Original Article

Formulation Design and *In vitro-In vivo* Evaluation of Moxifloxacin Ophthalmic Insert

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ABSTRACT

Background: Moxifloxacin is a fluoroquinolone derivative extensively used for ocular infection.
Objective: The main objective of study is to design and evaluate ophthalmic insert of moxifloxacin that could be use for sustained delivery of drug in to eye.
Method: The moxifloxacin ophthalmic insert was prepared by solvent casting method. The chitosan, methyl cellulose and hydroxyl propyl methyl cellulose K4M were used as release rate controlling biodegradable polymers. The drug excipients compatibility study was carried out by Fourier Transform Infrared Spectroscopy (FTIR) and study suggesting no interaction between drug and polymers. The ocuserts were characterized for weight variation, thickness, surface pH, folding endurance, moisture absorption, moisture loss, drug content uniformity, *in vitro* drug release, drug release kinetic, stability, sterility testing and ocular toxicity study. The ophthalmic inserts were evaluated for *in vivo* drug release studies.
Results: The uniformity of the weights of the films suggested uniform distribution of the drug and polymer in all formulations. Use of higher concentration plasticizer was observed to cause brittleness in the medicated discs, but use of greater amount of plasticizer displayed little opaqueness and good folding endurance. The ocular irritation test did not show any signs of irritation, inflammation and abnormal discharge.
Conclusion: The result indicated that the ophthalmic insert, F3 containing methyl cellulose (400 mg) released 71.5 % of drug, in a constant manner following zero order kinetics with adequate stability and non-toxic to eye, suggesting Moxifloxacin eye ocusert would be used for safe management of ocular disease with lesser frequency of administration.

Keywords: Moxifloxacin, *In vivo* study, Sustained release, Ophthalmic insert, Ocular toxicity, Solvent casting.

INTRODUCTION

The development current efficient diagnostic techniques and therapeutic chemical entities renders urgency to the development of greater successful and advanced ocular drug delivery systems. The objective of pharmacotherapeutics is the achievement of a minimum effective drug concentration at the targeted site of action for an estimated period of time. Eye, as a extensive tool for drug delivery, mostly intended for the local therapy as against systemic therapy in order to overcome the risk of eye damage from high blood concentrations of drug. The literature survey revels that the intraocular bioavailability of topically applied drugs is ranging from 5-10% of total administered, which is extremely poor.[1,2]

Eye preparations like drops and ointments are traditional ocular dosage forms, have disadvantages like frequent administration, poor availability, unpredictable doses and nasolacrimal fluid.[3-5] Various advanced ophthalmic drug delivery systems were developed to achieve a higher bioavailability of drugs like microspheres, nanoparticles, liposomes and ocular inserts along with other advantages like increased ocular residence, slow drug release and increased shelf life.[6-12]

Moxifloxacin is a novel broad spectrum antibiotic with half life of 12 to 16 h, which acts by inhibiting DNA topoisomerases and DNA gyrase. It is soluble in ethanol, methanol, glacial acetic acid, water and glycerol.[13]

The literature survey reveled that no such systematic scientific work has been done on moxifloxacin eye insert. Thus objective of this study to design and formulate moxifloxacin eye insert.

MATERIALS AND METHODS

Moxifloxacin was procured from Micro Lab. Pvt. Ltd., Bangalore, India. Methyl cellulose and Hydroxy Propyl Methylcellulose (HPMC K4M) and chitosan were procured from Loba Chemie Pvt. Ltd., Mumbai., India.

Preparation of moxifloxacin ophthalmic ocusert

Moxifloxacin ocuserts were prepared by solvent casting technique using chitosan, methyl cellulose and HPMC K4M as biodegradable polymer.[14] All polymers were dissolved completely in glacial acetic acid (1% v/v in water) followed by addition of dibutyl phthalate as plasticizer (30% w/w of polymer). Moxifloxacin was added in to the polymeric solution and mixed homogenously using bath sonicator until air bubble completely removed. After complete mixing of drug and polymer, 10 ml of the clear solution was poured into the clean Teflon coated petridish (Anumbra® of area 60 square cm) placed in plane surfaces. The glass funnel was placed in inverted manner with a cotton plug closed into the stem of the funnel on petridish at room temperature for 24 h, which facilitate evaporation of solvent slowly. After complete evaporation of solvent, cast films were obtained, cut into pieces by cork borer into circular pieces of definite size, wrapped in an aluminum foil and stored in a $CaCl_2$ desiccator at room temperature in a dark place for further evaluation studies. The chitosan films were cross linked by exposure to glutaraldehyde vapor in a chromatography chamber. The chamber was previously saturated with the vapour of 2% v/v glutaraldehyde for 24 h.

