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FORMULATION AND EVALUATION OF VAGINAL DRUG DELIVERY SYSTEM FOR ANTIVIRAL DRUG

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ABSTRACT:

Ritonavir, 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 Ritonavir using mucoadhesive polymer such as Carbopol 934P, Hydroxypropyl methyl cellulose (K4M, K100M) and sodium CMC. The different formulations of buccoadhesive tablet of Ritonavir 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, Ritonavir, 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. Ritonavir is a class of 'antiviral drug. It is the of choice of drug for the treatment of HIV, when it is given orally it is incompletely absorbed, it has low bioavailability (less than 5%) due to extensive hepatic metabolism[5-8], so the clinically efficacy of drug is less. Therefore, drug should be administered frequently. Also it has also short half life (1.1-1.7 hrs). Hence an attempt has been made to developed sustained drug delivery of Ritonavir. So the vaginal buccoadhesive drug delivery system is one of the best alternatives to avoid first pass metabolism and also to prolong the action of drug. Thus, to improve all the characteristics of drug candidate by preparing buccoadhesive sustained drug delivery system.

MATERIALS AND METHODS:

Ritonavir was obtained as a gift sample from Watson Pharmaceuticals, Goa, India. Carbopol 934P, HPMC K4M, HPMC K100M, sodium CMC, EC and MCC was procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

FTIR study:

The Ritonavir, physical mixture of Ritonavir 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 Ritonavir, physical mixture of Ritonavir and each polymer were scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer (Brooker, Alfa-T, Germany).

Preparation AND Evaluation of buccoadhesive tablets of Ritonavir:

Composition of vaginal buccoadhesive tablet was shown in Table-1. Ritonavir tablet were prepared by direct compression method. The drug can be incorporated in to the core tablet containing different ratio of mucoadhesive polymer and is covered with backing ethyl cellulose layer. All the ingredient of the formulation was passed through sieve no. 60 and mixing in mortar with a pestle to get uniform mixing. The blended powder (150 mg) of core was compressed on single stroke multi-station rotary tablet punching machine having 8 mm round shaped punch. After

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punching the core layer, upper punch was removed and ethyl cellulose (50 mg) was added over it and again compressed to obtain backing layer.

Weight variation:
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[9].

Content uniformity:

Ten tablets were randomly taken and triturated using glass mortar and pestle and accurately weighed. Exact quantity of triturated powder equivalent to 20 mg of drug was taken into 50 ml of volumetric flask and dissolved in minimum amount of methanol and made up to the mark with phosphate buffer pH 6.8 up to 50 ml. then sample were analyzed by using UV spectrophotometer at 238 nm.

Hardness and Friability:
The Monsanto hardness tester was used to determine the tablet hardness. The hardness of five tablets in each batch was measured and the average hardness was calculated.
Friability was evaluated by Roache 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[9].

Thickness:
Take five tablets from each batch of formulation and the thickness of the tablets were measured with the help of vernier caliper. The average thickness is calculated[9].

Surface pH Study:
The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects in an oral cavity. As acidic or alkaline pH may irritate the buccal mucosa, attempt was made to keep the surface pH close to the buccal pH. The tablets were allowed to swell for 2 h in 1 ml of distilled water. The surface pH was measured by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1 min[10].

Swelling index:
From each formulation, single tablet was taken and weighed, individually (W_1) and placed separately in petridish containing 5 ml of phosphate buffer PH 6.8. The petridish were kept at room temperature for 30 minutes, then buccal tablets were removed from petridish and excess of water was removed carefully by using filter paper. The swollen buccal tablets were reweighed (W_2) and % swelling index was calculated using formula[11].

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

Where, W_1 - Initial weight

W_2 - Final weight

Bioadhesion strength:
Bioadhesive strength of the buccal tablets was measured on the "Modified Physical Balance method". The method used goat buccal mucosa as the model mucosal membrane. The fresh goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH 6.8. 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. On the side of balance 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. 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].

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

Bioadhesion time:
The *in-vitro* mucoadhesion time was examined after application of the buccal tablet on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the goat buccal 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 6.8 and kept at 37 ± 1°C. After 2 minutes, stirring was applied slowly to simulate the buccal cavity

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environment, and tablet adhesion was monitored for 8 h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time[13].

***In-vitro* drug release:**

The USP dissolution test type II paddle apparatus was used to study the drug release from the tablets. The dissolution medium was 900ml of phosphate buffer pH 6.8. The release was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive. The slide was allocated to the bottom of the dissolution vessel. 5 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer at 238 nm[14].

Kinetics of *in-vitro* drug release:

To study the *in-vitro* drug release kinetics, data was applied to kinetic models such as zero order, first order, Higuchi, Hixson Crowell and Korsmeyer- Pappas.

RESULT AND DISCUSSION:

The Buccoadhesive drug delivery of ritonavir 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-e). This indicates no chemical interaction between the dug and polymer.

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 Ritonavir.

