Development and in vitro Evaluation of Bioadhesive Vaginal Tablet using Econazole Nitrate as a Model Drug
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Abstract
In this study, a bioadhesive dosage form of econazole nitrate for vaginal delivery was designed using a combination of bioadhesive polymers: Carbopol 941 p and sodium carboxymethylcellulose or methylcellulose in different ratios. The bioadhesive strength was evaluated by measuring the force required to detach the tablet from sheep vaginal mucosal membrane. It was found that the bioadhesive force was directly proportional to Carbopol 941 p content in the different formulae. The formulae were tested for their swelling behavior using agar gel plate method. The results showed that formulae containing a combination of Carbopol 941 p and sodium carboxymethylcellulose had greater swelling index than those containing a combination of Carbopol 941 p and methylcellulose. In vitro drug release study showed that the release of econazole nitrate from Formulae containing sodium carboxymethylcellulose was faster than its release from those containing methylcellulose. The dissolution profiles of the formula containing Carbopol 941 p alone and those containing various combinations of Carbopol 941 p and methylcellulose could be considered similar since their calculated similarity factor values were >50. Formula F3 composed of CP/NaCMC in a ratio 1:1 showed moderate swelling, good bioadhesion and retardation of drug release. Thus, it may be considered a good candidate for vaginal bioadhesive dosage forms.

Key words: Bioadhesive, econazole nitrate, vaginal tablet.

Introduction
Vaginal candidiasis (VC) is now recognized as a major health problem for women of childbearing age worldwide. The majority of genitourinary tract fungal infections are caused by Candida albicans.1 Approxi mately 75% will have a vaginal infection with a Candida strain during their life and about 40 to 50% of them will suffer a second one, and a small percentage will show a chronic course.2 Antifungal imidazole drugs are a mainstay in the treatment of fungal infections. Imidazole drugs have low aqueous solubility because of their hydrophobic structures. This can have a negative impact on antifungal efficacy, side effects, pharmacokinetic variability and the development of drug resistance.3 Intravaginally delivered drugs may fail to achieve high concentrations at the site of infection because of their fairly prompt removal from the vaginal compartment through physiological secretions, thus, limiting residence time and impairing therapeutic efficacy of the drug and make multiple administrations necessary for treatment.4,5 Moreover, conventional vaginal formulations are associated with disadvantages of leakage and messiness thereby causing inconvenience to the user.6 Attempts are being made to develop novel vaginal drug delivery systems that can meet the clinical as well as the requirements of the patients.7 Therefore localized mucosal dosage forms may represent a suitable formulation design to improve both the bioavailability of the drug and patient compliance.8

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Bioadhesion can be defined as a phenomenon of interfacial molecular attractive forces amongst the surfaces of the biological substrate and the natural or synthetic polymers, which allows the polymer to adhere to the biological surface for an extended period of time. In the pharmaceutical sciences, the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. The most commonly used mucosal adhesives are synthetic polyacrylates, polyacrylate derivatives, hyaluronic acid derivatives, pectin, tragacanth, carrageenan and sodium alginate. Econazole nitrate (EN) is an imidazole antifungal agent and is mostly administered topically for the treatment of skin infections and vaginal candidiasis. The minimum inhibitory concentration (MIC) of EN for complete inhibition of fungi is 0.001-1000 mg/mL. Ghelardi et al. found that a complexation of econazole with the mucoadhesive polycarbophil significantly improved the therapeutic benefit of the drug in the topical treatment of (CV) in mice. Albertini et al. have investigated the preparation of mucoadhesive microparticles as an innovative vaginal delivery systems for econazole nitrate (EN) able to enhance the drug antifungal activity prepared by spray-drying. The aim of this study is to investigate the use of a mucoadhesive polymer: Carbopol 941 P and sodium carboxymethylcellulose or methylcellulose in different ratios to develop EN vaginal tablets. The developed tablets were evaluated for their physical and mucoadhesive characteristics, and in vitro release of EN.

