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FORMULATION DEVELOPMENT AND CHARECTERIZATION OF NOVEL PREDNISONE MUCOADHESIVE LIPOSOMAL FORMULATION

Parthiban S., Priyanka Raj G.* and Senthil Kumar G. P.

Dept. of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka-571422, India.

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***Corresponding Author**
Priyanka Raj G.
Dept. of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka-571422, India.

ABSTRACT

The aim of the present investigation was to design a mucoadhesive liposomes containing Prednisone. Liposomes were prepared by the thin film hydration method by using chloroform as a solvent. Mucoadhesive liposomes containing prednisone formulations were prepared by different concentration of lecithin and cholesterol by thin film hydration technique. These formulations were evaluated for entrapment efficiency, particle size, zeta potential, surface morphology and *in-vitro* drug release. Particle size and zeta potential of the F4 formulation was found to be 212 nm, -164.9 mV respectively. Coating of liposomes resulted increase in particle size and also increases the zeta potential. Highest entrapment efficiency was observed in F1 and F3 92% and 94%. The percent drug release from F1-F4and CF1 was observed as follows F1-88.57%, F2-73.31%, F3-76.29%, F4-90.97%, and F1 coated as a CF1-69.85%. Release kinetics follows the Higuchi plot and non-Fickian diffusion mechanism.

KEYWARDS: Predisone, mucoadhesive liposome, thin film hydration method, *in-vitro* release.

INTRODUCTION

Mucoadhesive Drug Delivery System

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended periods of time.[1] In case of bioadhesive drug delivery, the term bioadhesion is used to describe the adhesion between

polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bioadhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces.[2]

MATERIALS AND METHOD

Prednisone was gifted from micro labs LTD. Karnataka, Soya lecithin was purchased from Pharma Sonic Biochem Extractions Ltd. Indore, Cholesterol, and other solvent like Chloroform and Methanol purchased from S d fine chem Ltd. Mumbai. Phosphate buffer PH 6.8 were prepared as described in the indian pharmacopoeia (1996).

PREPARATION OF PREDNISONE LIPOSOME

A. Preparation of liposomes[3]

Cationic multilamellar liposomes can be prepared by hydration of lipid film. The lipid mixture is dissolved in a small amount of chloroform and placed in a rotary evaporator at 40°C until a thin film is obtained, and allowed to stand overnight in a vacuum chamber to ensure complete solvent removal. Phosphate buffer pH 6.8 is used to hydrate the thin film. The hydrated thin film is melted in water bath at 70°C for 1 min and blended to obtain multilamellar liposomes. Then prepared liposome will be sonicated to reduce particle size.

B. Coating of liposomes[4]

Chitosan was previously dissolved in glacial acetic acid overnight at room temperature. In order to coat the liposomes with chitosan, 1 mL of chitosan with a concentration of 1 mg/mL was added dropwise to the same amount liposome volume under continuous magnetic stirring for 1 h. Finally, the liposomes were sonicated for 30 min with an ultrasonic batho produce uniform chitosan-coated liposomes.

Table 1: Formulation design for the preparation uncoated liposomes containing prednisone.

Formulation code	Drug	Soya lecithin	Cholesterol
F1	100	200	100
F2	100	300	100
F3	100	400	100
F4	100	500	100

Table 2: Coating of liposome containing Prednisone.

Formulation code	Drug	Soya lecithin	cholesterol	Chitosan % w/v
CF1	100	400	100	0.2%

CHARACTERIZATION OF LIPOSOMES

Drug entrapment efficiency

The drug entrapment efficiency was calculated using the total drug content of liposome dispersion and unentrapped drug content of the dispersion. The total dug content of the dispersion is determined estimating total drug entrapped and unentrapped. 5 ml of liposome dispersion was taken in a volumetric flask. The dispersion was subjected to sonication in bath sonicator for 30 minutes. Then the mixture was filtered and estimated after suitable dilution at by using UV Visible Spectrophotometer (Shimadzu, UV1800). For the free unentrapped drug, 5 ml of the liposome dispersion subjected to centrifugation at 18000 rpm using Remi centrifuge for 40 min at 50° C. The supernatant clear solution was collected separately and the free drug present in the supernatant was estimated after suitable dilution at 243.60nm wavelength by using UV Visible Spectrophotometer.

