent used in the treatment of hypercholesterolemia, has poor bioavailability (less than 5%) due to the first pass metabolism and thus the dosing frequency is more, as a result of which several side effects occurred with the current dosage form. The present study aimed to formulate and evaluate buccoadhesive tablets of Tenofovir disoproxil fumarate using mucoadhesive polymer such as Carbopol 934P, Hydroxypropylmethyl cellulose (K4M, K100M) and sodium CMC. The different formulations of buccoadhesive tablet of Tenofovir disoproxil fumarate were prepared by direct compression method and characterized for physicochemical parameters such as thickness, content uniformity, weight variation, hardness, and friability test. The swelling index, % matrix erosion, surface pH, bioadhesive strength, bioadhesive time and *in-vitro* drug release are also carried out which has been important aspect for success of buccoadhesive tablets. The FTIR study was carried out for drug and polymer compatibility. All the formulation showed satisfactory tablet properties. Formulation (F5) containing Carbopol 934P and HPMC K4M in the ratio of (1:1) showed good bioadhesive strength and maximum drug release of 95.80% in 8 hours. The surface pH of all tablets was found to be satisfactory, close to buccal pH, hence no irritation would observe with these tablets. FTIR studies showed no evidence of interaction between drug and polymers.

Keywords: Buccoadhesive tablets, Tenofovir, FTIR, Carbopol 934P, *in-vitro* drug release and release kinetics.

The incidence of vaginal candidiasis It is estimated that 75% of all women experience an episode of vulvovaginal candi-diasis in their lifetime, 50% of them experience a minimum of a second episode, and 5% have recurrent candidiasis (more than 4 episodes per year). within the USA there's an annual occurrence of 13 mi -llion cases of VC and 10 million visits to gyneco-logy surgeries for this problem alone. .[1-4] Apart from local effective drugs the vagina provides also a promising site for systemic drug delivery, thanks to its large extent and rich blood supply . This route of administration offers advantages compared to other routes Tenofovir Disoproxil Fumararte is an FDA Approved Prodrug for clinical use for the treatment of HIV infection, AIDS and AIDS related conditions either alone or in combination with other anti retroviral drugs.

Tenofovir is a prodrug form of Tenofovir, which is active in-vitro against HIV-1 and HIV-2. Tenofovir disoproxil fumar ate is absorbed rapidlyfollowing oral administration producing peak plasma concentration 0.30±0.09gm/ml with 25% oral bioavailability.

Therefore, mucoadhesive vaginal system will prevent the drug metabolism and increase the drug residence time thus it will improve the patients compliance and drug bioavailability and clinical efficacy.

MATERIALS AND METHODS:

Tenofovir disoproxil fumarate was obtained as a gift sample from Natco Pharma Ltd, hyderabad, India. All other chemicals were procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

Preparation of Vaginal mucoadhesive tablets of Tenofovir disoproxil fumarate:

Bioadhesive Vaginal tenofovir disoproxil fumarate matrix tablets were prepared by direct compression method. Tenofovir disoproxil fumarate and various concentration of HPMC K-15M, Xanthan gum and Guar gum were used as a Release retardant polymer. Carbopol-934P was used as bioadhesive polymer. The other excipient used was micro crystalline cellulose for its diluent property. All the ingredients were first sieved and then blended in mortar with pestle to obtain uniform mixing. Finally magnesium state and talc was mixed for lubrication which was then compressed by Karnavati multi-station tablet compression machine using 10 mm flat punch. The compressed tablets of each type of polymer were then evaluated for tablet characteristics such as thickness, weight variation and friability[6].