The films were exposed to the vapour for 2 and 4 h respectively, and then dried.[15,16] The dried films were stored in a desiccator for further study.

Drug polymer interaction study by FTIR

The FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) technique was used for infrared peak analyses in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.[17] The samples of pure drug moxifloxacin, polymers and drug polymer formulations were prepared separately by palletization technique in KBr using IR press. The infrared peaks of pure pioglitazone were analyzed and it was compared with the peaks (Spectra) obtained from FTIR spectra of drug polymer complexes (insert formulation) to identify deletion or additional formation of peaks.

Evaluation of moxifloxacin ophthalmic insert

Uniformity of weight of the films

Twenty films of same size were weighed on an electronic digital balance (Sartorius Electronic balance, BT-2245, Calcutta, West Bangle and India). Average weight and weight variation were calculated.[18,19]

Thickness uniformity of the films

Thickness of the ophthalmic insert was measured by using a film thickness tester (Model Mitutoyo 4026F, Tokyo, Japan) at various regions of the film (n = 3) was determined.[18,19]

Film surface pH

Ophthalmic insert were placed over agar plate for 1 h which facilitate swelling. The surface pH was determined using pH paper, which was placed on the surface of the swollen film.[20,21]

Folding endurance

This parameter was determined in triplicate by repeatedly folding a small strip of film at same place till ophthalmic insert broke and standard deviation was calculated.[20,21]

Moisture loss study

The ophthalmic insert of known weight and of predetermined size was placed in desiccator containing anhydrous Calcium chloride chloride, after three days film was reweighed and moisture loss was calculated by using following equation,[21,22]

$$\text{Moisture loss (\%)} = (W_i - W_f/W_i)\times 100 \quad \ldots(1)$$

Where, W_i is initial and W_f is final weight of film. Study is done in triplicate for each film formulation.

Moisture absorption study

The ophthalmic insert of known weight and of predetermined size was placed in desiccator containing 100 ml of saturated solution of aluminium chloride and 80% humidity was maintained, after three days film was reweighed and moisture gain was calculated by using following equation,[21,22]

$$\text{Moisture gain (\%)} = (W_f - W_i/W_i)\times 100 \quad \ldots.(2)$$

Where, W_i is initial and W_f is final weight of film. Study is done in triplicate for each film formulation.

Drug content uniformity study

Drug content was analyzed by dispersing ophthalmic insert in 20 ml of phosphate buffer pH. 7.4. The solution was stirred and filtered through Whatman filter paper no 1. About 1 ml solution was withdrawn, suitably diluted with fresh solution and content of drug in solution was measured by UV-Visible spectrophotometer (Shimadzu UV spectrophotometer, model 1700, Japan) at λ_{max} 288 nm.[21,22]

In vitro drug release study

The *in vitro* drug diffusion from the various ophthalmic inserts was studied using the glass cylindrical tube (Internal diameter 15 mm and length 100 mm). The diffusion cell membrane (Prehydrated cellophane membrane simulating with *in vivo* condition of corneal epithelium) was tied to one end of open cylinder, which acted as a donor compartment. An ophthalmic insert was placed inside this compartment. The entire surface of the membrane was in contact with the receptor compartment comprising of 25 ml of isotonic phosphate buffer (pH 7.4) in a 100 ml beaker. The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 37±0.5°C. At specific intervals of time (1 h), 1 ml aliquot of solution was withdrawn from the receptor compartment and replaced with fresh buffer solution. The aliquot solution was analyzed for the drug content by using UV-Visible spectrophotometer (Shimadzu UV spectrophotometer, model 1700, Japan) at λ_{max} 288 nm.[21,22]