In vitro diffusion studies

In vitro diffusion studies were carried by using cellophane membrane. The membrane was soaked overnight in phosphate buffer pH 6.8. 10 ml of prepared liposomal dispersion which contains 10 mg of drug was taken and placed in theone end of of the open tube. Dialysis tube was was placed in 500 ml beaker, containing 250 ml phosphate buffer pH 6.8. The temperature of the receptor phase was maintained at 37 ± 0.5° C and the it was stirred with magnetic stirrer to maintain homogeneous condition. The samples were withdrawn at different time intervals. Fresh medium was used to replace with equal volume of the sample withdrawn. The samples were analyzed at 243.60 nm in a UV-Visible spectrophotometer and amount of drug released at different time intervals was calculated.[5]

In vitro wash-off test for mucoadhesive testing

The mucoadhesive property of the polymer-coated liposomes was evaluated by an *in vitro* adhesion test. The method used was the modified *in-vitro* wash-off test. The mucoadhesion of the polymer-coated liposomes was compared with that of a non mucoadhesive material, uncoated liposomes containing Prednisone. Freshly excised pieces of sheep intestinal mucosa (2 × 2 cm) were tightened onto glass slides (3 × 1 inches) with thread. A volume of 0.5 ml of the liposomes, 0.2% and 0.4% (w /v) chitosan-coated liposomes, liposomes were spread onto

each wet-rinsed tissue specimen and immediately incubated at 37 ℃. The tissue specimens were taken out at 1 and 3 hrs. The samples were washed with 10.0 ml of PBS at each time interval.

Determination of mucoadhesive strength

From the 10.0 ml of the eluted buffer containing nonadhered drug, 500 µl aliquots were taken and liposomal lipids were dissolved by methanol. It was measured by a UV spectrophotometer. The concentration of prednisone eluted in the phosphate buffer pH 6.8 was measured and the remaining drug was assumed to be present in liposomes adhered to the intestinal mucosa. Hence, the percentage of mucoadhesive strength can be calculated by Eq.[6,7]

$$\text{Mucoadhesion \%} = \frac{\text{Amount of drug remaining in mucosa}}{\text{Amount of drug taken in test}} \times 100$$

RESULT AND DISCUSSION

FTIR spectra of pure Prednisone showed sharp characteristic peaks 1622, 1707.66, 1666.2 and 3289 Physical mixture showed all the characteristic peaks of pure drug, confirmed no interaction between the drug and excipients. Comparative studies of FTIR graphs are showed in Figure.1-2. The surface morphology was studied by Scanning electron microscopy (SEM). The SEM photographs of liposomes formulation F4 as shown in Figure. 3. Vesicle size distribution of F1-F4-CF1 graphs are showed in Fig.4. The % entrapment efficiency was found to decrease with increasing the cholesterol concentration. It is shown in Figure.5. Zeta potential of formulation F4 shown in figure.6. And it was found to -164.9 mV, respectively which indicate that they are sufficient to be stable. *In vitro* drug release of liposomes in phosphate buffer pH 6.8 was performed using dialysis tube diffusion technique. The *in vitro* drug release profile of liposomes formulations obtained from dialysis experiment was shown in Figure.7. The release of liposome Chitosan containing coated liposomes was varied according to concentration of soya lecithin and cholesterol. The progressive decrease in the amount of drug diffused through cellophane membrane from formulations F1 – F4 and CF1 attributed to gradual increase in soya lecithin and cholesterol content. It has been concluded that, if we increase the concentration of soya lecithin and cholesterol, the diffusion of drug also decreases. The amount of drug diffused from formulation CF1 was showed 69.85 %, was lower among the formulations F1 to F4 and CF1. Release kinetics follows the Higuchi plot and non-Fickian diffusion mechanism. It is showed in Table.3 and Figure.8. The

Mucoadhesive strength was measured by a UV spectrophotometer. The Mucoadhesive strength was measured by a UV spectrophotometer. Mucoadhesive strength formulation CF1. The amount of drug released in the formulation CF1 63% which showed sufficient mucoadhesive property.

