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# Formulation and In Vitro Evaluation of Mucoadhesive Antimicrobial Vaginal Tablets of Ciprofloxacin Hydrochloride

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**الخلاصة:**

ان عقار السيبروفلوكساسين هو عقار من مجموعة الفلوروكوينولون ذو الطيف الواسع، وذو فعالية في علاج مجموعة واسعة من الأمراض، بما في ذلك التهابات الجهاز البولي–التناسلي.

تم في هذه الدراسة إعداد أقراص مهبلية من هيدروكلوريد السيبروفلوكساسين بواسطة طريقة الضغط المباشر باستخدام مزيج من المكوثرات الملتصقة بالنسيج المخاطي مثل الكاربوبول، الكربوكسي مثيل سليلوز وألجينات الصوديوم في نسب مختلفة. تم تقييم الحبوب المحضرة عن طريق قياس قدرتها على الانتفاخ، مقدار الاس الهيدروجيني لسطح الحبة، قابلية الالتصاق ودراسة قدرة التحرر الدوائي.

وجد ان قوة الالتصاق تتناسب طرديا مع محتوى الكاربوبول في الصيغ المختلفة وتم تعزيزها باضافة الكربوكسي مثيل سليلوز. اشارت دراسات الانتفاخ الى ان الصيغ الحاوية على مزيج من الكاربوبول والكربوكسي مثيل سليلوز أو ألجينات الصوديوم تميزت بقابلية انتفاخ اعلى من الصيغ الحاوية على الكاربوبول لوحده، كما وجد ان الصيغ الحاوية على الكاربوبول والكربوكسي مثيل سليلوز لها قدرة انتفاخ اعلى من مثيلاتها من الصيغ الحاوية على الكاربوبول وألجينات الصوديوم. في دراسة التحرر الدوائي تم بيان تحرر أسرع لهيدروكلوريد السيبروفلوكساسين من مثيلاتها من الصيغ الحاوية على ألجينات الصوديوم.

بينت الصيغة (F5) المتكونة من الكاربوبول/الكربوكسي مثيل سليلوز بنسبة 1:2 انتفاخا معتدلا وقابلية التصاق أوتأخير لتحرير الدواء جيدة وبالتالي يمكن اعتبارها مرشحة جيدة كقاعدة لحبوب مهبلية ملتصقة.

## Abstract:

Ciprofloxacin is a broad spectrum fluoroquinolone, effective in the treatment of a wide range of infections, including genitourinary tract infections. In this study, bioadhesive vaginal tablets of ciprofloxacin hydrochloride were prepared by direct compression method using a combination of bioadhesive polymers carbopol 934P(Cp), carboxymethylcellulose (CMC) and sodium alginate (SA) in different ratios.

The prepared tablet formulations were characterized by measuring their swelling capacity, surface pH, bioadhesive properties, and *in-vitro* drug dissolution. It was found that the bioadhesive force was directly proportional to

carbopol 934P content in different formulae and was further enhanced by the inclusion of carboxymethylcellulose. Swelling studies indicated that formulae containing a combination of carbopol 934P and sodium alginate or carboxymethylcellulose had greater swelling index than those containing carbopol 934P alone. Formulations containing Carbopol 934P and carboxymethylcellulose were found to swell to a greater extent than those composed of similar ratios of carbopol and sodium alginate. *In vitro* drug release study showed that the release of ciprofloxacin hydrochloride from formulae containing carboxymethylcellulose was faster than from those containing sodium alginate.

Formula F5 composed of CP/CMC in a ratio of 2:1 showed moderate swelling, suitable bioadhesion and retardation of drug release. Thus, it may be considered a good candidate as a base for bioadhesive vaginal tablet.

