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Carbopol - Polycarbophil Based *in situ* pH Sensitive Ophthalmic Gel of Fluconazole

Sharma Hemant K.*, Gupta Mukesh and Gupta Rakesh

Department of Pharmaceutics, Alwar Pharmacy College, M.I.A. Alwar-301030 (Rajasthan)

ABSTRACT

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists, the major problem encountered to pharmaceutical scientist is rapid pre-corneal elimination of the drug, resulting in poor bioavailability and therapeutic response, because of high tear fluid turnover and dynamics. *In situ*-forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this gel provides a response to environmental changes. *In-situ* gelling systems are viscous polymer based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physico-chemical parameter like temperature, ionic strength, or pH. A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action, which is compromised mainly due to pre corneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered can be altered by increasing the retention time of medication into the eye by using *in situ* gel forming systems, thereby preventing the tear drainage.

KEYWORDS: *In-situ* gel, Pre-corneal residence, Ocular bioavailability, pH triggered systems and their method of preparation, modified dissolution test apparatus, simulated tear fluid.

***Corresponding Author:**

Hemant Kumar Sharma

Department of Pharmaceutics, Alwar Pharmacy College,

North extension, M.I.A. Alwar-301030 (Rajasthan)

E Mail - hemantkumarsharma.alwar@gmail.com,

Mob. No.- +91-9785634242

INTRODUCTION

General Fungal Infections of Eye and its Medications

Fungal infections of the eye are important amongst the clinical conditions responsible for ocular morbidity and blindness. In tropical countries, including India, keratitis is the most frequently encountered fungal infection, although the orbit, lids, lachrymal apparatus, sclera, conjunctiva and intra-ocular structures may also be involved.

- ***Keratomycosis***

Mycotic keratitis in the tropical and subtropical zones is largely due to filamentous fungi, although yeasts, particularly *Candida* may also be responsible in a small percentage of cases. The most common predisposing factor is trauma to the eye with vegetative matter.

- ***Orbital Cellulitis***

Orbital cellulitis is an infection of the soft tissue surrounding the orbit. Orbital cellulitis of fungal origins the most serious ocular infection with significant potential morbidity, including loss of vision, cavernous sinus thrombosis, intracranial spread of infection and occasionally death.

- ***Endophthalmitis***

Endophthalmitis is an inflammatory reaction of intraocular fluid or tissues. It can be both infectious and noninfectious. Infectious (post-operative, post-traumatic or endogenous) endophthalmitis is one of the most serious and vision threatening complications of ophthalmic surgery. [1]

*In situ gelling systems*I

In situ forming gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers which show sol-gel phase transition and thus trigger drug release in response to external stimuli are the most investigated. *In situ* hydrogels are providing such “sensor” properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition. These “intelligent” or “smart” polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released. [2]

A polymer used to prepare *in situ* gels should have following charteristics:-

1. It should be biocompatible.
2. It should be capable of adherence to mucus.
3. It should have pseudo plastic behavior.

4. It should have good tolerance and optical clarity.
5. It should influence the tear behavior.

The polymer should be capable of decreasing the viscosity with increasing shear rate there by offering lowered viscosity during blinking and stability of the tear film during fixation. [3]

pH induced in situ gel systems:

Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymer. Gelling of the solution is triggered by a change in pH. At pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. The polymers with a large number of ionisable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The polymers which show pH induced gelation are cellulose acetate phthalate (CAP) latex, carbomer and polymethacrilic acid (PMMA), polyethylene glycol (PEG). [4]

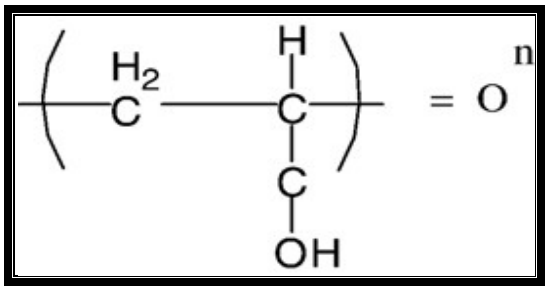

Figure 1 Structure of Carbomer.

