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Development And Evaluation Of Mucoadhesive Microsphere Of Cefpodoxime Proxetil

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ABSTRACT

The present study was aimed to develop a microparticulate dosage form of cefpodoxime proxetil by varying the ratio of mucoadhesive polymers such as sodium alginate, sodium CMC and carbopol-934P by using w/o emulsification solvent evaporation technique to prolong its gastric residence time and thus improving the oral bioavailability of the drug.

Microspheres prepared were found discrete, spherical and free flowing. All these formulations prepared were evaluated for surface morphology, particle size analysis, swelling index, drug entrapment efficiency, *in-vitro* mucoadhesion *in-vitro* drug release profile and release kinetics. The average particle size was found to be in the range of 33.30±1.93 to 41.56±3.32 µm. The swelling index of formulation FC1, FC2, FC3, FC4, FC5, and FC6 were ranges from 0.66±0.09 to 1.62±0.08. The microspheres exhibits good mucoadhesive properties and showed high drug entrapment efficiency. Percent drug loading efficiency of microspheres was found in the range of 53.00 ± 2.65 to 68.00 ± 3.44%. At the end of 8 hrs % mucoadhesion for formulation FC1, FC2, FC3, FC4, FC5, and FC6 was found to be in the range of 06.89±0.92 to 25.53±1.65. Cefpodoxime proxetil release from these microspheres was slow and extended and dependent on the type of polymer used. Formulations FC3 containing Sod. CMC showed the maximum release 91.89% after 10 hrs. Among all the formulation, formulation FC3 containing Sod. CMC and FC2 containing Carbopol 934P showed the best reproducible results and the mucoadhesive profile with good surface morphology. The work has demonstrated that microspheres, particularly those of Sod. CMC are promising candidate for the sustained release of Cefpodoxime proxetil in the stomach.

KEYWORDS: Cefpodoxime proxetil, Mucoadhesion, Solvent Evaporation, Bioavailability.

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INTRODUCTION

Gastroretentive drug delivery systems are reported beneficial to many drugs for improving their bioavailability, therapeutic efficacy and by possible reduction of dose. These systems offer various pharmacokinetics advantages like maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutics levels minimizing the risk of resistance especially in case of antibiotics.[1]

Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems.[2]

Microparticles are defined as spherical polymeric particles ranging in size from 1– 1000 µm.[3]

These microparticle constitutes an important part of these drug delivery systems, by virtue of their small size and efficient carrier characteristics. However, the success of these novel microparticles is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes. It can be achieved by coupling bioadhesion characteristics to microparticles and developing novel delivery systems referred to as "bioadhesive microparticles".[4]

Bioadhesive microparticles have advantages such as efficient absorption and enhanced bioavailability of drugs owing to their high surface to volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site.[5,6]

Cefpodoxime Proxetil (CP) (1-[(isopropoxycarbonyl) oxy] ethyl ester of (Z)-7-[2-(2-amino-1, 3-thiazol-4-yl)-2- methoxyiminoacetamido]-3-methoxymethyl-3- cephem-4-carboxylic acid) is the orally active ester prodrug of third generation Cephalosporin. CP is used orally for the treatment of mild to moderate respiratory tract infections, uncomplicated gonorrhea and urinary tract infections.[7]

Cefpodoxime Proxetil is a prodrug and gets hydrolyzed to its parent moiety Cefpodoxime Acid (CA) by non specific Cholinesterase enzyme in the intestinal wall/plasma . It has 50% oral bioavailability. The reasons for this poor bioavailability of CP are low aqueous solubility and preabsorption luminal conversion of CP into CA by action of digestive Cholinesterase .[7]

Bioavailability of CP can be improved simply by eliminating preabsorption conversion of CP to CA.[8,9] It also requires control release owing to its short biological half life of 2-3 h.[10]

However, the high solubility, chemical and enzymatic stability, and absorption profile of CP in acidic pH values of stomach, points to the potential of a gastroretentive (GR) dosage form in altering the absorption profile of CP.[11]

Despite the mucoadhesion, the advantage of using microspheres as oral mucoadhesive drug delivery system is that the small size microspheres can be trapped in the reductus of the stomach and stay there longer.[11]

The objective of the present work is to improve the oral bioavailability of Cefpodoxime proxetil by formulating gastroretentive mucoadhesive microspheres which will provide protection from intestinal milieu using various mucoadhesive polymer.