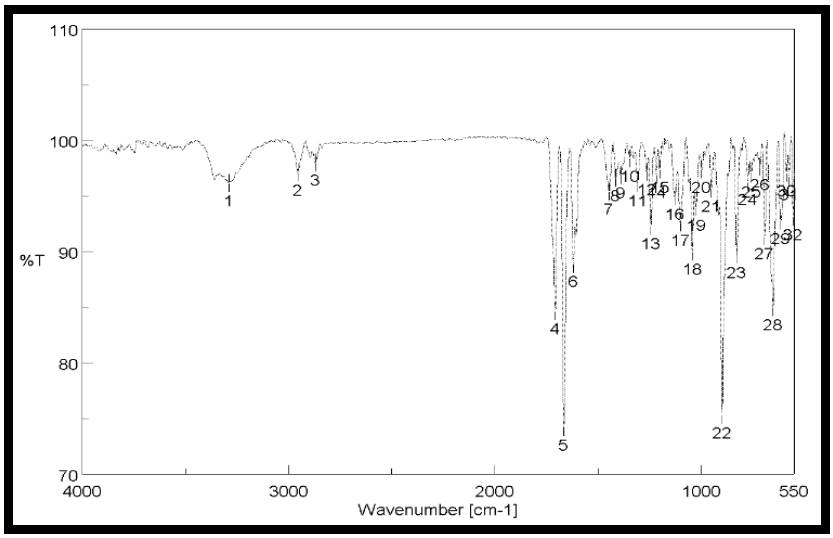

Figure.1: FT-IR Spectroscopy of Prednisone.

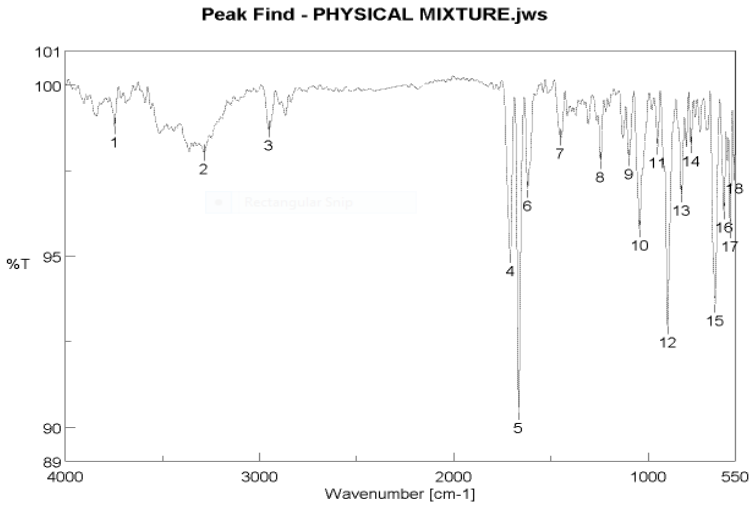

Figure.2: FT-IR Spectroscopy of physical mixture.