Drug release kinetic study

To determine the exact mechanism of drug release from the ophthalmic inserts, the in vitro drug release data of various ophthalmic insert formulation was analyzed using zero order, First order and Higuchi square root equation.[23,24]

Accelerated stability study

The stability study of the optimized ophthalmic insert (Formulation F3) was carried out by subjecting inserts in to three storage conditions such as at temperature (25±2), (37±2) and (45±2) °C for a period of 3 months. All the polymeric inserts were observed for any physical changes such as colour, appearance, flexibility or texture, pH and the drug content (Spectrophotometrically) was estimated at interval of 1 week.[25]

Statistical analysis

Statistical data analyses were performed using the mean, standard deviation, standard error of mean and one way ANOVA at 5 % level of significance $p < 0.05$.[26,27]

Sterility testing

The sterility test of optimized ophthalmic insert formulation F3 was carried out according to the method prescribed in Indian Pharmacopoeia for identifying the presence of viable forms of Bacteria, fungi and yeast using fluid thioglycollate media and chopped meat medium having positive and negative control.[28]

Ocular toxicity study

The method was performed according to the OECD test guide line for testing of chemical TG423.[29] The study protocol was approved by the Institutional Animal Ethics Committee (Regd. No. 1339/ac/10/CPCSEA). The potential ocular irritation of the ocusert under Draize Irritancy Test were evaluated in 6 male healthy rabbits weighing about 1.5 Kg. The rabbits were observed for any redness, inflammation (or) increased tear production.[30,31]

In vivo studies

Among three formulations, formulation F3 (matrix containing 4 % SCMC and 1 % MC in combination) was chosen for the animal studies. Eight male healthy rabbits weighing 1 to 2 kg each were divided into 2 equal groups. They were kept in 2 cages with husk bedding and were fed with rodent pellet diet and water as much as required. A dark and light cycle of twelve hours was maintained. To the first group

plain discs (without drug) were placed in the cul-de-sac of the left eye. To the second group medicated discs were placed in the cul-de-sac of the left eye. Before inserting the discs into the eye the sides of the plain discs and medicated discs were sterilized under UV light for 15 min at a 0.305 m height from a fixed UV lamp. The eyelids were closed by using cotton and non irritant adhesive tape until sampling. After 8 h, the plain discs and medicated discs were taken out, dried at room temperature and estimated for remaining amount of drug spectrophotometrically by using plain discs as control. All experimental protocols involving laboratory animals were approved by Institutional Animal Ethics Committee (Regd. No. 1339/ac/10/CPCSEA).[32,33]

RESULTS AND DISCUSSION

In the present study, efforts were exerted to prepare ophthalmic inserts of Moxifloxacin using polymers like Methyl Cellulose, hydroxyl propyl methyl cellulose. The FTIR study reveals (Fig 1), no such occurrence of additional peaks or deletion of peaks for major functional groups was observed by correlating with FTIR data of pure drug.[34,35] Thus there were no such physical interactions occurred between physical mixtures of drug and polymers. The weight of the ophthalmic inserts varied between 2.1±0.003 to 3.5±0.005 mg (Table 2). The identical weights of the films reveled the better distribution of the drug and polymer.[14] The thickness of the ocusert was found to be in the ranges of 0.18±0.04 to 0.55±0.04 mm (Table 2). The formulations were not very thick and hence did not cause irritation. In the medicated moxifloxacin ophthalmic insert, use of less amount of plasticizer caused the insert brittleness, but use of greater amount of plasticizer caused lesser opaqueness and better folding endurance. Folding endurance (Table 2) was found to be highest for F2 (358.33±1.9) and lowest for F5 (263.13±1.7). The formulation F1 has shown the minimum percentage moisture absorption, 5.48±0.1 %, as it contains polymer of less hydrophilic nature, as evident from Table 2. It can be concluded that the HPMC and MC have more tendency to absorb moisture as compared to Chitosan.[12] The formulation F2 showed maximum moisture loss of 12.1±0.9 % and formulation F4 showed minimum moisture loss of 8.45±0.8 %. The ophthalmic insert formulations containing Chitosan showed greater tendencies to lose moisture in comparison to insert containing HPMC and MC.[14] The surface pH of prepared inserts was found be in range of 6.5 to 7.1 (Table 2). This reveled that the formulated inserts will not affect on the pH of the tear fluid in the eye.[14] The sterility test of insert formulation F3 was carried out using Indian Pharmacopoeia method as standard, for detecting the presence of bacteria, fungi and yeast.[22] The study revealed that the formulations were found to be sterile. The rabbits subjected to ocular irritation tests, did not show any signs of irritation, inflammation and abnormal discharge. The drug content study of all ophthalmic formulations found to be in the ranges of 95.5±0.7 to 98.6±0.6 %. The drug content study of all ophthalmic formulations revealed that almost all insert possess good drug content. Out of 6 ophthalmic formulations (F1 to F6) tried, the formulation F3 containing methyl cellulose (400 mg) was found to be promising, since it showed prolonged release with 71.5 % at end of 10 h. The prolonged release has helped in rate control release of drug.[12] The release constants were calculated from the slope of the respective plots. It indicates that the release of drug from the films might have followed zero order kinetics (Table 3). The stability study on optimized ophthalmic formulations showed that the optimized