Materials and Methods

Materials
Econazole nitrate (EN) supplied by Samarra Drug industries, carbopol 941(CP), (Goodrich,USA), Sodium carboxymethylcellulose (NaCMC), Methylcellulose (MC), Sodium lauryl sulfate (SLS), and Magnesium stearate (BDH Chemicals, LTD, Liverpool, England). Agar no.1 (Oxoid Limited, England), all other reagents are of analytical grade.

Methods

Preparation of EN Bioadhesive Tablets

Different formulae of EN bioadhesive tablets were prepared, as shown in table (1), by mixing CP alone or its mixture with either NaCMC or MC at different ratios with the drug in a glass mortar. Magnesium stearate equivalent to 1% was added to the mixture as lubricant then the formulations were directly compressed into tablets using flat face 12 mm punch. Each tablet weighed approximately 750 mg and had thickness of about 4.2 mm.

Table 1: The composition of various EN bioadhesive tablet

<table>
<thead>
<tr>
<th>Formula #</th>
<th>EN (mg)</th>
<th>CP/Na CMC</th>
<th>CP/ MC</th>
<th>Mg Stearate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>150</td>
<td>3:0</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>F2</td>
<td>150</td>
<td>2:1</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>F3</td>
<td>150</td>
<td>1:1</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>F4</td>
<td>150</td>
<td>1:2</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>F5</td>
<td>150</td>
<td>-</td>
<td>2:1</td>
<td>7.5</td>
</tr>
<tr>
<td>F6</td>
<td>150</td>
<td>-</td>
<td>1:1</td>
<td>7.5</td>
</tr>
<tr>
<td>F7</td>
<td>150</td>
<td>1:2</td>
<td>-</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Total weight of the polymer(s) per tablet is 600 mg in all of the formulae.

Evaluation of Bioadhesive Tablets

Hardness: The hardness of the tablet was measured with the help of a Monsanto hardness tester. Three tablets from each batch of formulations were tested. Then average hardness and standard deviation were calculated.

Friability: The friability test was done using Roche’s Friabulator. Twenty tablets from each formulation were weighed (w1) and tested at a speed of 25 rpm for 4 min. After removing of dust, tablets were re-weighed (w2) and friability percentage was calculated using the following equation:

\[
\text{Friability} = \frac{w_1 - w_2}{w_1} \times 100
\]

Weight Variation: 20 tablets from each formulation were weighed and mean and standard deviation of the weight were determined.

Tablet Thickness: thickness of the tablets was measured on 3 tablets with a micrometer caliper.

Drug Content Uniformity: One tablet of each formula was ground in a mortar; an accurately weighed amount of the powder equivalent to 50 mg of EN was transferred into 100 ml volumetric flask and dissolved with methanol. The resulting solution is filtered and assayed spectrophotometrically for EN at 271 nm. The drug content was determined using preconstructed calibration curve of EN in

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methanol as shown in fig.(1). No interference from any of the tablet components with the absorbance of EN was observed under the conditions of the assay procedure. The test was performed in triplicates.

![Figure 1: Calibration curve of ECN in methanol.](image)

**Surface pH**

Tablet's surface pH was determined by adding 2 ml of distilled water to one tablet of each formula, placed in separate beakers, they were allowed to swell at room temperature for 2 hours. pH measurement was done by contacting the electrode with the tablet surface for one minute.\(^{15}\)

**Swelling Study**

Vaginal tablets were weighed individually (\(w_1\)), and placed separately in 2% agar plates at 25°C ± 0.1. The tablets were removed at ½,1,2,3, and 4 hours, excess surface moisture was removed by wiping with filter paper and then the tablets were reweighed (\(w_2\)). The swelling index was calculated using the following formula:\(^{16}\)

$$\text{Swelling index } \% = \frac{w_1 - w_2}{w_2} \times 100$$

--- eq. (2)