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil was a gift sample from Apco Pharma Ltd, Haridwar (Uttarakhand, India). Sodium carboxymethylcellulose (sodium CMC), having a viscosity of 1,500– 3,000 cps of 1% w/v aqueous solution at 25 °C was procured from Qualigens fine Chemicals, Mumbai. Carbopol 934P was obtained from Titan Biotech ltd, Bhiwadi, Rajasthan. Sodium alginate, liquid paraffin, span 20, n-Hexane were purchased from Loba Chemicals, Mumbai.All other reagents used were of analytical grade.

Methods Preparation of microspheres:[12,13]

Mucoadhesive microspheres of Cefpodoxime proxetil were prepared by emulsification solvent evaporation method using various ratios of sodium carboxy methyl cellulose, sodium alginate and carbopol 934 P. For this, 200 mg of drug dissolved in 5 ml of methanol, and then it was mix in 45 ml of 2% aqueous polymer solution. Then drug and polymer solution was added drop wise to 400 ml of the liquid paraffin containing 0.5 % span 20 as an emulsifying agent with constant stirring at 1000 rpm. The constant stirring was carried out using magnetic stirrer. The beaker and its content were heated at 80^0C with constant stirring for 4 hrs until the aqueous phase was completely removed by evaporation. The liquid paraffin was decanted and collected microsphere were washed 5 times with n-hexane, filtered through whattman's filter paper and dried in hot air oven at 50°C for 2 hours.

Table 1: Composition of various formulations of microspheres.

S.NO.	Formulation code	Drug	Sodium alginate	Carbopol-934P	Sodium CMC
1.	FC1	200 mg	800 mg	--	--
2.	FC2	200 mg	--	800 mg	--
3.	FC3	200 mg	--	--	800 mg
4.	FC4	200 mg	400 mg	400 mg	--
5.	FC5	200 mg	400 mg	--	400 mg
6.	FC6	200 mg	--	400 mg	400 mg

All formulations were prepared at 2% polymer concentration and 1000 rpm stirring speed. Span 20 (0.5%) used as emulsifying agent.

Surface Morphology:

The surface morphology and structure were visualized by scanning electron microscopy (Evo-40, Zeiss, Germany) at Advanced instrumentation research facility, JNU, New Delhi. The samples were prepared by lightly sprinkling the microspheres powder on a double side adhesive tape which already shucked to on aluminum stubs. The stubs were then placed into fine coat ion sputter for gold coating. After gold coating samples were randomly scanned for particle size and surface morphology.[14]

Particle Size Analysis:

The mucoadhesive microspheres were examined by optical microscope. The freshly prepared suspension of microspheres was examined on an optical microscope and size of the microspheres was measured by using a pre-calibrated ocular micrometer and stage micrometer. Around 100 particles of each formulation were observed and counted.

Swelling Index: [15, 16]

50 mg of microspheres were allowed for swelling in SGF (pH -1.2) for 4 hrs, the excess adhered liquid was removed by blotting with filter paper and weighed.

$$\text{Swelling index } (\boldsymbol{SI}) = \frac{\mathbf{Ws - Wo}}{\mathbf{Wo}}$$

where, Wo is initial weight of the dry microspheres,

Ws is final weight of swollen microspheres.