**Keywords:** Bioadhesion, ciprofloxacin hydrochloride, carbopol 934P, carboxymethyl cellulose, sodium alginate, vaginal drug delivery

## Introduction:

In recent years, there has been a growing interest in the use of vagina as a route of drug delivery, not only for local but also for systemic delivery of several therapeutic agents[1]. Compared to the traditional oral route, vaginal administration provides certain advantages by producing little or no exposure to the rest of the body when local effect is required; they also enable the use of prolonged dosing regimens, lower daily doses, and provide continuous release of medication [2].

Vaginal drug delivery has been widely used for the administration of a variety of locally acting drugs such as antifungal, antibacterial, antiprotozoal, antichlamydial, and antiviral agents. They have been used for the therapy of local disorders including vaginitis, candidiasis, trichomoniasis, urinary tract infections and sexually transmitted diseases (STDs) [3,4]. Mucosal-vaginal drug delivery, which is a special category of local delivery, allows longer drug residence time in the vaginal cavity, reduces the dosing frequency and quantity of drug administered such that the drug delivery and the therapeutic efficacy of locally acting drugs may be improved due to the increased availability at the vaginal epithelium through bioadhesion[5,6].

Various mucoadhesive vaginal drug delivery systems have been developed in the form of semi-solid and solid dosage forms including mucoadhesive vaginal gels, tablets, films and mucoadhesive vaginal suppositories.[7] Among these dosage forms, vaginal mucoadhesive tablets appear to be useful, particularly for the therapy of insistent vaginal infections as they are easy to use, portable and can accurately administer the required quantity of drug and avoid the leakage and messiness that can be associated with conventional vaginal drug delivery systems (e.g., pessaries, ointments, foams, creams, gels), and therefore increase patient compliance [8, 9].

A variety of bioadhesive polymers are used for intravaginal drug delivery including poly (acrylic acid) derivatives, chitosan, cellulose-derivatives such as carboxymethylcellulose (CMC), sodium carboxymethylcellulose (NaCMC), methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), sodium hyaluronate, carrageenan, xanthan, gelatine, sodium alginate, starch, pectin and tragacanth [10].

Ciprofloxacin is a broad spectrum fluoroquinolone derivative. It is effective in the treatment of a wide range of infections including urinary tract infections, acute uncomplicated cystitis and sexually transmitted diseases (gonorrhea and chancroid)[11]. Several clinical studies support the use of ciprofloxacin in the prevention or treatment of complicated urinary tract infections (UTIs), using different dose regimens including a low dose (200 mg) once-daily ciprofloxacin regiment, conventional twice daily tablet, or a new once-daily extended-release tablet formulation [12-15].

The aim of this study was to develop a once-a-day mucoadhesive vaginal tablet of ciprofloxacin HCl to improve adhesion to vagina in order to prolong residence time and consequently reduce dosing frequency and obtain a long therapeutic concentration at the site of infection. This study addresses the possible use of a mixture of carbopol in different ratios with sodium alginate, or carboxymethylcellulose for the preparation of mucoadhesive vaginal tablets of ciprofloxacin HCl. The formulated vaginal tablets were evaluated for their physicochemical properties, bioadhesive strength, *in vitro* swelling index and *in vitro* release studies.

## Materials and Methods:

Ciprofloxacin HCl (Zhejiang Xinhua, china), carbopol 943 (CP) (Goodrich,USA), sodium alginate (SA) (Himedia lab, India), carboxymethylcellulose (CMC) and magnesium stearate (BDH Chemicals, LTD, Liverpool, England). All other reagents are of analytical grade.

**Preparation of Tablets:**

Seven bioadhesive tablet formulations were prepared; the composition of each formula is given in Table 1. Each tablet contains 250 mg ciprofloxacin HCl. An exactly weighed quantity of powder mixture was filled into a die of 15 mm diameter and directly compressed using single punch tablet press (Korsch EKO, Berlin, Germany) equipped with flat faced punches.

All formulations contained 1 % of magnesium stearate as lubricant. The tablets prepared weighed approximately 1000 mg and had thickness of about 4.2 mm. Total weight of the polymer(s) per tablet is 750 mg in all of the formulae.