Table 1: Formulation of Tenofovir disoproxil fumarate Mucoadhesive vaginal tablet

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tenofovir	25	25	25	25	25	25	25	25	25
Carbapol 934	40	30	20	40	30	20	40	30	20
HPMC	20	30	40	---	---	---	---	---	---
Guar gum	---	---	---	20	30	40	---	---	---
Xanthan Gum	---	---	---	---	---	---	20	30	40
MCC	230	230	230	230	230	230	230	230	230
Talc	5	5	5	5	5	5	5	5	5
Total	300	300	300	300	300	300	300	300	300

Evaluation of Vaginal Mucoadhesive Tenofovir disoproxil fumarate Tablets

FTIR study:

The Tenofovir disoproxil fumarate, physical mixture of Tenofovir disoproxil fumarate and each polymer was triturate with dried potassium bromide using mortar and pestles, the mixture after grinding in to fine powder was kept uniformly in suitable die and compress by using hydraulic press at high pressure. The Tenofovir disoproxil fumarate , physical mixture of Tenofovir disoproxil fumarate and each polymer were scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer (Brooker, Alfa-T, Germany

Tablet Description:

General appearance of tablets involves the measurement of number of attributessuch as tablets size shape colour, odour, taste, surface texture, physical flaws and consistency and ligibility of any identity marking.

Thickness

The thickness of tablet was measured by vernier callipers. Three tablets of each formulations were taken randomly and thickness was measured individually.

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 a 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.

Friability was evaluated by means of friability test apparatus known as Roaches friabilator. Twenty weighed tablet were placed in the friabilator and then operated at 25 rpm for 4 minutes. 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

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 pass 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.

Drug content uniformity

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 0.1g of Tenofovir disoproxil fumarate, add 60 ml of 0.1 M sodium hydroxide and disperse with the aid of ultrasound for 15 minutes. Add sufficient quantity of 0.1 M sodium hydroxide to produce 100.0 ml, mix well and filter. To 10.0 of the filtrate add 50 ml of water, 5.8 ml of 2 M hydrochloric acid and sufficient water to produce 100.0 ml. To 5.0 ml of the resulting solution add sufficient 0.1 M hydrochloric acid to produce 50.0 ml and mix well. Measure the absorbance of the solution at the maximum at about 255 nm , using 0.1 M hydrochloric acid as the blank. Calculate the content of tenofovir disoproxil fumarate taking at 253 nm.[7-9]

Swelling index

From each formulation, single tablet was taken and weighed, individually [designated as W_1] and placed separately in petridish containing 5 ml of acetate buffer PH 4.6. The petridish were kept at room temperature for 30 minutes, then vaginal tablets were removed from 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[10].

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

Where, W_1 Initial weight

W_2 Final weight

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[11].

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.

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

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. The 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[12].

Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81

Bioadhesion time determination

The *ex-vivo* mucoadhesion time was examined after application of the vaginal tablet on freshly cut ship vaginal mucosa. 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].

***In-vitro* dissolution study**

The release rate of Tenofovir disoproxil fumarate from Bioadhesive tablets was determined using USP dissolution testing apparatus II (Paddle type). 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 253 nm[14].

Data treatment (Release Kinetics)[15,16]

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

Stability Studies [17, 18]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. ICH guidelines the length of study and storage conditions: Accelerated testing - 40°C/75% RH for six months. The accelerated stability study of the best formulations was carried out as per the ICH guidelines.

RESULT AND DISCUSSION:

The Buccoadhesive drug delivery of tenofovir disoproxil fumarate was prepared by direct compression method using different concentration of mucoadhesive polymer such as carbopol 934P, sodium CMC, HPMC K4M, HPMC K100M. The drug and polymer compatibility was studied by FTIR spectroscopy. The FTIR spectra of drug and physical mixture of each polymer was studied and showed no changes in the peaks of physical mixture when compare to standard shown in Fig.1 (a-f). This indicates no chemical interaction between the dug and polymer.