Carbomer

Cross-linked poly (acrylic acid) of high molecular weight, commercially available as Carbopol R, is widely used in ophthalmology to enhance precorneal retention to the eye. Carbopol R934 is a synthetic polymer composed of 62% of carboxyl groups with a high molecular weight formed by repeating units of acrylic acid, cross-linkedwith either allyl sucrose or allylethers of pentaerythritol. Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers (e.g. cellulose derivatives, and polyvinyl alcohol). Concentration of Carbopol increases in the vehicle, its acidic nature may cause stimulation to the eye tissues. In order to reduce the total polymer content and improve the gelling properties, an ocular drug delivery system based on a combination of Carbopol and methylcellulose has been developed. Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. Carbopol are in compatible with

cationic polymers, strong acids, high level of electrolytes and they swell in water 1000 times when exposed to water to form gelation pH of 4-6 do not dissolve in water. [3, 5]

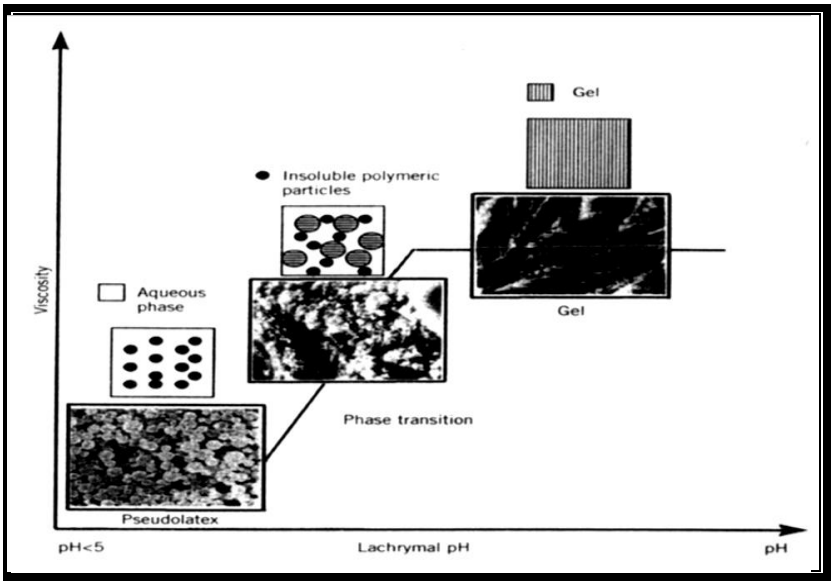

Figure 2 Schematic representation of pH dependent *in situ* gel.

❖ *Advantages of in situ gelling system*

1. *In situ* gels are the most advanced formulation available for ocular drug delivery.
2. Avoiding systemic side effects as conventional ophthalmic formulations drained out from eye and goes to systemic circulation through oesophageal route.