**Ex vivo Bioadhesive Strength Measurement**

The balance method reported by Parodi\(^{17}\) with some modification was used for determining the ex vivo bioadhesive strength. A female sheep was sacrificed and the sheep vaginal mucosa was obtained immediately after slaughter. The mucosal membrane was separated from other tissues, thoroughly and carefully washed with normal saline and kept frozen at - 18°C until the time of experiment.\(^{18}\) At the time of experiment the tissue was thawed at room temperature in normal saline and carefully cut to fit the mouth of a glass beaker filled with citrate buffer pH 4.2. The tissue was held tightly onto the beaker with a rubber band, and then it was tightly fitted into a glass beaker filled with citrate buffer. A tablet was glued to the bottom of the left pan of a balance and the beaker with the tissue on top was positioned under the left pan so that it almost touched the tablet. A plastic container was put on the right pan. The two pans were balanced, and then a 5 gm weight was added to the left pan which caused the lowering of the pan along with the glued tablet over the tissue beneath. The assembly was kept in that position for 5 minutes, and then water (equivalent to weight) was added into the container on the right pan at a rate of 100 drops/min. Water addition was continued until the tablet detachment take place.\(^{19, 20}\) The experiment was performed in triplicates and mean ± SD were reported.

**Determination of Solubility**

The solubilities of EN in the dissolution media were determined by adding excess amount of the drug into two flasks one containing 1% SLS in distilled water and the other contained 1% SLS in citrate buffer pH 4.2. The flasks were stoppered and kept shaken in a water bath at 37°C for 48 hrs. Samples were withdrawn, filtered, properly diluted, and determined spectrophotometrically. The solubility study was done to confirm the existence of sink condition during the dissolution of the vaginal tablet.

**In vitro EN release Study**

The release of EN from the prepared vaginal tablets was determined using USP dissolution apparatus II (paddle method). The dissolution media were 900 ml of either 1% SLS in distilled water or 1% SLS in citrate buffer pH 4.2 kept at 37°C ± 0.1. A tablet was glued to the bottom of the jar, and the apparatus was rotated at 50 rpm. Two different media were used to examine the difference between the release of the drug in water and in buffer. Samples (5 ml) were withdrawn at specified time intervals and replaced by an equal volume of the dissolution medium. EN was determined spectrophotometrically at 271 nm.\(^{14}\) Dissolution was performed as triplicates.

**Dissolution Data Analysis**

The dissolution profiles of the prepared formulae in citrate buffer were compared using \(f_2\) similarity factor.\(^{8,21}\) The similarity factor is a logarithmic reciprocal square-root transformation of the sum of squared error and is a measurement of the similarity in the percentage of dissolution between two curves.\(^{21}\)
EN Release Mechanism Study

The mechanism of EN release was determined using the following equations:\(^\text{(4)}\)

\[
f_2 = 50 \log \frac{Q}{Q_0} + 2/ \sqrt{0.5 \times 100} \quad \text{--- eq.}(3)
\]

Where \(n\) is the sampling number, \(R\) and \(T\) are the percent dissolved of the reference and test products at each time point \(t\). Two dissolution profiles are considered similar when the \(f_2\) value is greater than or equal to 50.\(^{\text{(22)}}\)

Release Kinetics study

In order to determine kinetics of drug release from the vaginal bioadhesive tablets, drug release data were fitted to zero order, first order, and Higuchi square root.\(^{\text{(26,27)}}\)

Zero-order equation:

\[
Q = Q_0 + k_d t \quad \text{--- eq.}(6)
\]

First-order equation:

\[
\log Q = \log Q_0 + k_t t/2.303 \quad \text{--- eq.}(7)
\]

Higuchi’s equation:

\[
Q = k_d t^{1/2} \quad \text{--- eq.}(8)
\]

Where \(Q\) is the amount of drug dissolved in time \(t\), \(Q_0\) is the initial amount of drug in the solution (most times, \(Q_0 = 0\)), \(K_0\), K1, K2 are the zero, 1st order and Higuchi release constants respectively.\(^{\text{(26)}}\)

Statistical analysis

ANOVA based on least significant difference test (LSD) was used for comparison of differences in means of bioadhesive strength of the tablets, swelling indices, and zero order dissolution rates. Student’s t-test was used to compare the difference in mean dissolution rate constants of each formula in buffer and in distilled water. In all cases, \((P<0.05)\) was considered significant. Statistics were done using Microsoft Excel 2007.