Drug Entrapment Efficacy:[11]

25 mg of dried microsphere were weighted accurately and drug was extracted from microspheres by digesting for 24 hrs with 10 ml of SGF (pH 1.2). During this period the suspension was agitated. After 24 hrs the suspension was centrifuged at 2000 rpm for about 3 minutes. The solution was filtered through 0.45 mm membrane filter, and the filtrate was analyzed for drug content at 263 nm.

Entrapment efficiency was calculated according to equation.

$$\textbf{Drug entrapment efficiency} = \frac{\textbf{Practical drug content}}{\textbf{Theoretical drug content}} \text{ x } 100$$

In-vitro Mucoadhesion Test:[17]

The mucoadhesive properties of the microspheres were evaluated by in vitro wash-off test as reported by Lehr et al. A 1-cm by 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Microspheres were spread onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid (pH 1.2). At hourly intervals up to 10 hours, the number of microspheres still adhering onto the tissue was counted. Percent mucoadhesion was given by the following formula.

$$\textbf{\% mucoadhesion} = \frac{\textbf{no.of particles}}{\textbf{no.of applied microspheres}} \times \textbf{100}$$

In-vitro Drug Release:[18]

Microspheres equivalent to 100 mg of Cefpodoxime proxetil were filled in hard gelatin capsules, dissolution was performed using USP paddle type dissolution test apparatus at 37±1 ^{o}C, rotational speed of 50 rpm in 900 ml SGF (pH 1.2). Samples (5 ml) were withdrawn at predetermined time intervals and equally replaced with fresh dissolution medium, filtered through 0.45 mm membrane filter, diluted suitably and analyzed spectrophotometrically at 263 nm. All the experimental units were analyzed in triplicate (n=3).

Kinetic Modeling And Mechanism of Drug Release:[19]

To study the drug release kinetics[15] the obtained data fitted in zero order, first order, Higuchi and KorsmeyerePeppas models to determine the corresponding release rate and mechanism of drug release from the mucoadhesive microspheres.

RESULT AND DISCUSSION

To enhance the bioavailability, an attempt was made to prepare the gastro retentive mucoadhesive microsphere of cefpodoxime proxetil using various ratios of polymers such as sodium alginate, sodium CMC and carbopol-934P. Emulsification solvent evaporation method was used for preparation of mucoadhesive microsphere of cefpodoxime proxetil. Methanol was used as solvent for dissolving cefpodoxime proxetil. Liquid paraffin was used as liquid manufacturing vehicle which is nonsolvent for both drug and polymer. The compositions of various microsphere were given in Table 1.

Surface Morphology:

Surface morphology of the mucoadhesive microspheres was examined by scanning electron microscopy. The SEM photograph showed that the blend of sodium CMC and carbopol-934P produced spherical with smooth surface microspheres due to their high solubility in water.[20]