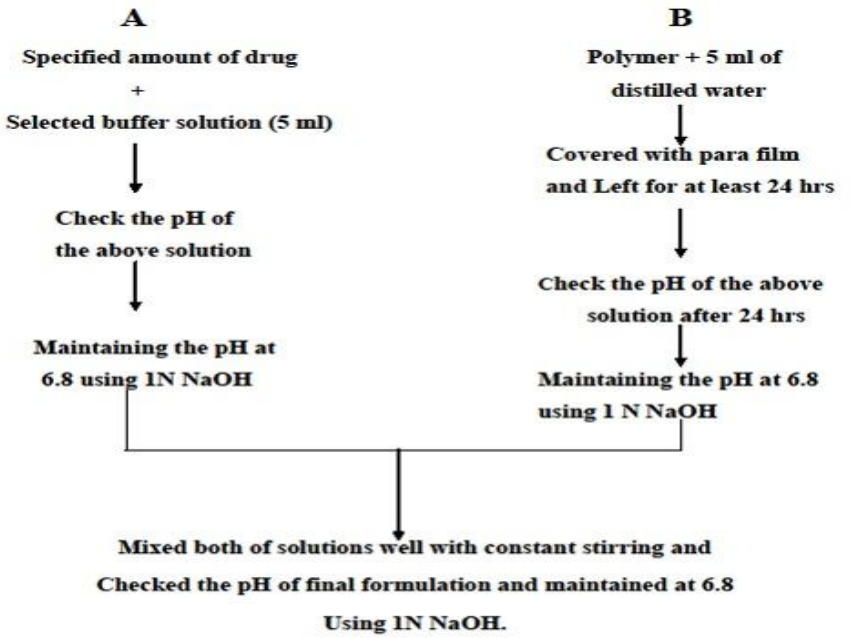

Figure 3 Method of preparation

3. Eye drops and other similar formulations need a large amount of drug as these formulations having poor ocular residence time and corneal absorption.\
4. pH sensitive gels having excellent property of transforming from sol form to gel form instantly when coming in contact to ocular fluid and exhibiting better therapeutic level.

Fluconazole remains one of the most frequent prescribed triazoles because of its excellent bioavailability, tolerability, and side-effect profile. [6]

Carbopol 980 - Advantages With Use of Carbopol Gels as Vehicles are

- Good rheological properties resulting in long statement on the administration site.
- Good alternative to oil-based ointment formulations.
- Anionic hydrogels with good buffering capacity which contributes to maintenance of the desired pH.
- High viscosity already at low concentrations.
- Wide concentration interval and characteristic flow behavior.
- Compatibility with many active ingredients.
- Bioadhesive properties.
- Good thermal stability.
- Excellent Organoleptic characteristics.
- Good patient acceptability.

Applications of Carbopol Polymers

The readily water-swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide:

- Controlled release in tablets.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals. Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants. [7]

EXPERIMENT

Material

Fluconazole was gifted from Heliox Pharma, Baddi, India. Carbopol 980 and polycarbophil were purchased from Lubrizol Advanced Materials, Inc.

Table 1 Optimized formulations

S. NO	Formulation code	FLUCONAZOLE USP	carbopol 980	Polycarbophil
1	F9	10	100 mg / 1.0%	-
2	F17	10	90 mg / 0.9%	20mg / 0.2 %
3	F18	10	100 mg / 1.0%	20mg / 0.2 %
4	F27	10	100 mg / 1.0%	40mg / 0.4 %

Evaluation of in situ Ph sensitive ocular gel

- **Physical Evaluation**

❖ **Visual appearance**

It is an important parameter in case of ocular preparations, since the formulation should be free from any foreign matter as well as free from air bubbles**.** To make sure the visual appearance of formulations should be observed visually before a clear background or light.

❖ ***Clarity***

The clarity of the formulations before and after gelling was determined by visual examination of the formulations under light alternatively against white and black backgrounds. [8]

- ***pH Measurement***

pH of each of prepared ophthalmic formulations was determined by using pico^{+} digital pH meter. The pH meter was calibrated before each use with standard pH 4, 7 and 9.2 buffer solutions. The formulation pH was maintained at 6.8 with the help of 1NaOH solution.

- ***Rheological Evaluation***

Viscosities of the formulated gels were determined using Brookfield Viscometer (Model: DV-1 Prime, Brookfield Engineering Lab., Inc., USA). Spindle no. 64 was used for ocular gels and 25 rpm at 25° C. [9]

- ***Drug Content***

Each formulation of 1g was dissolved in 10 ml STF (simulated tear fluid). The solution was filtered through 45µ membrane (whatman filter paper), above filtrate was pipette out and the absorbance was measured at 261 nm, using double beam UV visible spectrophotometer.

➢ *Gelling Time*

The individual ophthalmic formulations (1ml) were added into 2 ml of Simulated tear fluid (37℃ +/- 1℃) contained in glass vials. The duration of gel formation was recorded as gelling time.