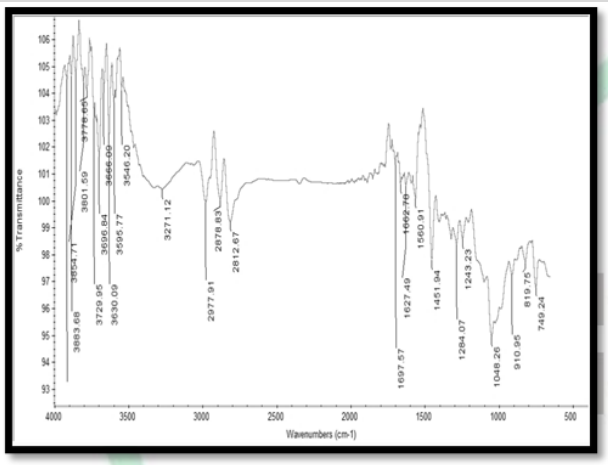

Figure 1(b): FTIR spectrum of pure Tenofovir disoproxil fumarate

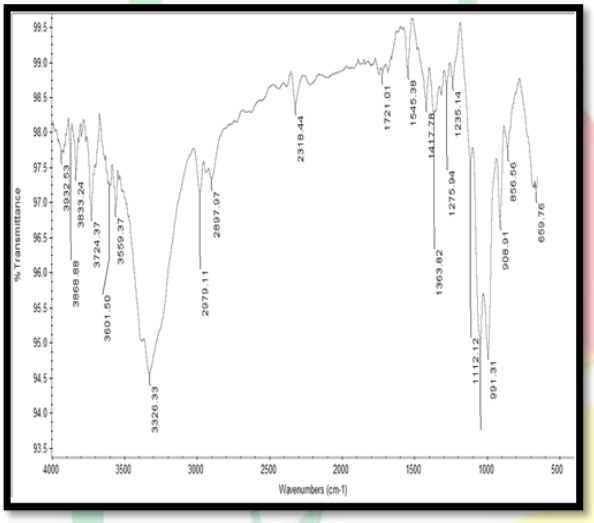

Figure 6.1.3 : FTIR Spectra of tenofovir disoproxil fumarate with Carbapol 934P

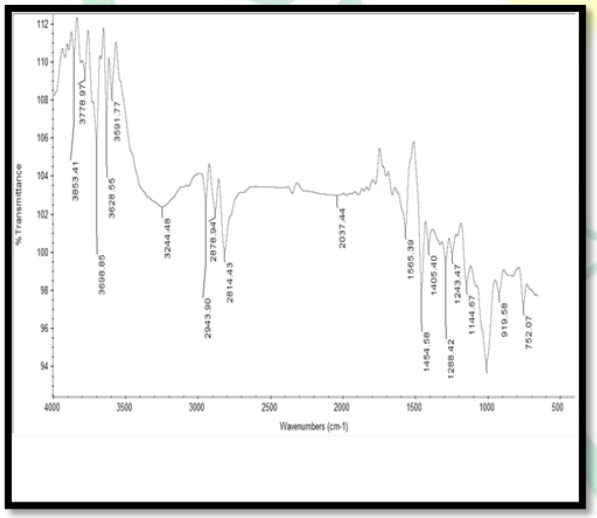

Figure 1(c): : FTIR Spectra of tenofovir disoproxil fumarate with HPMC K-15

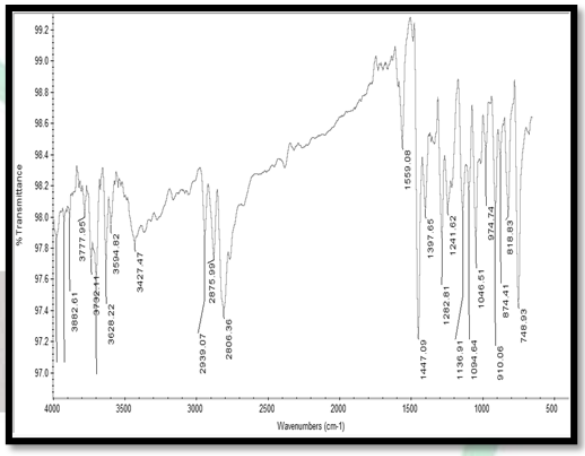

Figure 1(d): : FTIR Spectra of tenofovir disoproxil fumarate with Xanthan gum

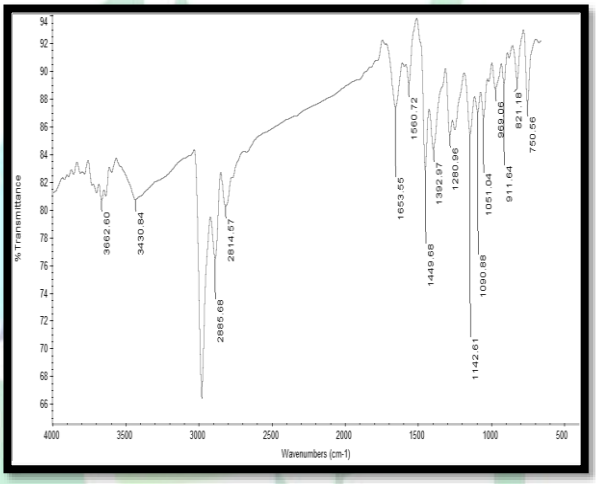

Figure 1(e): : FTIR Spectra of tenofovir disoproxil fumarate with Guar gum

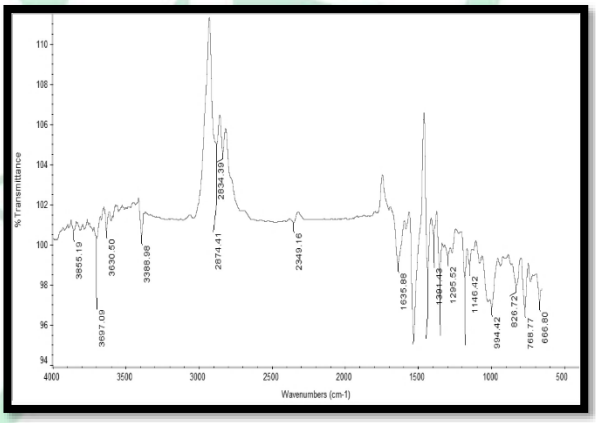

Figure 1(f): : FTIR Spectra of Physical Mixture

The physical properties of the buccoadhesive tablet were shown in Table No. 2. The average weight of the tablet was found to be in the range of 199.00 mg to 211.66 mg for all the formulation. The tablets showed thickness in the range of 2.88 to 3.24 mm. The percentage drug content of all the formulation was found to be 95.51 to 99.98 %. Also the tablets have satisfactory hardness and friability values thus it has good mechanical strength. Therefore all the formulation complies with that of the standard. Surface pH of all the formulation was found in the range of 6.33 to 7.0. These results reveal that all the formulation have acceptable pH in the range of salivary pH (5.5 to 7.0). Thus the formulations do not cause any local