Formulation code	Drug content (%)	Friability (%)	Thickness (mm)	Average weight (mg)	Surface pH
F1	99.48 ±0.40	0.53 ±0.06	3.21±0.020	209.82 ±0.5	6.88±0.02
F2	99.98±0.31	0.54 ±0.03	3.21± 0.057	209.66 ±0.5	6.93±0.02
F3	98.45 ±0.51	0.54 ±0.08	2.88± 0.072	199.00 ±2.0	6.97±0.03
F4	99.56 ±0.00	0.56 ±0.02	3.21± 0.011	211.66 ±0.5	7.0±0.03
F5	98.91 ±0.23	0.56 ±0.05	3.22± 0.041	207.74 ±1.5	6.82±0.01
F6	95.51 ±0.31	0.53 ±0.06	3.24 ± .032	201.33 ±0.5	6.89±0.02
F7	99.46 ±0.35	0.59 ±0.05	3.22± 0.026	204.56 ±0.5	6.33±0.02
F8	97.42 ±0.32	0.58 ±0.02	3.24± 0.025	208.69 ±0.5	7.22±0.03
F9	97.13±0.29	0.55 ±0.06	3.27± 0.026	204.83 ±0.5	6.91±0.03

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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 Ritonavir.

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. 3-5. 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 buccal 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.

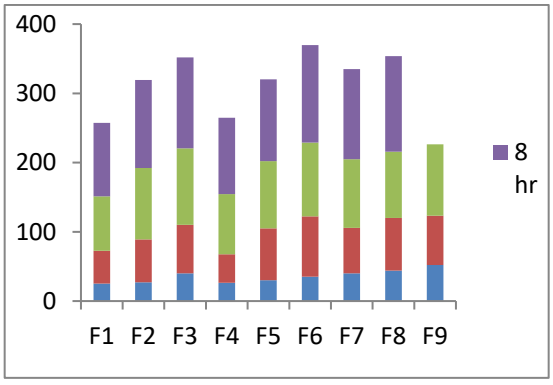

Fig-2: Percent Swelling Index of various formulations.

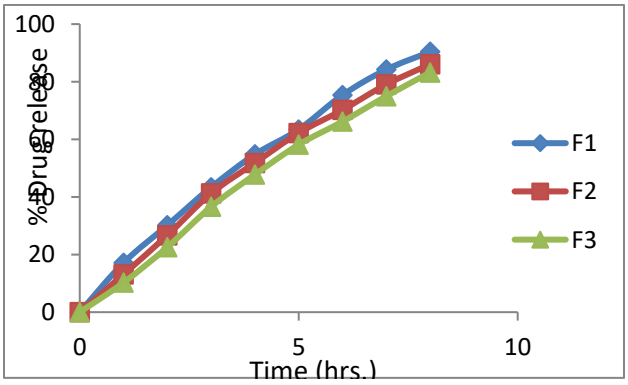

Fig 3: Percent Drug release of Formulation F1, F2, F3

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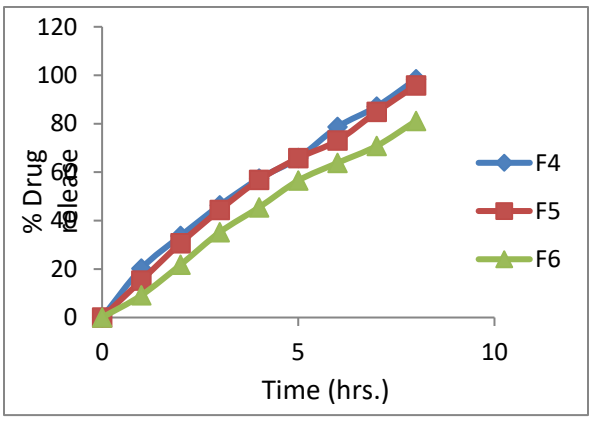

Fig 4: Percent Drug release of Formulation F4, F5, F6

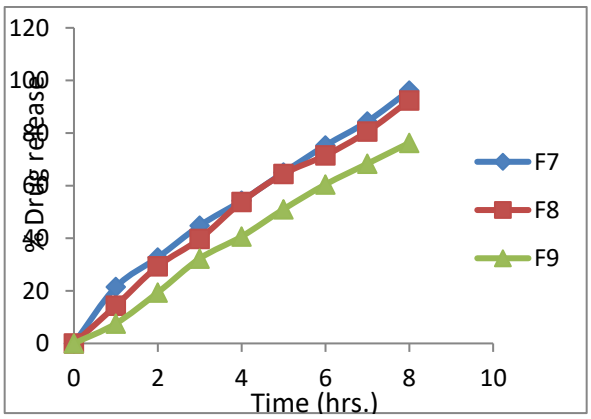

Fig 5: Percent Drug release of Formulation F7, F8, F9.

It was concluded that by increasing the concentration of Carbopol 934p in the formulations the drug release rate from the tablet was found to be decreased, but when the concentration of secondary polymers is increase, the drug release rate was found to be increased. This may be attributed to increased hydration followed by increased swelling of polymers with increase in concentration.

The *in-vitro* release kinetic studies i.e. zero-order, first order and Higuchi and Hixson-Crowell were conducted for all formulations and the data is shown in Table-4. The value of regression correlation co-efficient (R2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release.

Conclusion:

The overall studies indicated that the polymers Carbopol 934p and HPMC K4M in the ratio of 1:1 showed satisfactory mucoadhesive properties. Among the all formulations, the formulation F5 using these polymers in the above ratio with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F5 will be useful for buccal administration for the treatment of hypercholesterolemia. So, the buccoadhesive tablets of Ritonavir may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of ritonavir through Buccal mucosa.

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