➢ *Gelation Capacity*

The individual ophthalmic formulations (1ml) were added into 2 ml of Simulated tear fluid (37℃ +/- 1℃) contained in glass vials. The transition of solution to viscous gel was observed visually. [10]

1.	NaCl- 350mg
2.	$NaHCO_3$- 100mg
3.	$CaCl_2$ dihydrate-40mg
4.	Distilled water-500ml

Simulated tear fluid (STF)

➢ *In-vitro drug release*

Dissolution studies were carried out for Optimized formulation, employing modified USP dissolution test apparatus (DS-8000). Previously soaked cellophane membrane (in STF) was stretched over the glass cylinder and this glass cylinder was attached to the shaft of USP apparatus I (Basket type) in place of basket. The dissolution media was STF (50 ml) maintained at 37 ± 0.5 ℃. The sample (1 ml) was withdrawn at regular interval of 1 hr for 7 hrs and was replaced immediately with the same volume of STF. The samples withdrawn were observed Spectrophotometrically at 261 nm. [11]

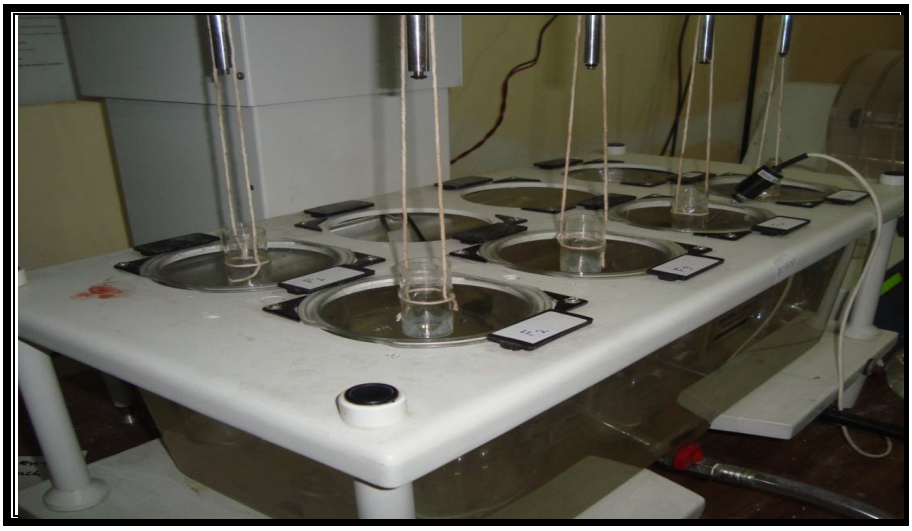

Figure 4 Modified USP dissolution test apparatus.

RESULT AND DISCUSSION

- ***Identification of pure drug (FT-IR spectra)***

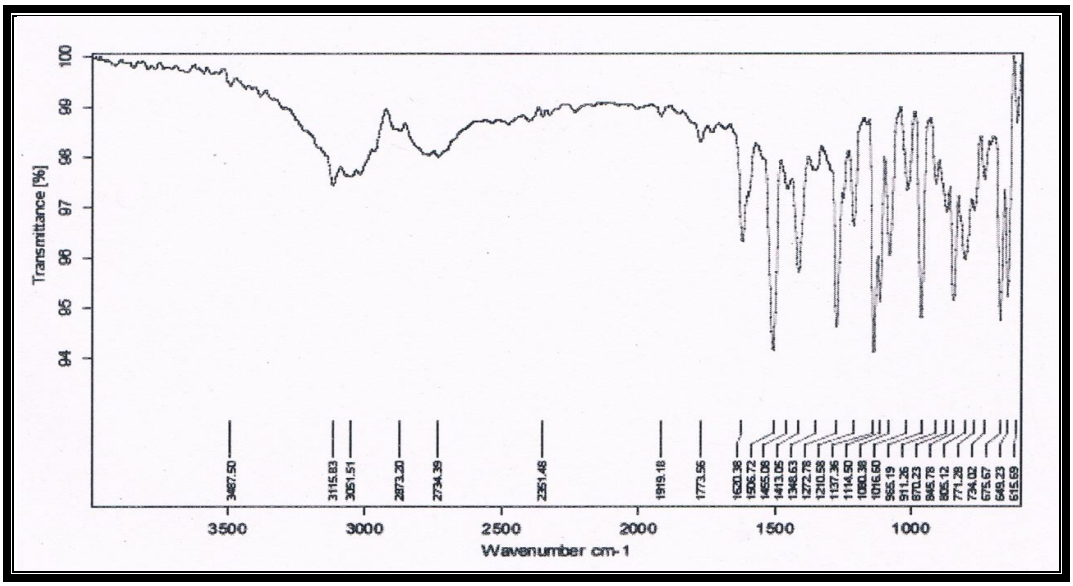

Figure 5 IR spectra of pure drug (Fluconazole).