**Evaluation of bioadhesive vaginal tablets:**

**Thickness:**

The thicknesses of vaginal tablets were determined using vernier calipers. Three individual tablets from each batch were used and the average thickness was calculated.

**Weight Variation Test:**

Weight variation test was performed on ten tablets selected randomly from each batch using an electronic balance (Kern, ABS/ABJ-BA, Germany). Each tablet was weighed individually and average values were calculated. According to the U.S Pharmacopoeia for tablets weighing more than 324 mg, a 5% maximum difference is allowed [16].

**Hardness:**

Hardness test were conducted for three tablets from each batch using Monsanto hardness tester and average values were calculated.

**Friability:**

The friability of tablets was determined using Roche friabilator and the value obtained is expressed as percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at (25) rpm for 4 minutes. The tablets were weighed again ($W_{final}$). The % friability was then calculated using the formula-1:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100 \qquad \text{..... (1)}$$

% Friability of tablets less than 1% is considered acceptable.

**Drug Content Uniformity:**

One tablet of each formulation was ground in a mortar to a powder form. An accurately weighed amount of the powder, equivalent to 100 mg of ciprofloxacin HCl was transferred to a 100-mL volumetric flask. Seventy milliliters of 0.1 N HCl was then added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with 0.1 N HCl. The mixture was then filtered through filter paper and 1 mL of the filtrate was suitably diluted with 0.1 N HCl and analyzed spectrophotometrically (UV-9200, Beiotech, UK) for ciprofloxacin HCl at $\lambda_{max}$ of 278 nm using 0.1 N HCl as blank. [17] The content was calculated using a pre-constructed calibration curve for the drug. The assay was conducted in triplicate.

**Surface pH:**

Tablet's surface pH was determined by adding 5 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. Measurement of pH was done by bringing the electrode near the surface of the tablet after equilibrating for one minute. [18] All experiments were performed in triplicate for each sample, and the mean values and SDs were calculated.

**Tablet swelling study:**

Swelling characteristics of the bioadhesive tablets were evaluated by determining the initial weight of the tablet ($W_1$) then the tablet was placed separately in a 50 mL glass beaker containing citrate/phosphate buffer pH 4.8 at

25 ± 0.5 °C. Tablets were removed at different time intervals (½, 1, 2, 3, and 4 hours) and reweighed ($W_2$) after removing excess water on the surface with a filter paper.

Each experiment was performed in triplicate. The swelling index was calculated using the following formula 2 [19]:

$$\text{Swelling index} = (W_2 - W_1)/ W_1 \quad \ldots\ldots (2)$$

**In vitro mucoadhesion study:**

The mucoadhesive performance of the prepared vaginal tablets was evaluated using a modified balance method employing fresh sheep's vaginal tissue [20].

A piece of sheep vaginal mucosa was obtained immediately after slaughter, it was cut to a size of (2.0 cm × 2.0 cm) and tied to a glass slide with a thread, and was then moistened with citrate/phosphate buffer (pH 4.8). This was then kept below the left hand pan of a double pan torsion balance. The tablet was mechanically attached to the bottom of the left pan of the balance. Previously weighed plastic beaker was placed on the right hand pan and the two pans were balanced by adding an appropriate weight on the right hand pan. Then, the weight was removed from the right-hand pan, this caused lowering of the left side pan along with the tablet attached to it, such that the tablet becomes in contact with the previously hydrated vaginal mucosa attached to the glass slide, located beneath the left side pan. The balance was kept in this position for 1 minute contact time. Water was added slowly to the beaker on the right hand pan until the tablet detached from the mucosal surface. The weight of water was measured. This detachment force gave the mucoadhesive strength of the tablet in grams.