formulation (F3) was found to be stable as evident from data given in Table 4.

CONCLUSION

The study revealed that the ophthalmic insert formulation F3 containing methyl cellulose would be optimized formulation for successfully delivery of Moxifloxacin with zero order release manner for extended period of time. Hence Moxifloxacin eye ocusert would be used for successful management of ocular disease.

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Table 1. Formulation design of moxifloxacin ophthalmic insert containing biodegradable polymers

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Chitosan	400	500	-	-	-	-
Methyl Cellulose	-	-	400	500	-	-
HPMC K4M	-	-	-	-	400	500
Dibutyl phthalate	120	150	120	150	120	150
Moxifloxacin	300	300	300	300	300	300
Glacial acetic acid (ml)	10	10	10	10	10	10

Table 2. Evaluation of various moxifloxacin ophthalmic inserts formulations

Evaluation parameters	Formulation code					
	F1	F2	F3	F4	F5	F6
Weight (mg) (X±SD)	2.5±0.04	3.5±0.02	2.3±0.09	3.0±0.06	2.1±0.03	3.1±0.05
Thickness (mm) (X±SD)	0.27±0.6	0.18±0.4	0.45±0.2	0.32±0.8	0.55±0.4	0.34±0.7
pH (X±SD)	7.4±0.12	7.3±0.15	7.1±0.12	7.0±0.13	7.2±0.10	7.5±0.13
Folding endurance (X±SD)	339±1.6	358± 1.9	315±1.4	332± 1.4	263± 1.7	265± 1.3
Moisture loss (%) (X±SD)	11.5±1.1	12.1±0.9	9.3±0.71	8.45±0.8	9.6±0.5	9.9±0.8
Moisture absorption (%) (X±SD)	5.48±0.1	7.13±0.4	8.2±0.2	9.4±0.7	7.4±0.5	9.8±0.7
Drug content (%) (X±SD)	95.5±0.7	98.5±1.0	96.2±0.7	97.9±0.9	97.8±1.1	98.6±0.6
% Cumulative drug release, 10 h study (X±SD)	92.5±1.5	90.6±1.3	71.5±1.6	95.2±1.4	97.1±1.2	96.0±1.7
ANOVA						
Source of Variation	*SS*	*Df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	874.054	5	174.8109	0.01498	0.999914	2.437693
Within Groups	490111	42	11669.3			
Total	490985	47				

Each value is expressed as mean ± standard deviation (n = 3). Standard error of mean is less than 0.981. Data are found to be significant (*F value* < *F crit*) by testing through one way ANOVA at 5 % level of significance.