Results and Discussion

Physical evaluation of tablets

The physical properties of the tablets and drug content are summarized in table (2). The mean weight of vaginal tablets ranged from 748.4 to 763 mg. No batch varied more than 5% of the average mass. Concerning the uniformity of drug content, all of the formulations were acceptable since the amount of EN in each of the tested tablets was within the range of 97.5%–101% indicating uniform mixing of the tablet formulation. These results are in compliance with the requirements of USP 28.\(^{\text{(28)}}\) Average hardness of tablets belonging to various formulae indicated high strength, that was also evident in the results of the friability test which were less than 1% for all formulae.

<table>
<thead>
<tr>
<th>Table 2: Results of the physical evaluations conducted on EN bioadhesive vaginal tablets prepared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula #</td>
</tr>
<tr>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
</tr>
<tr>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
</tr>
<tr>
<td>F5</td>
</tr>
<tr>
<td>F6</td>
</tr>
</tbody>
</table>
Surface pH

The surface pH values of the prepared formulae were acidic and ranged from 2.75-4.8. Formulae with pH < 4.2 are not favorable because they are too acidic and may cause tissue irritation. Formula F3 has a pH value similar to that of the vaginal tract.

The swelling index

The swelling behavior of a bioadhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The swelling of the tablets as a function of time is shown in fig.2, at initial stage, there was an initial rapid rise in SI due to the entry of water via metastable pores in the polymer matrix of the tablets. This mechanism, known as swelling hysteresis, was followed by swelling caused by diffusion processes.

![Figure 2: Swelling index of vaginal tablets formulae F1 to F7.](image)

The swelling indices (at 4 hrs) of the various vaginal tablets are summarized in table (3). The results showed that formula F1 containing CP alone had significantly lower SI (p<0.05) than those containing mixtures of CP and NaCMC. The SI was directly proportional to the ratio of NaCMC in the formulae, this appears to be due to the excessive water uptake of NaCMC containing tablets attributed to greater hydrophilic nature of NaCMC. Water causes ionization of carboxylic groups of NaCMC and Carbopol with subsequent repulsion and relaxation of the polymer chains that result in increase in water penetration and hence increase in SI with time. The structural integrity of multilayered formulations may be disrupted by the hydration of the mucoadhesive component. As seen in formula F4 which showed extensive swelling that resulted in disrupting the structural integrity of the tablet. On the other hand, the inclusion of MC in the formulation caused a reduction in the SI. MC hydrates on contact with water forming a viscous gel layer at the surface of the tablet, which might hinder water penetration contributing to the decreased swelling observed in formulae F5, F6, and F7.

<table>
<thead>
<tr>
<th>Formula #</th>
<th>SI (%) at 4hr</th>
<th>Bioadhesive strength (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>65.1±1.54</td>
<td>1.159±0.12</td>
</tr>
<tr>
<td>F2</td>
<td>117±1.53</td>
<td>0.646±0.024</td>
</tr>
<tr>
<td>F3</td>
<td>129±8.4</td>
<td>0.6223±0.02</td>
</tr>
<tr>
<td>F4</td>
<td>182±3.63</td>
<td>0.49±0.08</td>
</tr>
<tr>
<td>F5</td>
<td>61±3.2</td>
<td>0.343±0.035</td>
</tr>
<tr>
<td>F6</td>
<td>56±3.9</td>
<td>0.392±0.05</td>
</tr>
<tr>
<td>F7</td>
<td>47.3±4.02</td>
<td>0.294±0.15</td>
</tr>
</tbody>
</table>

Bioadhesive strength measurement

The results of bioadhesive strength measurement are shown in fig. (3). It was found that formula F1 showed the maximum bioadhesion. The high bioadhesive property of CP is reported to be due to: (i) carboxyl groups present on its acrylic acid backbone, which possess an ability to interact with sialic acid molecules present in the mucus layer through hydrogen bond and (ii) to the formation of secondary mucoadhesive bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, while other polymers undergo only superficial bioadhesion.