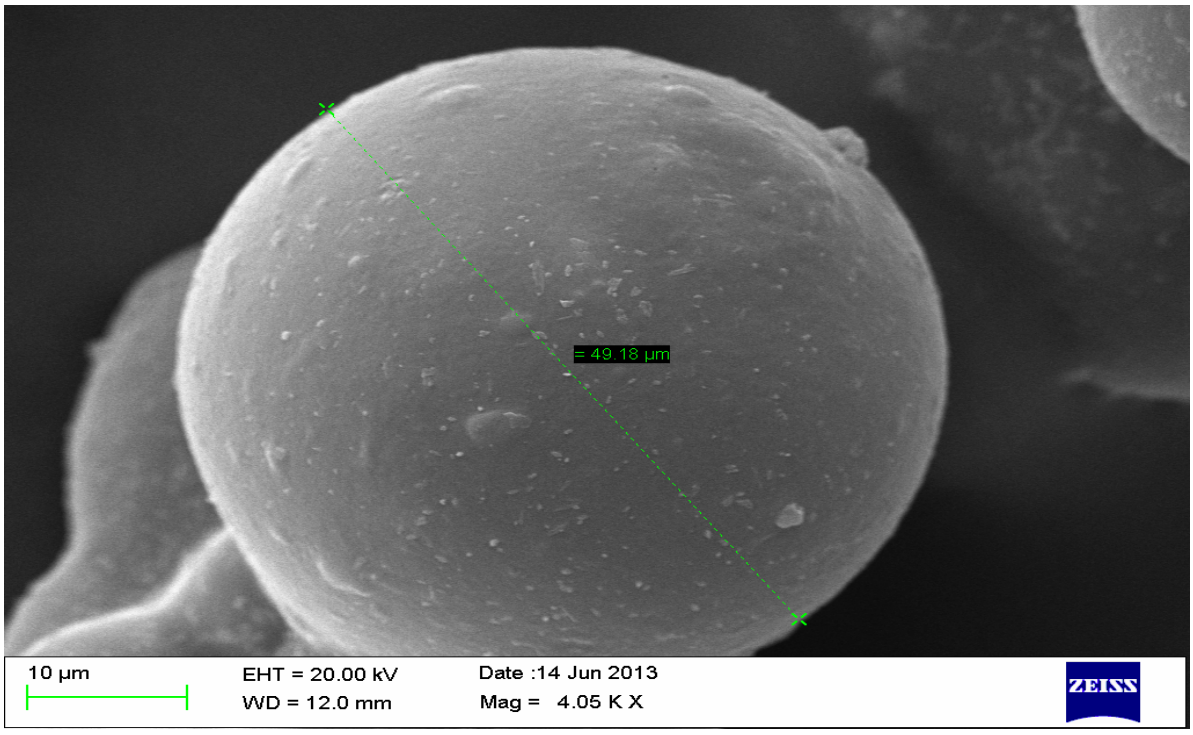

Figure 1: SEM photograph of formulation FC3.

Microspheres of sodium CMC alone produced smooth surface, spherical shape microspheres. While sodium alginate microspheres were of irregular shape with a rough morphology due to less water solubility and non uniform evaporation of water from the surface of microspheres. The SEM of microspheres of formulation FC3 is shown in figures 1.