Table 3. The drug release kinetic data of various moxifloxacin ophthalmic insert formulations

Formulations	Zero order kinetics	First order kinetics	Higuchi kinetics
	Regression coefficient (R^2)		
F1	0.9547	0.9294	0.9902
F2	0.9321	0.9462	0.9923
F3	0.9715	0.8143	0.9818
F4	0.9103	0.8635	0.9824
F5	0.9171	0.8632	0.9859
F6	0.9595	0.8840	0.9835

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Table 4. Accelerated stability study of optimized moxifloxacin ophthalmic insert formulation (F3) in different storage conditions as per ICH guidelines

Temp. (°C)	Parameters	Period of studies in week						
		1st day	2nd	4th	6th	8th	10th	12th
25±2	Drug content (%)	96.2	96.1	95.9	95.6	95.4	95.4	95.1
	pH	7.1	7.1	7.1	7.0	7.0	6.9	6.9
37±2	Drug content (%)	96.2	95.9	95.4	95.3	95.3	95.1	94.8
	pH	7.1	7.0	7.0	7.0	6.9	6.9	6.7
45±2	Drug content (%)	96.2	95.6	95.2	95.0	94.9	94.7	94.7
	pH	7.1	7.1	7.0	6.8	6.8	6.7	6.5

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3.25	6	0.541667	0.0023	0.01	2.3718
Within Groups	82223.12	35	2349.233			
Total	82226.412	41				

Data are found to be significant (*F value* < *F crit*) by testing through one way ANOVA at 1 % level of significance.

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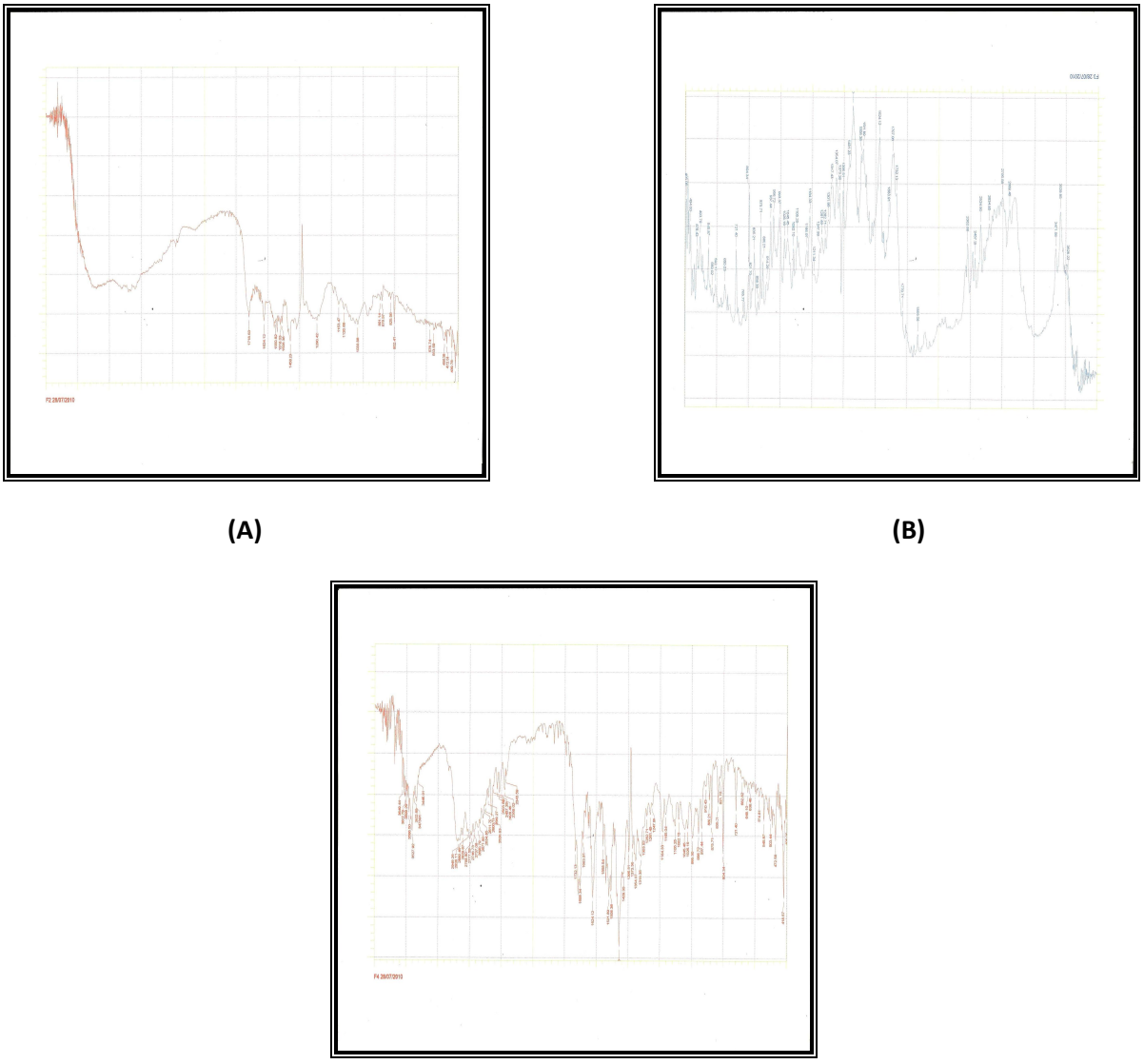