Mucoadhsive force was than calculated according to the following equation [21]:

$$\text{Force of adhesion, Newton (N)} = \frac{\text{bioadhesive strength}}{1000} \times 9.81 \quad \ldots\ldots\ldots (3)$$

Bioadhesive studies were carried out in triplicate and average bioadhesive strength was determined. After each measurement, the tissue was gently and thoroughly washed with fresh buffer solution and left for 5 minutes before continuing with next trial.

**In vitro drug release:**

Tablet drug release was evaluated, using a USP paddle type dissolution apparatus (Copley Scientific LTD, England). One side of the tablet was wetted with citrate/phosphate buffer (pH 4.8) and fixed to the bottom of the dissolution jar. After 2 minutes, the vessel was filled with 900 mL of citrate/phosphate buffer (pH 4.8) at 37°C and stirred at 50 rpm. Samples (5 mL) were withdrawn at specified time intervals and replaced by an equal volume of the dissolution medium maintained at 37°C to maintain sink conditions [19].

Samples were filtered using millipore filter and ciprofloxacin HCl absorbance was determined by UV spectrophotometer (UV-9200, Beiotech, UK) at $\lambda_{max}$ of 278 nm. [17] Concentrations were obtained using a previously constructed calibration curve with citrate/phosphate buffer pH 4.8 used as blank. The % amount drug released at each time point was expressed as a fraction of the total drug amount in tablets. Experiments were carried out in triplicate.

**Release kinetic studies:**

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration .The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time ,dependent process based on Fickian diffusion Eq. (3).

$Ct = C0-k0t$---------- Equation (1) where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$LogCt= LogC0- k1t / 2.303$ ----------Equation (2) where, C0 is the initial concentration of drug and K1 is first order constant.

$C = Kt^{1/2}$ -------equation (3) where, C is cumulative % drug release, K is the constant reflecting the design variables of the system. Korsmeyer derived a simple relationship which described drug release from a polymeric system Equation (4). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:n

$Ct/ C\infty = Kt^n$ -------equation (4) where $Ct/ C\infty$ is fraction of drug released at time t, k is the rate constant and n is the release exponent. n is the diffusional release exponent indicative of the operating release mechanism A value of release exponent, $n = 0.45$, $0.45< n < 0.89$, and $0.89< n <1.0$ indicates Fickian (case-I), non-fickian (anomalous) and zero order (case-II) transport, respectively[22].

The model fitted were plotted : cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model), cumulative % drug release vs. square root of time (higuchi model), log cumulative % drug release vs. log time (korsmeyer model) [23]. The best fit model was selected as the one with the highest value of regression coefficient ($R^2$).

**Statistical Analysis:**

Differences in drug release parameters from the bioadhesive vaginal tablets were statistically analyzed using one-way analysis of variance (Anova) test, by using the Microsoft 2010 Excel software. Differences were considered significant at ($P < 0.05$) level.

## Results and Discussion:

### Physical evaluation of tablets:

The physical properties of the tablets and drug content are summarized in table-2. The diameter of all the formulations were found within the acceptable range i.e. ± 5% of the respective average diameter. The mean weight of vaginal tablets ranged from 0.9996 to 1.007 gm. 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 ciprofloxacin HCl in each of the tested tablets was within the range of 97.5%–101% indicating uniform mixing of the tablet formulation. Average hardness of tablets of various formulae indicated high strength that was also evident in the results of the friability test which were less than 1% for all formulae.

### Surface pH:

The surface pH of all formulations was acidic and ranged from 2.64-4.68. It is desirable to have a formula with surface pH within the normal range of vaginal pH, i.e. 4 -5 [24], this will cause little irritation and thereby show better patient acceptability. Use of carbopol alone as a bioadhesive polymer is associated with a drawback of having formulations with very low surface pH values because carbopol is a polyacrylic acid derivative containing high concentrations of carboxyl groups within its structure. [25] Such observation reflects that carbopol alone cannot be incorporated in the design of bioadhesive vaginal tablets.