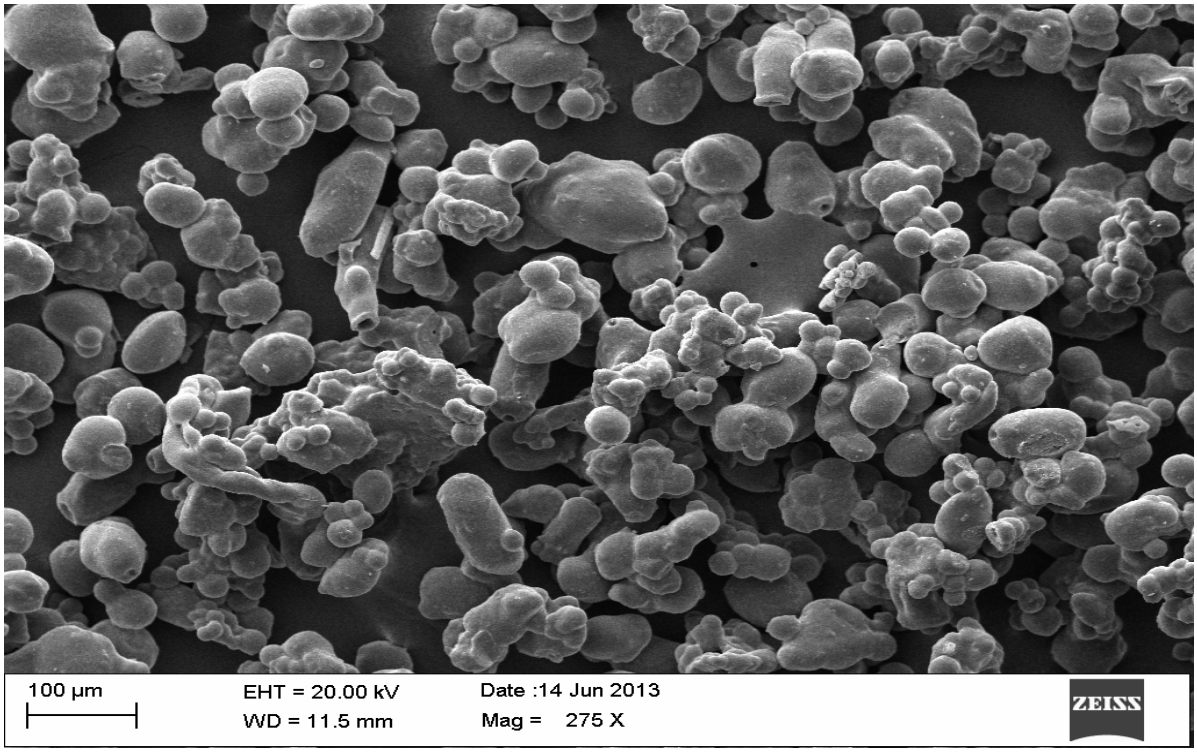

Figure 2: SEM photograph of formulation FC2 showing population of microspheres.

Particle Size Analysis:

Particle size analysis of different formulations was done by optical microscopy. The average particle size was found to be in the range of 33.30±1.93 to 41.56±3.32 µm. The mean particle size was significantly increases with increasing polymer concentration this may be due to high viscosity of polymer solution. Since high viscosity of polymer solution requires high shearing energy for breaking of droplets of the emulsion. Particle size decreased with increasing stirring speed due to the fact that increased in stirring speed, produce high energy, which leads to further decrease in droplets size.

Table 2: Comparative % yield, Particle size, % drug entrapment and % mucoadhesion of microspheres.

S.NO.	Formulation code	% Mucoadhesion after 1 hrs	% Drug entrapment	Particle size (µm)	% yield
1.	FC1	82.45±2.56	53±2.65	41.46±3.32	74.86±3.24
2.	FC2	88.68±2.45	68±3.44	33.30±1.93	70.76±2.43
3.	FC3	90.56±2.67	60±2.32	37.63±2.71	72.68±2.82
4.	FC4	74.88±2.44	55±3.45	36.57±3.28	73.36±2.48
5.	FC5	85.75±2.48	57±2.76	34.42±2.64	72.77±2.23
6.	FC6	71.66±1.86	62±2.68	38.66±2.38	70.58±2.64

Values are represented as mean ± standard deviation (n=3). All formulation were prepared at 2% polymer conc. and 1000 rpm stirring speed.

Swelling Index:

Formulation FC1 containing sodium alginate showed minimum swelling index about 0.66±0.09 where as formulation FC2 containing carbopol-934P showed maximum swellability about 1.62±0.08 as compared to other formulations. Rank order of swelling index of various formulations was found to be as follows:

FC2 > FC4 > FC6 > FC5 > FC3 > FC1

The high swelling property of formulation FC2 microspheres could be attributed to their ionized ability to uncoil the polymer into an extended structure. Higher swelling of carbopol microspheres than other formulation was likely due to its higher molecular weight.

The low swelling property of formulation FC1 containing sodium alginate is due to acid resistant property of sodium alginate.

Drug Entrapment Efficiency:

Drug content in different formulations was estimated by UV spectrophotometric method. Percent drug loading efficiency of microspheres was found in the range of 53.00 ± 2.65 to 68.00 ± 3.44% (Table 7.19). Formulation FC2 containing carbopol-934P showed maximum % drug loading about 68 % whereas formulation FC1 containing sodium alginate showed minimum % drug loading about 53% as compared to other formulations. Rank order of % drug loading of various formulations was found to be as follows.

FC2 > FC6 > FC3 > FC5 > FC4 > FC1

The high entrapment efficiency of carbopol could be attributed to high molecular weight and their ionized ability to uncoil polymer into an extended structure. Where as low entrapment efficiency of formulation FC1 containing sodium alginate is due to less solubility and irregular surface of microspheres.