Pure fluconazole has characteristic IR peaks at 3487.50 cm^{-1}[OH Stretching], 2873.20cm^{-1}[CH_2 Stretching], 3051.51 cm^{-1} [CH Aromatic Stretching], 1620.38 cm^{-1}[C=N Stretching], 1455.08[CH Aromatic bending]cm^{-1} and 1080.38[C-F Stretching]cm^{-1}.

- ***Drug- Excipients Compatibility Study***

The IR spectrum of ternary mixtures of API with Excipients (Carbopol and polycarbophill) were interpreted and identified.

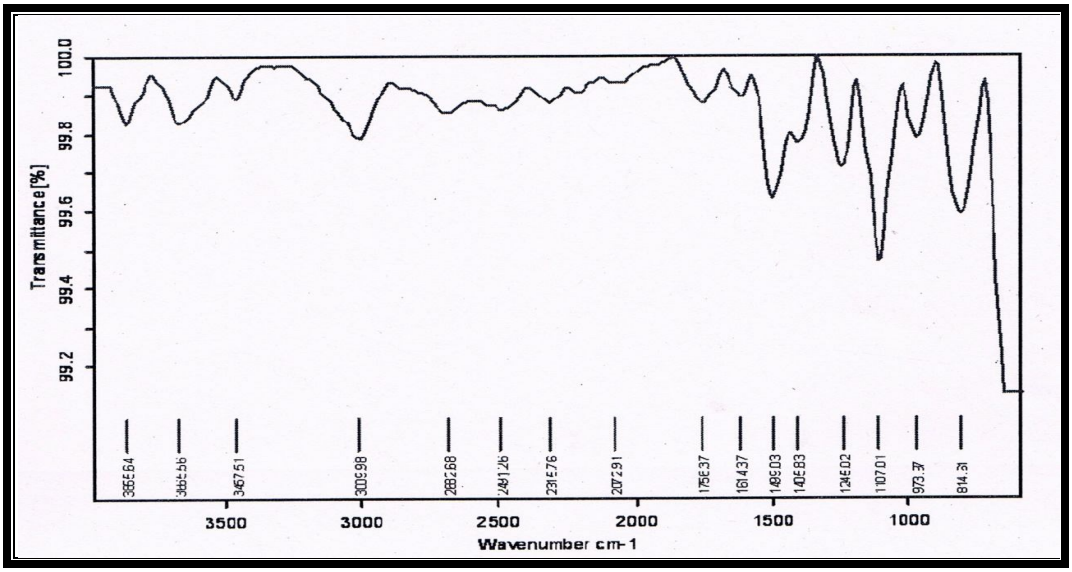

Figure 6 IR spectra of drug and excipients mixture.

The IR spectrum of API and mixtures of API with excipients were interpreted and identified. The main absorption bands of the drug were present in the mixtures with same degree of sharpness and position indicating that there is absence of physical and chemical interactions among both active component and the excipients.

Mixtures of API has characteristic IR peaks at 3457.51 cm^{-1}[OH Stretching], 2882.88cm^{-1}[CH_2 Stretching], 3009.98 cm^{-1} [CH Aromatic Stretching], 1614.37 cm^{-1}[C=N Stretching], 1405.83[CH Aromatic bending]$cm^{-1}$and 1107.01[C-F Stretching]cm^{-1}.

Evaluation of Visual appearance, Clarity, pH, and Drug Content

All the prepared *in situ* gelling systems were evaluated for preliminary steps such as visual appearance, clarity and pH.

Table 2 Preliminary evaluation of visual appearance, clarity.

S. No.	Formulation	Visual Appearance	Clarity
1.	F9	Transparent	Clear
2.	F17	Transparent	Clear
3.	F18	Transparent	Clear
4.	F27	Transparent	Clear

pH measurement

The pH of the formulations was determined using pH meter.