The inclusion of other polymers in the system caused higher surface pH readings, so in case of inclusion of sodium alginate there was an increase in surface pH value because of introduction of hydroxyl groups which reduced the availability of free carboxylic acid groups present in the structure of carbopol. Formulae F4, F5 and F6 have proper pH values similar to that of vaginal tract.

### Swelling studies:

Swelling property of a vaginal tablet is an important parameter which influence the mucoadhesion and drug release ability of formulations; therefore, it must be investigated to achieve proper mucoadhesion and have a prolonged drug release.

Shortly after swelling, adhesion does occur, but with a weak bond formed. To develop maximum adhesion strength, an optimum water concentration is needed for polymer particles. Some reports showed direct relation between swelling and mucoadhesion, other did not [26, 27].

Swelling index of various mucoadhesive vaginal tablet formulations was studied for a period of 4 hours. The obtained values are summarized in Table 3 and are shown in figure-1. Among formulated tablets, those containing CP alone Formula-1 exhibited the lowest swelling index.

For tablet formulations composed of carbopol: polymer mixture, the swelling index study indicated that the rate of swelling was proportional to sodium alginate or carboxymethylcellulose content and inversely proportional to

CP content. Such behavior could be attributed to greater hydrophilic nature of sodium alginate or CMC relative to carbopol. Similar results were observed with atenolol buccoadhesive tablets [28].

Furthermore, the swelling index of tablets containing various ratios of CP/ sodium alginate was lower than that of tablets containing similar ratios of CP/CMC. Such behavior could be attributed to greater hydrophilic nature of CMC relative to sodium alginate.

Although the swelling index values varied for formulas composed of polymer combinations, it was observed that a statistically significant ($P < 0.05$) increase in the rate of swelling was evident only for formulas F4 and F7 containing 1:2 ratios of CP/SA and CP/CMC, respectively in comparison to formula F1 composed on carbopol 934 alone.

**In vitro mucoadhesion study:**

The in vitro bioadhesive strength study was performed and the results are shown in Table 3. In general, the tablets showed good mucoadhesive forces with values ranging between 0.18-0.98 N.

Regarding CP/SA combination tablets (formulas 2-4), the highest force of adhesion was observed in formula F2. Replacement of carbopol with increasing amounts of sodium alginate in tablet formulations produced tablets that exhibited lower bioadhesive strength than those prepared with carbopol alone. This may be due to replacement of the more bioadhesive polymer carbopol with a lower bioadhesive polymer, sodium alginate [29]. These results are in agreement to those obtained by John et al [30] for atorvastatin calcium buccoadhesive tablets.

For the CP/CMC combination tablets (formulas 5–7), the highest force of adhesion was observed with F5. Replacement of carbopol with increasing amounts of carboxymethylcellulose in tablet formulations produced tablets that exhibited higher bioadhesive strength than those prepared with carbopol alone. This may be due to the fact of higher bioadhesion property of carboxymethylcellulose relative to carbopol [31], or due to the increase in the number of carboxylic groups which can form hydrogen bonds with tissue, in addition to faster hydration of carboxymethylcellulose as indicated from the swelling study.

**In vitro Release Study:**

The release of ciprofloxacin in citrate/phosphate buffer (pH 4.8) for different formulations are shown in figures 2 and 3 respectively.

Release profiles of ciprofloxacin from sodium alginate containing formulations are shown in figure 2. The released percent of ciprofloxacin at 6 h for the formulations F2, F3 and F4 were 55.37 %, 57.28 % and 62.06 %, respectively. No significant difference in release profiles was obtained between the formulations containing CP: SA at the ratios of 2:1, 1:1 and 1:2 ($P > 0.05$); however formulation F4 (CP: SA ratio 1:2) showed a significantly higher release ($p < 0.05$) when compared to formula F1 containing carbopol alone. Increasing

the amount of sodium alginate, which is a water-soluble polymer in the formulations probably results in formation of porous channels causing a faster release of drug. Similar observations were found with Ìkinci et al [32] during their study in formulation of buccal bioadhesive nicotine tablets.