In-vitro Mucoadhesion Test:

To assess the mucoadhesive property of microspheres, *In-vitro* wash-off test was performed for all the formulations. Adhesion of the polymer with the mucus membrane mediated by hydration in the case of hydrophilic polymers. Upon hydration, these polymers become sticky and adhere to mucus membrane. In the case of sodium CMC anionic nature of polymer responsible for mucoadhesion.

Sodium CMC and carbopol are characterized by the presence of carboxyl functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer. When mobile at the wet mucosal surface, they orientate these mucoadhesive sites towards mucosa and make interactions through formation of strong hydrogen bonding with mucin.[21]

At the end of 8 hrs % mucoadhesion was found to be 12.54±1.66, 15.68±1.39, 25.53±1.65, 14.63±1.38, 13.48±1.22, 08.88±1.56.

The rank order of % mucoadhesivity of all the formulations was found to be as follows (after 8 hrs):

FC3 > FC2 > FC4 > FC5> FC1 > FC6

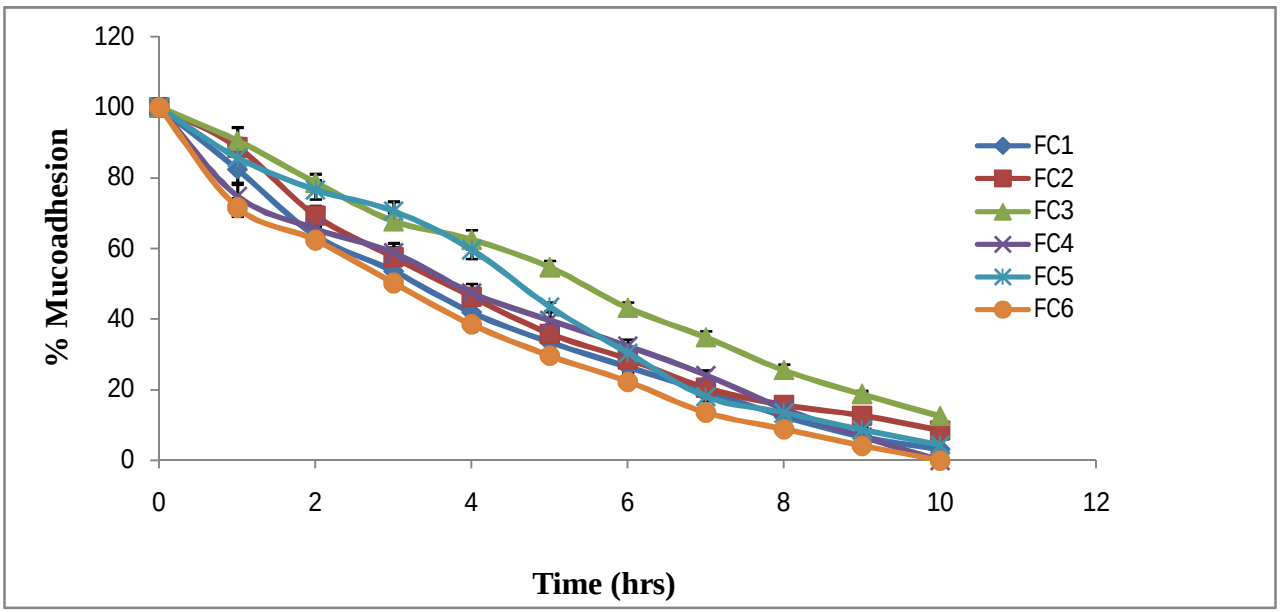

Figure 3: Comparative % mucoadhesion of microspheres.