irritation to the mucosal surface. Swelling index of formulations was shown in Fig.2. Swelling index was determined with respect to time. The swelling index of the tablets was increased with increasing concentration of hydrophilic polymer. The polymer absorbed large volumes of water rapidly and swells to its maximum hydrated size without dissolving in aqueous media. HPMC is a hydrophilic polymer which swells slowly to form a gel which then dissolves in the presence of water. The gelling property of this polymer will provide the binding strength. Hence the integrity of tablet was maintained for further period of time until most of HPMC was dissolved.

Table No-2: Physical properties for Buccoadhesive tablet of tenofovir disoproxil fumarate

Formulation	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Average weight (mg)	Drug content (%)	Surface P^H
F1	4.25 ±0.01	5.4± 0.2	0.53 ± 0.06	484± 0.5	100 .15	4.5 ±0. 02
F2	4.22 ±0.04	5.1± 0.3	0.54 ±0.03	496± 0.5	99. 24	4.61 ±0. 4
F3	4.22 ±0.02	5.5. ±0.2	0.54 ±0.08	422± 0.5	100 .57	4.59 ±0. 2
F4	4.25 ±0.01	5.2± 0.3	0.56 ±0.02	420± 0.5	99. 93	4.6 ±0. 01
F5	4.21 ±0.01	5.6± 0.3	0.56 ±0.05	410± 0.5	99. 81	4.5 ±0. 04
F6	4.26 ±0.03	5.3. ±0.2	0.53 ±0.06	415± 0.5	99. 66	4.4 ±0. 02
F7	4.21 ±0.05	5.9± 0.2	0.59 ±0.05	420± 0.5	9.8 3	4.45 ±0. 3
F8	4.25 ±0.01	5.7± 0.1	0.58 ±0.02	490± 0.5	100 .05	4.57 ±0. 1
F9	4.23 ±0.04	5.1± 0.2	0.55 ±0.06	412± 0.5	98. 41	4.6 ±0. 01