In the same way, release profiles of ciprofloxacin from carboxymethyl-cellulose containing formulations are shown in figure 3. The released percent of ciprofloxacin at 6 h for the formulations F5, F6 and F7 were 56.33 %, 74.48 % and 78.30 %, respectively. No significant difference in release profiles was obtained between the formulations containing CP: CMC at the ratios of 2:1, 1:1 and 1:2 ($P > 0.05$); however formulation F7 (CP: CMC ratio 1:2) showed a significantly higher release rate ($p < 0.05$) when compared to formula F1 containing carbopol alone.

It is evident from figures 2 and 3 that the release of ciprofloxacin from tablets composed of CP and SA combinations (formulas F2-F4) was slower than those composed of CP and CMC combinations (formulas F5-F7). This may be due to the neutral cellulose groups of carboxymethylcellulose which have a weak binding force with the drug compared with the hydroxyl groups of sodium alginate [33].

These results indicate that the drug release rate from the tablets increases as the concentration of added hydrophilic polymers (sodium alginate and carboxymethylcellulsoe) increase. This may be due to altered the structural properties of the tablet matrix achieved and by increased porosity which allows for more rapid penetration of the dissolution medium into the tablet leading to facilitated drug release behavior.

During the study, it was observed that the tablets begin to swell with time without any observed erosion over the period of 6h, suggesting that the drug release is controlled by diffusion.

**Evaluation of drug release kinetics:**

*In-vitro* drug release data obtained up to 6 hr of F1 to F7 were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations and best-fit parameters were calculated to ascertain the pattern of drug release. Summary of the drug release models used and their regression coefficients are summarized in Table-4.

Formulations F3 and F4 follow Higuchi model which is most common for homogeneous polymer matrices. It describes drug release process based on Fick's law and release being dependent on square root of time. The rest of the formulations follow zero order kinetics.

Furthermore, drug release profiles were analysed using Korsmeyer-Peppa's model to analyse drug transport mechanism based on their release exponent ($n$). The obtained results are summarized in table-5.

Drug release from formulations F4 and F7 were found to follow Fickian transport; for the rest of the formulations, drug release was by anomalous transport mechanism ($n$ = 0.45–0.89) indicating a non-Fickian release kinetic,

which means that the drug release is controlled by a combination of mechanisms of diffusion and polymer relaxation through the hydrated matrix rather than the process of diffusion alone.

## Conclusions:

In conclusion, ciprofloxacin HCl vaginal tablet formed of carbopol 934P and carboxymethylcellulose in a ratio of 2:1 (formula F5) was found to be the best formulation regarding all the properties evaluated in order to achieve the aim of this study. It gave a suitable release rate. Moreover, the formed tablets have reasonable swelling and good bioadhesive property. These tablets are expected to enhance patient's compliance by offering a once-a-day vaginal bioadhesive formulation for local effect of ciprofloxacin HCl for the treatment of genitourinary infections.

| Code | Polymer mixture | Ratio of each polymer |
|---|---|---|
| $F_1$ | Carbopol alone | - |
| $F_2$ | Cp: SA | 2:1 |
| $F_3$ | Cp: SA | 1:1 |
| $F_4$ | Cp: SA | 1:2 |
| $F_5$ | Cp: CMC | 2:1 |
| $F_6$ | Cp: CMC | 1:1 |
| $F_7$ | Cp: CMC | 1:2 |