In-vitro Drug Release Study:

% drug release from microspheres was optimized by preparing 6 formulations of microspheres using various ratios of polymers, for this *in-vitro* drug release study of all the formulations containing drug were performed in 0.1 N HCl (pH-1.2) at 37.0 ± 1^0C. It was found that the release profile of cefpodoxime proxetil were different for the different formulations. Cefpodoxime proxetil release form these microspheres was slow, extended and dependent on the type of polymer used.

Formulation FC3 containing sodium CMC showed the maximum release 91.89±2.45 % after 10 hrs, due to rapid swelling property and high dissolution of sodium CMC in dissolution environment (0.1 N HCl, pH-1.2).

Dissolution medium permeation in to the microspheres is facilated due to high swelling action of the sodium CMC which leads to more medium for the transport of the drug is available.

While sodium alginate microspheres (FC1) showed the least drug release 57.48±2.62 % after 10 hrs due to less swelling action and irregular surface of microspheres as compared to sodium CMC microspheres. The slowing of drug release from sodium alginate microspheres is probably due to the less swelling action of the polymer leads to reducing in access of the solvent to the microspheres

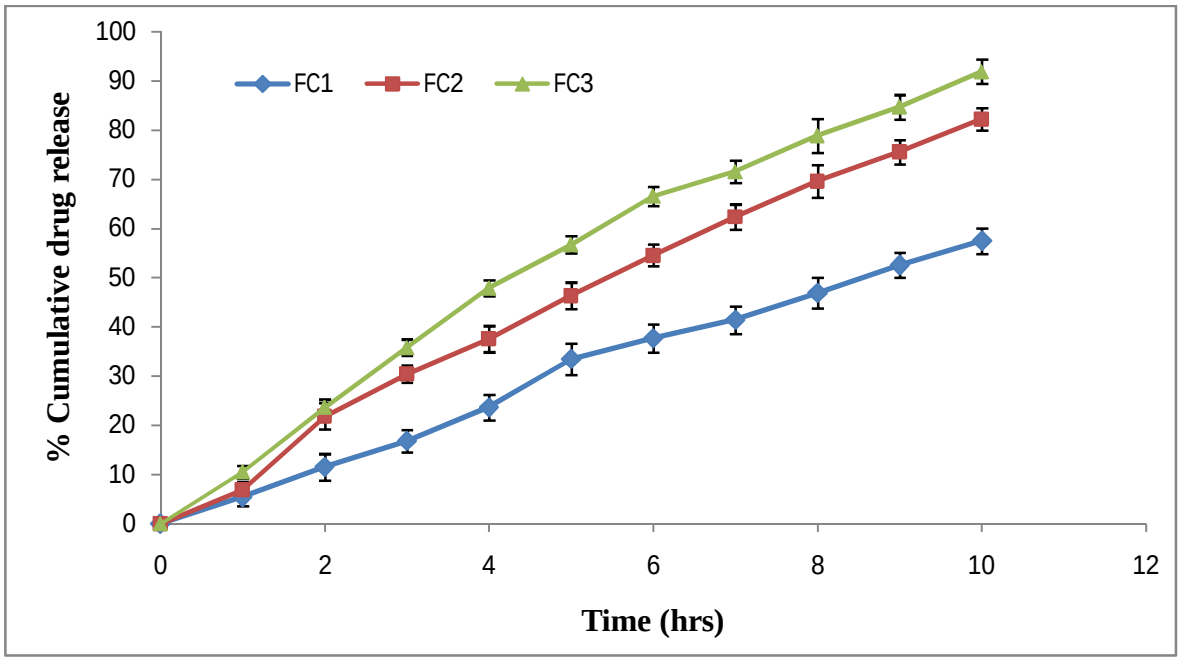

Figure 4: Comparative cumulative % drug releases from microsphere of formulation FC1, FC2 and FC3.