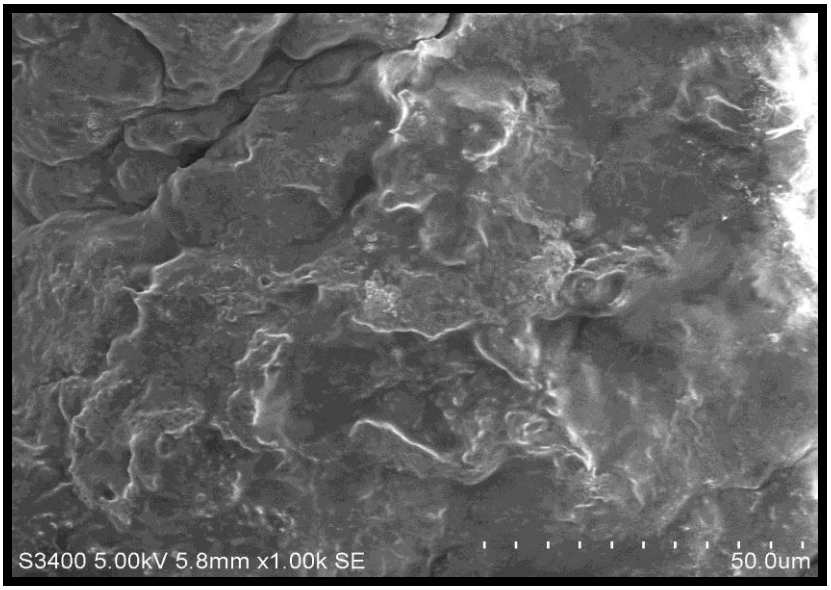

Figure.3: SEM of liposomes formulation F4.

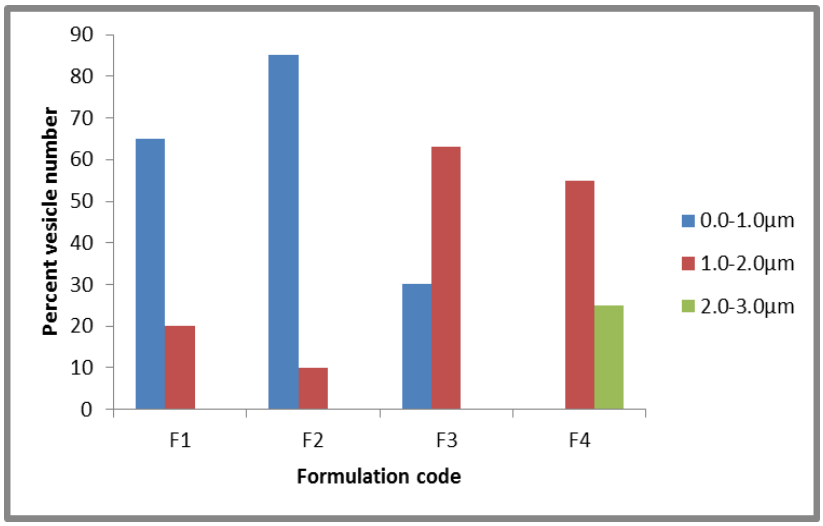

Figure. 4: vesicle size analysis of liposomal formulation.

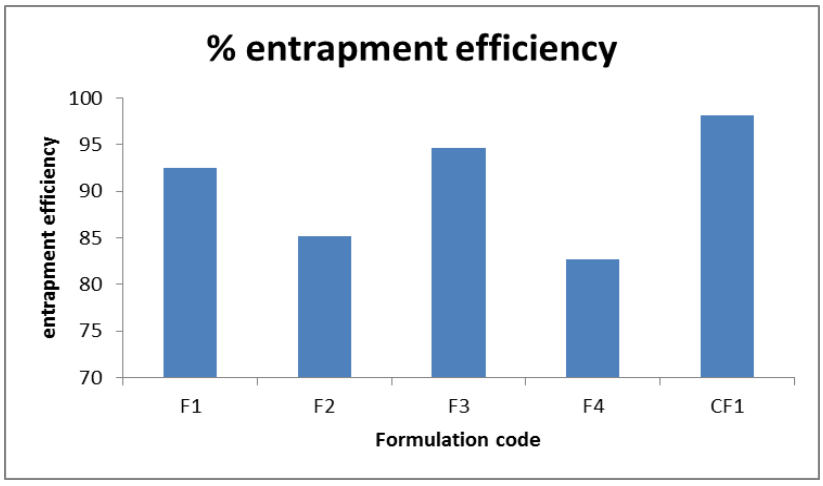

Figure 5: % entrapment efficiency of formulation F1- F4- CF1.