**Table-1: The composition of various ciprofloxacin HCl bioadhesive tablet formulations.**

| Code | Physical parameter | | | | | |
|---|---|---|---|---|---|---|
| | Average weight ± SD (mg) | Thickness# ± SD (mm) | Hardness # ($Kg/cm^2$) | Friability (%) | Content Uniformity #± SD (%) | Surface pH # |
| F1 | 0.996 ±0.03 | 4.20 ±0.02 | >12 | 0.17 | 98.4 ± 0.6 | 2.64 ±0.28 |
| F2 | 1.007 ±0.03 | 4.24 ± 0.01 | >12 | 0.04 | 99.2 ± 0.8 | 3.47 ±0.07 |
| F3 | 0.999 ±0.02 | 4.30 ±0.03 | >12 | 0.24 | 101 ± 0.5 | 3.69 ±0.19 |
| F4 | 1.000 ±0.02 | 4.22 ± 0.02 | 7.5 | 0.38 | 97.5±0.5 | 4.51 ±0.12 |
| F5 | 0.997 ±0.04 | 4.26 ±0.01 | >12 | 0.20 | 99.3 ± 0.7 | 4.68 ±0.21 |
| F6 | 0.998 ±0.05 | 4.28 ± 0.03 | >12 | 0.02 | 99.2 ± 0.7 | 4.36 ±0.11 |
| F7 | 1.001 ±0.04 | 4.25 ± 0.02 | 7 | 0.54 | 98.3 ± 0.2 | 2.67 ±0.55 |

**Table-2: Physical parameters (mean ± SD) for ciprofloxacin mucoadhesive vaginal tablet formulations.** #: n =3 (where n= number of replications)

| Code | Swelling index (SI) at 4hr | Bioadhesive strength (N) |
|---|---|---|
| F1 | 0.59 ±0.011 | 0.58 |
| F2 | 0.62 ± 0.015 | 0.39 |
| F3 | 0.72 ± 0.009 | 0.37 |
| F4 | 0.97 ± 0.015 | 0.18 |
| F5 | 0.67 ± 0.020 | 0.98 |
| F6 | 0.92 ± 0.010 | 0.9 |
| F7 | 1.80 ± 0.020 | 0.68 |

**Table-3: Results of the swelling index at 4 hr and bioadhesive strength**

| Code | Zero order $R^2$ | First order $R^2$ | Higuchi $R^2$ | Best fit model |
|---|---|---|---|---|
| F1 | 0.9834 | 0.9553 | 0.9276 | Zero order |
| F2 | 0.9836 | 0.9148 | 0.9851 | Zero order |
| F3 | 0.9778 | 0.9144 | 0.9816 | Higuchi |
| F4 | 0.9557 | 0.922 | 0.9784 | Higuchi |
| F5 | 0.9737 | 0.9027 | 0.9723 | Zero order |
| F6 | 0.9884 | 0.9343 | 0.975 | Zero order |
| F7 | 0.9898 | 0.9648 | 0.9776 | Zero order |

**Table-4: Drug release model fitting to various models and their regression coefficients**

| Formula code | Korsemeyer-Peppas parameters | | | Transport mechanism |
|---|---|---|---|---|
| | Release exponent (n) | Kinetic constant (k) | Regression coefficient ($R^2$) | |
| F1 | 0.5298 | 2.8928 | 0.9044 | Anomalous |
| F2 | 0.6 | 2.9254 | 0.9783 | Anomalous |
| F3 | 0.554 | 3.0452 | 0.9621 | Anomalous |
| F4 | 0.3149 | 3.5406 | 0.9501 | Fickian |
| F5 | 0.7056 | 2.7769 | 0.9743 | Anomalous |
| F6 | 0.5866 | 3.2131 | 0.9606 | Anomalous |
| F7 | 0.327 | 3.7118 | 0.9467 | Fickian |