Table 3 measurement of pH

S. No.	Formulation	pH Mean±S.D.
1.	F9	6.7±0.11
2.	F17	6.6±0.08
3.	F18	6.5±0.10
4.	F27	6.7±0.12

- **Rheological Evaluation**

Table 4 Viscosity of optimized formulations.

S. No.	Formulation	Viscosity (Centipoise) Mean±S.D.
1.	F9	857±66
2.	F17	1014±71
3.	F18	1240±46
4.	F27	1110±69

- **Drug Content**

Table 5 Drug content of optimized formulations.

S. No.	Formulation	Drug content % Mean±S.D.
1.	F9	89.23±0.033
2.	F17	90.48±0.039
3.	F18	92.68±0.038
4.	F27	97.75±0.041

The drug content of the optimized formulations of *in situ* gel was estimated and the results were in the official limits with range**.** The drug content determination also revealed that the drug was uniformly distributed throughout the gel.

- ***Gelling Time***

Gelling time or gelation time for optimized formulations was recorded as:-

Table 6 Gelation time of optimized formulations.

S. NO.	Formulation code	Gelation time (min.) mean ± SD
1	F9	306±9
2	F17	321±12
3	F18	367±10
4	F27	423±7

➢ *Gelation Capacity*

Table 7 Evaluation of gelling capacity

Formulations	Gelling Capacity
F9	++
F17	++
F18	+++
F27	+++

Note: ++ gelation immediate and remains for few hours, +++ shows gelation immediate and remains for extended period.

➢ *In Vitro Drug Release*

The *in vitro* release of Fluconazole from the prepared optimized formulations was studied through modified USP dissolution Test Apparatus using glass hollow tube. The release studies of optimized *in situ* gelling systems were carried out up to 7 hours was done through cellophane membrane using diffusion cell.

- ***In situ* ocular gel formulation %CDR**

Table 8 *In vitro* drug release studies of all optimized *in situ* ocular gel formulation.

Time (hr.)	F9	F17	F18	F27
0	0	0	0	0
1	22.5±0.031	28.75±0.029	28.75±0.022	26.25±0.017
2	39.2±0.052	48.075±0.037	48.075±0.028	45.525±0.028
3	52.475±0.038	62.775±0.042	61.525±0.036	62.675±0.020
4	63.5±0.026	71.5±0.024	72.725±0.029	75.15±0.031
5	69.725±0.023	79.125±0.027	82.875±0.039	86.6±0.029
6	72.3±0.026	83.125±0.024	90.7±0.037	94.5±0.028
7	72.4±0.024	82.175±0.029	91.15±0.033	96.275±0.025

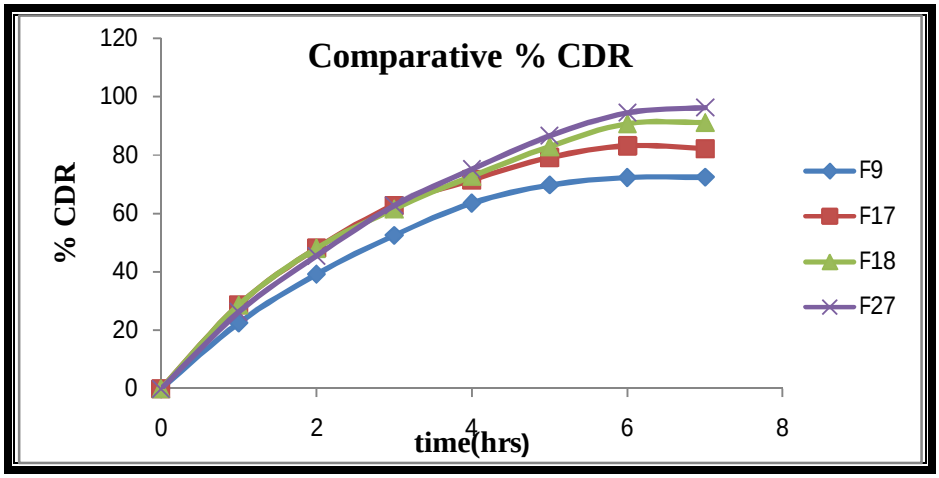

Figure 7 Comparative *In vitro* drug release studies of optimized formulations.