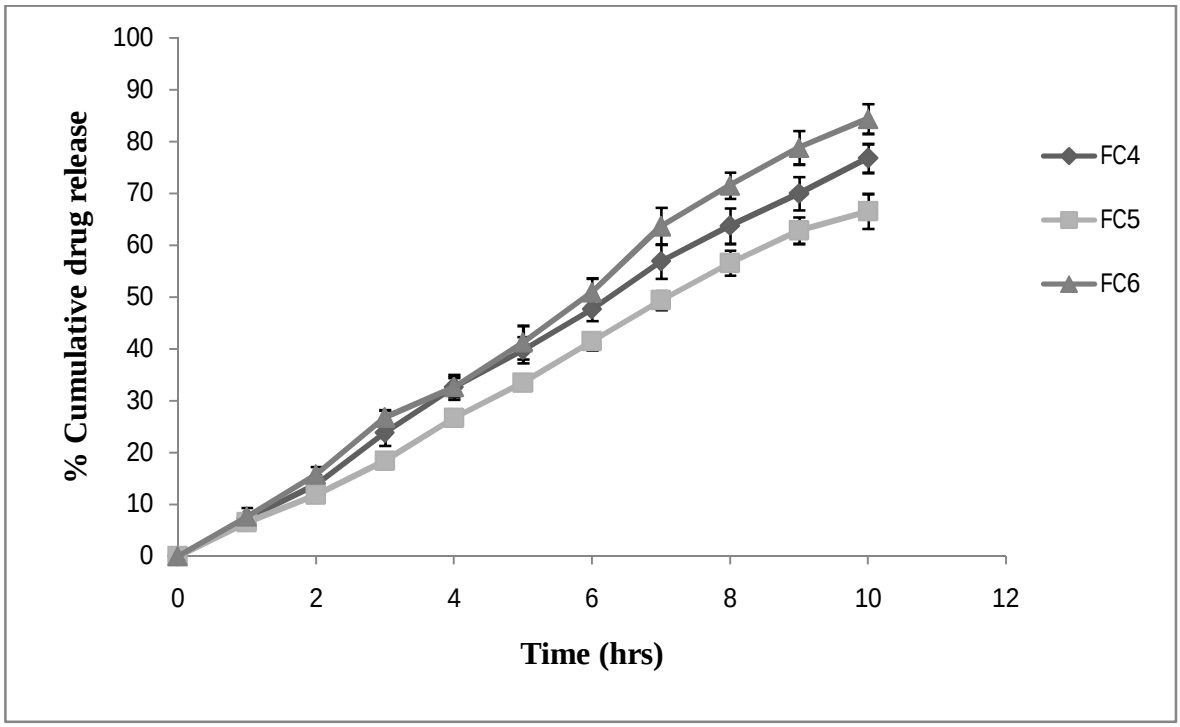

Figure 5: Comparative cumulative % drug releases from microsphere of formulation FC4, FC5, FC6.

Table 3 : Correlation coefficient (R^2) after fitting of dissolution data into various release kinetic models.

S. NO.	Formulation code	Zero order	First order	Higuchi	Korsmeyer Peppas
		R^2	R^2	R^2	R^2
1.	*FC1*	0.993	0.973	0.925	0.995
2.	*FC2*	0.991	0.978	0.947	0.972
3.	*FC3*	0.979	0.958	0.959	0.985
4.	*FC4*	0.998	0.978	0.959	0.940
5.	*FC5*	0.996	0.984	0.908	0.997
6.	*FC6*	0.995	0.955	0.910	0.996

CONCLUSION:

The concept of formulating mucoadhesive microspheres containing cefpodoxime proxetil offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, mucoadhesive microspheres of cefpodoxime proxetil were prepared successfully by w/o emulsification solvent evaporation method using various combination of polymers like sodium alginate, sodium CMC and carbopol-934P. The satisfactory results were obtained in all prepared formulations and based on the results FC6 was best one when compared to other formulations. Hence Cefpodoxime proxetil oral mucoadhesive microspheres could be promising one as they increase bioavailability, minimize the dosing frequency, reduces the side effects and improve patient compliance.

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