**Table-5: Drug release model fitting to Korsmeyer-Peppas's and their regression coefficients**

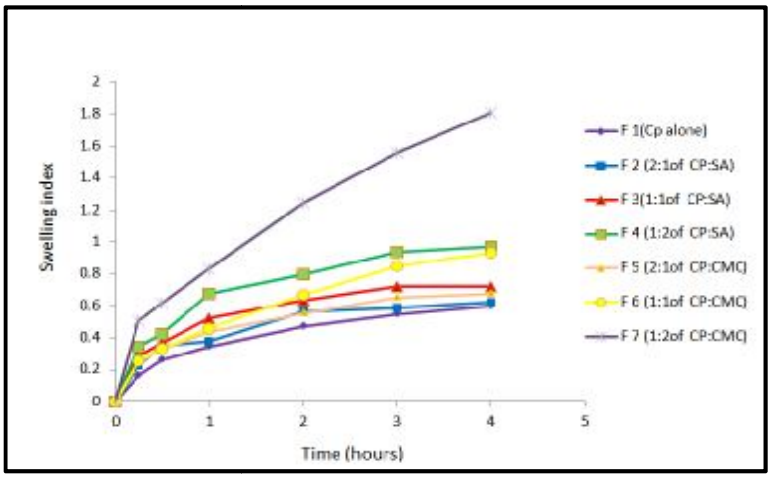


**Figure-1: Swelling index profile of formulations F1to F7. Each point represents Mean±SE; n=3.**

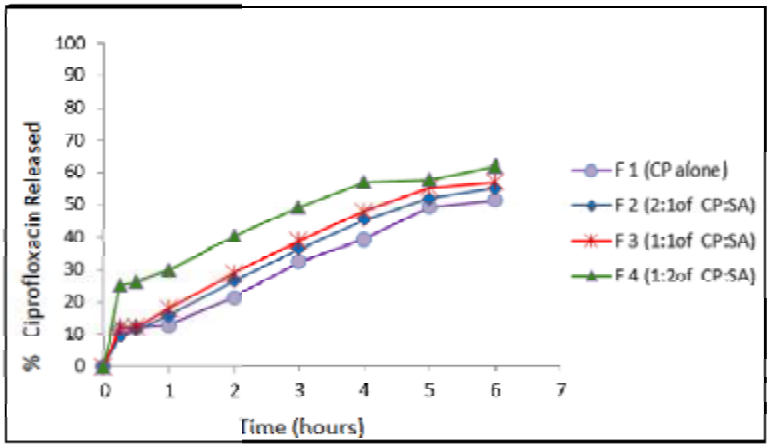


**Figure-2: In-vitro drug release profiles of formulations, F2 to F4 compared to formulation F1 in citrate/phosphate buffer pH 4.8. Each point represents Mean±SE; n=3.**

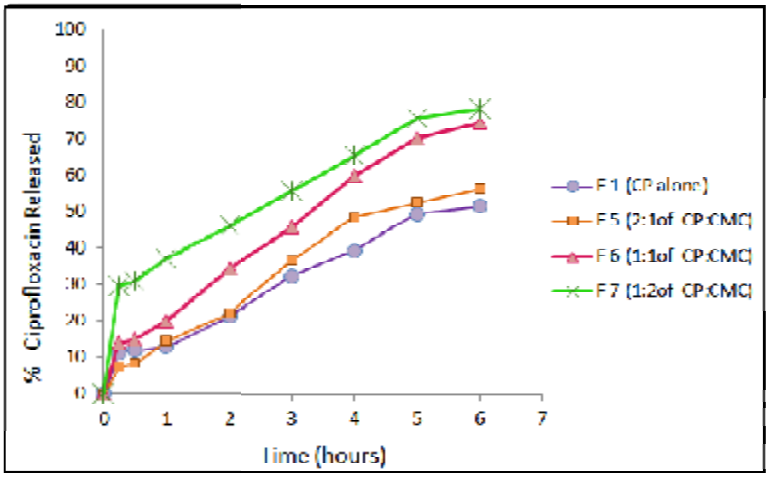


**Figure-3: In-vitro drug release profiles of formulations F5 to F7 compared to formulation F1 in citrate/phosphate buffer pH 4.8. Each point represents Mean±SE; n=3.**

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