The result bioadhesive properties of tablet were shown in Table No.3. As the concentration of polymer in the formulation increase the bioadhesive strength was increase. The strength of tablet was dependent on the property of mucoadhesive polymers, which adheres to the mucosal surface and also on the concentration of polymer used. The polymers in the maximum concentration were necessary to achieve maximum duration of bioadhesion. The decrease in the polymer concentration resulted in decrease in bioadhesive time. The primary and secondary polymer in the ratio of 1:2, 1:1, 2:1 were used for preparing tablets. The highest bond strength was possessed by the formulation which containing the more concentration of Carbopol 934P. Decreasing the content of the Carbopol 934P resulted in decreased adhesion force. But the optimum concentration of carbopol 934P is necessary for the bonding with the mucosa.

Table No-3: Bioadhesive properties for Buccoadhesive tablet of Tenofovir disoproxil fumarate .

Formulation Code	Bioadhesive strength (gm)	Bioadhesion time (hrs)
F1	14± 0.117	6.2
F2	16±0.814	7.0
F3	18±0.798	7.4
F4	18±0.547	7.1
F5	21±0.334	8.0
F6	22±0.062	8.6
F7	17±0.144	7.3
F8	21±0.010	8.2
F9	23±0.062	8.7

The duration of bioadhesion decreased with decreasing concentration of Sodium CMC and HPMC. The duration of bioadhesion of the formulated bioadhesion tablets were determined and found to be around 8 hours except the formulation containing sodium CMC.

The drug release pattern was studied for all formulations for 8 hrs and the results are shown in Fig. 4. The drug release pattern of buccoadhesive tablets varied according to their type and ratio of polymers. The most important factor affecting the rate of release from vaginal tablet is the drug and polymer ratio. The formulation F1, F2, F3

contained the Carbopol 934p and sodium CMC polymers in the ratio of 1 : 2, 1: 1 and 2 : 1 respectively. The in vitro drug release profile of formulations F1, F2, F3 at 8 hrs showed 83.21%, 86.09% and 90.39% drug release respectively. Similarly the formulations F4, F5, and F6 contained drug Carbopol 934p and HPMC K4M polymers in the ratio of 1 : 2, 1: 1 and 2 : 1 respectively. The *in vitro* drug release profile of formulations F4, F5 and F6 at 8hrs showed 81.15%, 95.80% and 98.37 drug release respectively. The formulation F7, F8, F9 contained the Carbopol 934p and HPMC K100M polymers in the ratio of 1: 2, 1: 1 and 2 : 1 respectively. The in vitro drug release profile of formulations F7, F8, F9 at 8 hrs showed 77.25%, 92.36% and 96.12% drug release respectively.