The addition of a NaCMC caused a significant reduction in the bioadhesiveness (p<0.05), the bioadhesion decreased progressively with increasing the ratio of NaCMC. Similar results were reported by Emane et al. NaCMC is a salt of an anionic polymer, which generates the carboxylic group in water and then swells and dissolves; it has excellent recognized mucosal properties but the considerable swelling characterizing NaCMC may be one of the factors responsible for its reduced adhesion, as swelling induces over-extension of hydrogen bonds and other forces. Besides, water molecules may bind to polymer groups required for bioadhesion. Formulae F5, F6, and F7 containing MC which is a nonionic polymer exhibited the least bioadhesive
bonding. The cross linking of CP affects also elasticity of the chains as water penetrates inside the polymer network and this leads to entrapment of the drug inside the cross linked network of the polymer. On the other hand, Water causes ionization of carboxylic groups of CP with subsequent increase in water penetration. The higher the uptake of water by the polymer, the greater the amount of drug diffused from the polymer matrix. These reasons may explain the greater in release of EN in distilled water.Formulae prepared using mixtures of CP and NaCMC, exhibited faster release than formula F1. The increase in drug release was directly proportional with NaCMC content, as shown in figure (4.a).

In vitro EN Release Study

The results of release study of EN bioadhesive tablets in citrate buffer pH 4.2 and in distilled water are shown in figures (4.a,4.b,5) respectively. Generally, the release was higher in distilled water than in buffer. The release profiles for the different formulae in water were significantly different (p < 0.05) from those in buffer except for formulae F3 and F4. Formula F1 containing CP alone showed very slow release in both of the dissolution media. At pH 4.2, CP carboxylic groups are mostly unionized; this is associated with high coiling and proximity of carboxylic groups leading to intramolecular hydrogen bonding. The cross linking of CP affects also elasticity of the chains as water penetrates inside the polymer network and this leads to entrapment of the drug inside the cross linked network of the polymer. On the other hand, Water causes ionization of carboxylic groups of CP with subsequent increase in water penetration. The higher the uptake of water by the polymer, the greater the amount of drug diffused from the polymer matrix. These reasons may explain the greater in release of EN in distilled water.Formulae prepared using mixtures of CP and NaCMC, exhibited faster release than formula F1. The increase in drug release was directly proportional with NaCMC content, as shown in figure (4.a).

**Figure 4.a : Release profile of EN in citrate buffer pH 4.2 of formulae 1,2,3 and 4.**

**Figure 4.b : Release profile of EN in citrate buffer pH 4.2 of formulae F1, F5, F6 and F7.**

Figure 3: Bioadhesive strength measured for the formulae F1 to F7.

**Derermination of Solubility**

The solubilities of ECN in 1% SLS in distilled water and 1% SLS in citrate buffer pH 4.2 were found to be 4.37mg/ml and 4.4 mg/ml respectively. The drug concentration in the dissolution medium should not exceed 15% to 20% of saturation solubility of the drug in order to provide sink conditions. In order to provide sink conditions.

**In vitro EN Release Study**

The results of release study of EN bioadhesive tablets in citrate buffer pH 4.2 and in distilled water are shown in figures (4.a,4.b,5) respectively. Generally, the release was higher in distilled water than in buffer. The release profiles for the different formulae in water were significantly different (p < 0.05) from those in buffer except for formulae F3 and F4. Formula F1 containing CP alone showed very slow release in both of the dissolution media. At pH 4.2, CP carboxylic groups are mostly unionized; this is associated with high coiling and proximity of carboxylic groups leading to intramolecular hydrogen bonding. The cross linking of CP affects also elasticity of the chains as water penetrates inside the polymer network and this leads to entrapment of the drug inside the cross linked network of the polymer. On the other hand, Water causes ionization of carboxylic groups of CP with subsequent increase in water penetration. The higher the uptake of water by the polymer, the greater the amount of drug diffused from the polymer matrix. These reasons may explain the greater in release of EN in distilled water.Formulae prepared using mixtures of CP and NaCMC, exhibited faster release than formula F1. The increase in drug release was directly proportional with NaCMC content, as shown in figure (4.a).
As NaCMC becomes hydrated and forms a swollen gel, dissolution and surface erosion of this waterlogged gel occur simultaneously, resulting in rapid release. These results are in agreement with those obtained by Emami et al. Formulae F5, F6 and F7 showed slow release, as shown in figure (4.b), which may be attributed to the build-up of an excessively viscous gel around the tablet which is more resistant to water penetration and erosion.