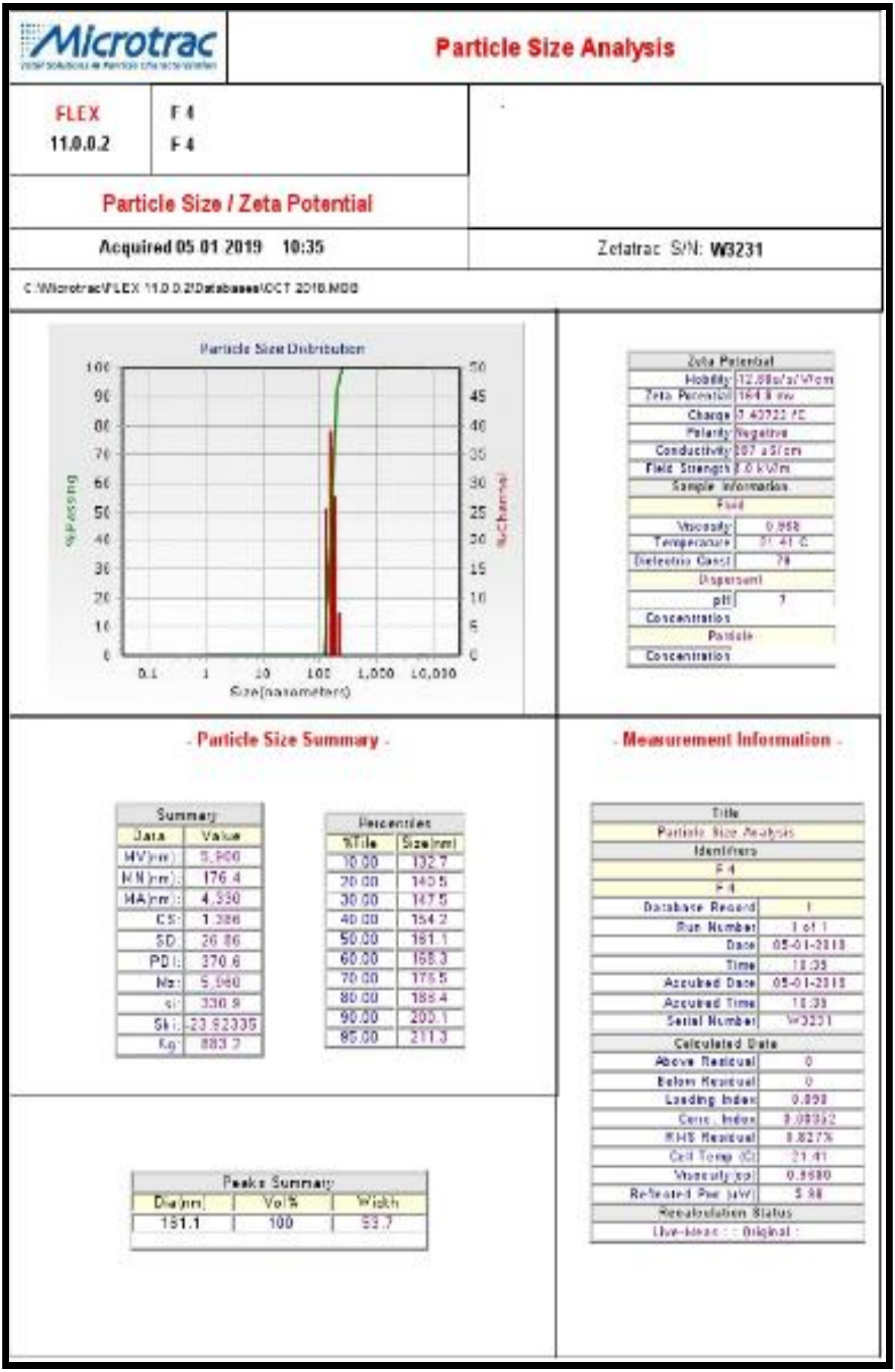

Figure.6: Particle size analysis of formulation F4.