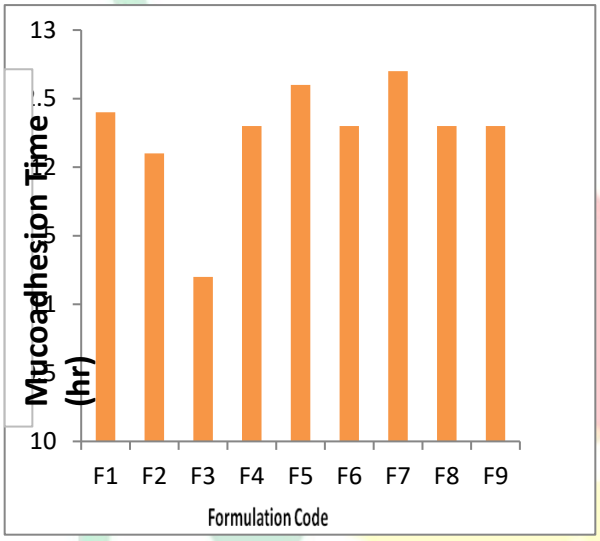

Fig-2: Percent Swelling Index of various

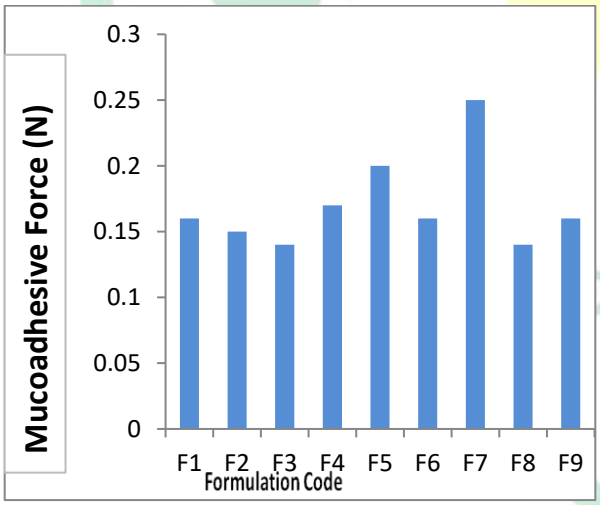

Fig-3: In vitro bioadhesion force study of formulations

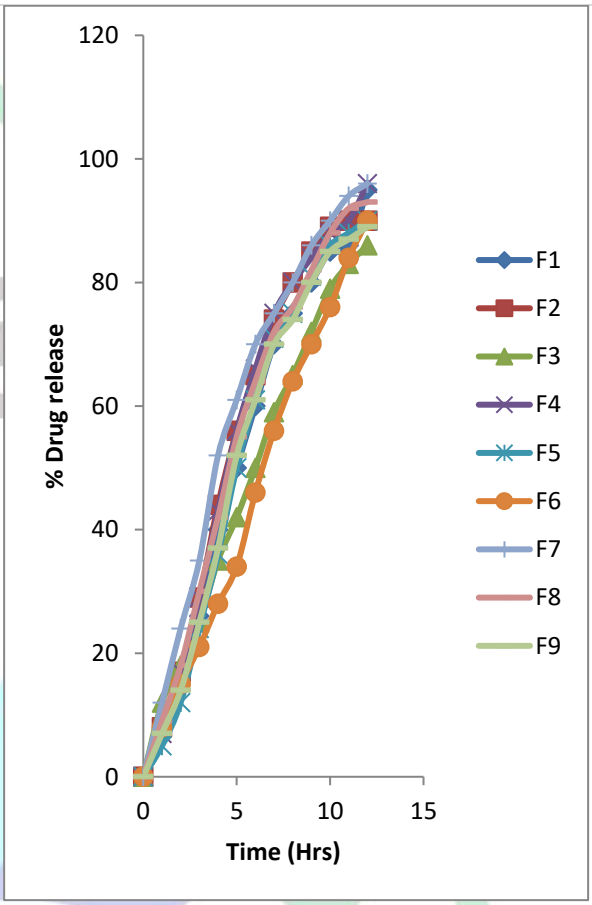

Fig-4: Percent drug release of Mucoadhesive vaginal tenofovir disoproxil fumarate tablets Formulations

Drug release kinetics of optimized formulation:

In case of most of the formulations the R^2 values were higher for First order model than for 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 0.5 – 1.0 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.

Table 4: Drug release kinetics of optimized formulation F7

Formulation Code	Zero order	First order	Higuchi	Koremayer Peppas
	R^2	R^2	R^2	n
F7	0.935	0.939	0.962	0.740

The optimized formulation (F-7) was subjected to stability studies at 40°C / 75% RH for 90 days. Samples were withdrawn at 30 days of time intervals and evaluated for physical properties, drug content and drug dissolution. Results showed that on 90th day 99.10 % ±1.10 drug content available in formulation and hence this change did not show any significant changes during stability studies. And also this study showed no change in drug dissolution.

Conclusion:

The present study formulate and evaluate the vaginal mucoadhesive drug delivery system of Tenofovir disoproxil fumarate and ritonavir were delivery the drug in sustained release manner for the period of 12 hrs. Also it was found that Carbapol 934P and Chitosan were act as promising polymers for vaginal mucoadhesive drug delivery systems. The Drug and polymers were found to be compatible. Swelling studies indicated significant water uptake and contributed in drug release. The optimized formulation sustained the release up to 12 hrs.

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