A combination of polymers may show additive or synergistic release retardation. Synergism in gelling ability of a combination of polymers may be due to molecular interaction between the individual polymers. The similarity factor values for the release profile in citrate buffer are summarized in Table (4), which shows that formulae F1, F5, F6 and F7 have a similar dissolution profile since $f_2$ values are greater than 50. This may suggest that combining MC with CP does not have a considerable effect on the release of the drug. Formulae F3 and F4 don’t resemble any other formula since their $f_2$ values were less than 50. Table (5) shows the exponents $n$, related to drug release kinetics, which were in all cases greater than 1, except formula F4, indicating that drug release follow super case II mechanism in which the release is time dependent and controlled by the relaxational process due to the swelling of the polymeric network.

Table 4: Values for the similarity factor $f_2$ for the release profiles in citrate buffer.

<table>
<thead>
<tr>
<th>Formula #</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>39.67169</td>
<td>29.07959</td>
<td>11.89739</td>
<td>73.10762</td>
<td>55.12816</td>
<td>68.22848</td>
</tr>
<tr>
<td>F2</td>
<td>-</td>
<td>48.08251</td>
<td>17.92629</td>
<td>43.41324</td>
<td>50.32749</td>
<td>45.33722</td>
</tr>
<tr>
<td>F3</td>
<td>-</td>
<td>-</td>
<td>23.31974</td>
<td>31.26696</td>
<td>35.83019</td>
<td>32.1486</td>
</tr>
<tr>
<td>F4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12.68356</td>
<td>14.27366</td>
<td>13.12512</td>
</tr>
<tr>
<td>F5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64.85141</td>
<td>82.20482</td>
</tr>
<tr>
<td>F6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>67.99835</td>
</tr>
</tbody>
</table>

Table 5: Values for k, n and $r^2$ by regression of log $M_t/M_\infty$ vs. log t.

<table>
<thead>
<tr>
<th>Formula #</th>
<th>K</th>
<th>n</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.0214</td>
<td>1.487</td>
<td>0.99</td>
</tr>
<tr>
<td>F2</td>
<td>0.046881</td>
<td>1.365</td>
<td>0.99</td>
</tr>
<tr>
<td>F3</td>
<td>0.063533</td>
<td>1.344</td>
<td>0.994</td>
</tr>
<tr>
<td>F4</td>
<td>0.334195</td>
<td>0.786</td>
<td>0.994</td>
</tr>
<tr>
<td>F5</td>
<td>0.0281</td>
<td>1.377</td>
<td>0.988</td>
</tr>
<tr>
<td>F6</td>
<td>0.040926</td>
<td>1.246</td>
<td>0.964</td>
</tr>
<tr>
<td>F7</td>
<td>0.036308</td>
<td>1.26</td>
<td>0.988</td>
</tr>
</tbody>
</table>

Table 6: Release kinetic parameters with correlation coefficient for designed formulae of EN Bioadhesive Vaginal Tablets in Citrate Buffer.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Zero order $r^2$</th>
<th>1$^{st}$ order $r^2$</th>
<th>Higuchi $r^2$</th>
<th>Highest correlation or best fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.978</td>
<td>0.911</td>
<td>0.945</td>
<td>Zero order</td>
</tr>
</tbody>
</table>
Conclusion
The results of the present investigation indicate that formula F3 which is composed of CP and NaCMC in a ratio of (1:1) may be considered a good candidate for vaginal bioadhesive dosage forms, since it has a suitable drug release profile, good bioadhesion, moderate swelling, and a surface pH of 4.2 simulating to that of the vagina which may prevent the irritation to the vaginal mucosa. The bioadhesion of the developed formula will provide a longer period of residence time, which could result in more available therapy thus enhancing patients' compliance.

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