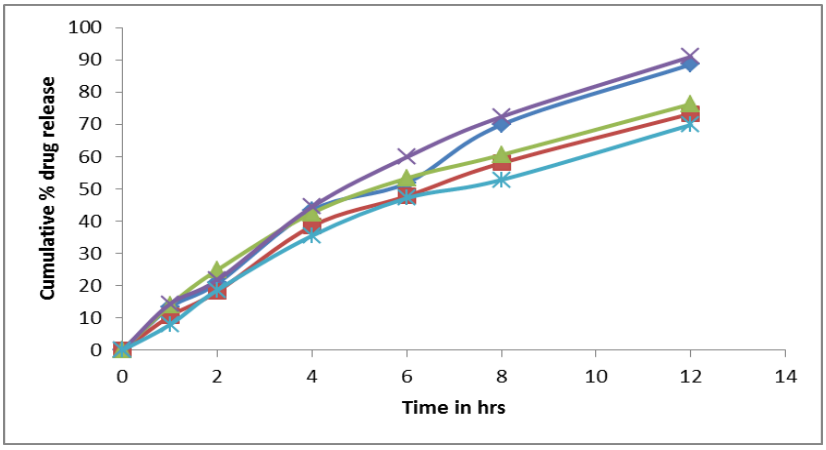

Figure.7: % *in-vitro* drug release of formulation F1- F4-CF1.

RESULT OF MODELLING FITTING

Table 3: Data for different kinetic model.

Formulation code	Zero order	First order	Higuchi plot	Peppas plot	
				r^2	'n'
F1	0.963	0.622	0.973	0.714	1.306
F2	0.959	0.478	0.970	0.578	1.166
F3	0.938	0.567	0.987	0.668	1.234
F4	0.966	0.611	0.969	0.705	1.315
CF1	0.920	0.558	0.975	0.659	1.225

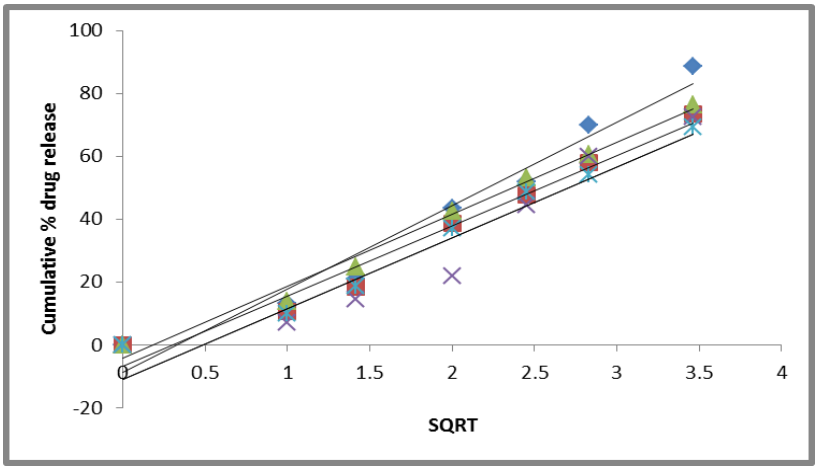

Figure 8: Higuchi drug release kinetics for F1-F4-CF1.

CONCLUSION

In this study, a mucoadhesive liposomal formulation of Prednisone was developed with desirable drug delivery properties. The chitosan-coated liposomes had good *in vitro* stability, strong mucoadhesiveness, and enhanced cellular uptake. Therefore, the chitosan-coated carbopol gel formulation appears to have the potential to improve the bioavailability of Prednisone.

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