(A) **(B)**

(C)

Figure 1. FTIR spectra of pure drug + chitosan (A), pure drug + methyl cellulose (B) and pure drug + HPMC (C) insert formulations at resolution of 1 cm^{-1}

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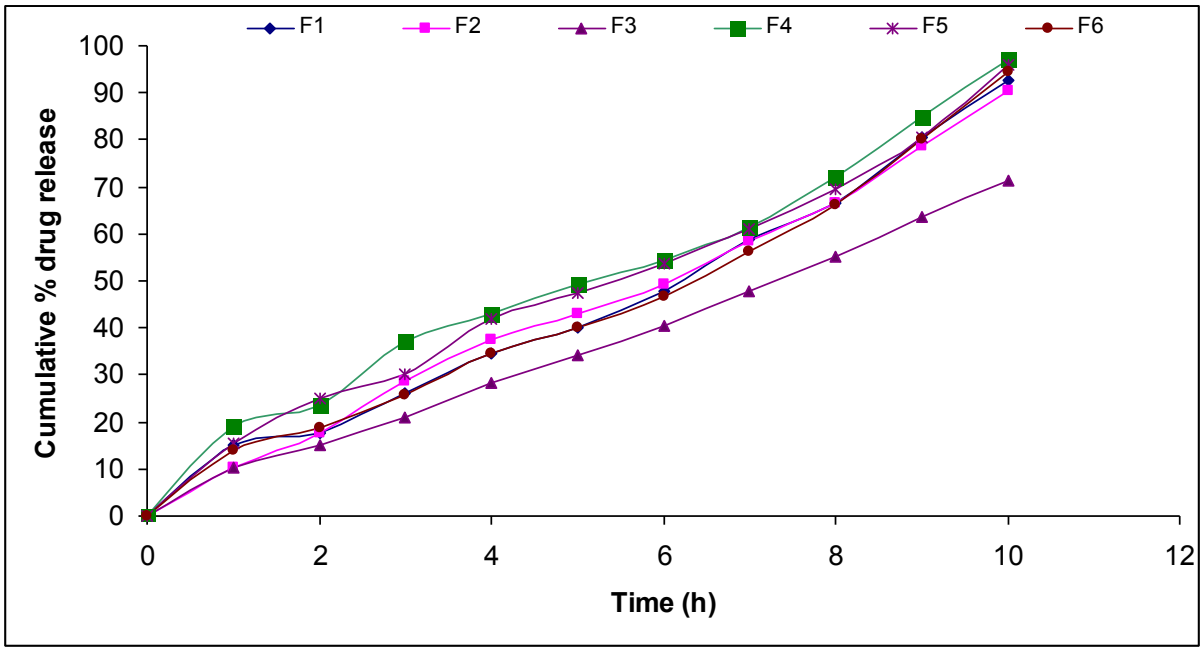

Figure 2. The drug release data of moxifloxacin ophthalmic insert formulations in phosphate buffer pH 7.4