In vitro drug release studies were carried out for F9, F17, F18 and F27 formulations, employing modified dissolution test apparatus. The release rate of drug from *in situ* ocular gel systems depends on the drug partition coefficient and drug solubility in the oil and aqueous phases. F27 *in situ* ocular gel showed maximum percentage of drug release at the end of 7 hr, followed by the release of the drug from F18, F17 and F9 and *in situ* ocular gel [Figure 6]. The order of % cumulative drug release was

F27> F18> F17> F9.

➢ *Drug Release Kinetics*

Prepared *in situ* gelling systems were evaluated for the *in vitro* gelation capacity. All the formulations gave satisfactory results. The release kinetic of fluconazole *in situ* ocular gel was studied by various kinetic models as zero order plot, first order plot, higuchi plot and korsmeyer-Peppas.

Zero order Kinetic

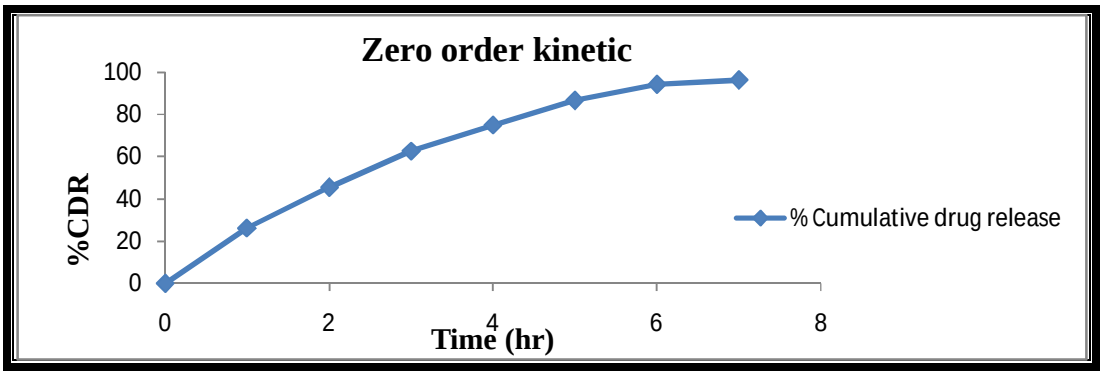

Figure 8 Zero order plot for drug release kinetics for fluconazole *in situ* ocular gel (F27).

First order kinetic

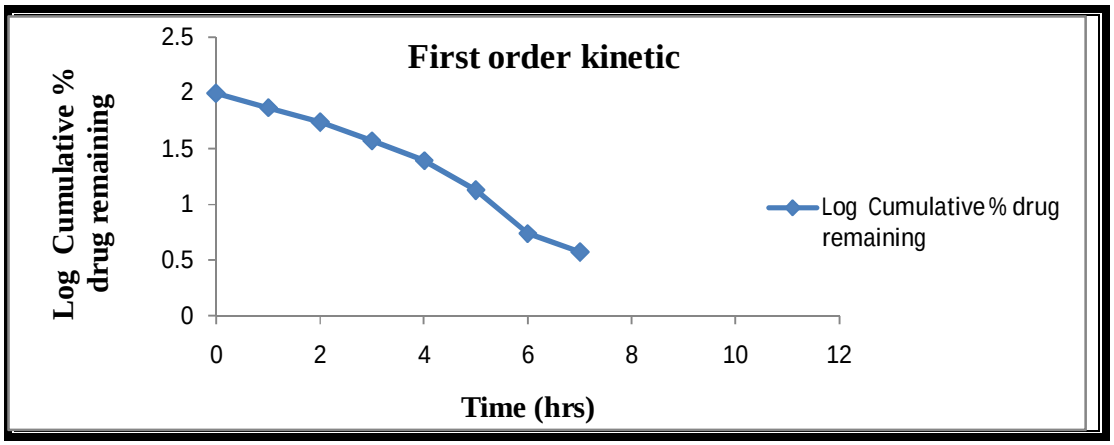

Figure 9 First order plot for drug release kinetics for fluconazole *in situ* ocular gel (F27).

- **Higuchi model**

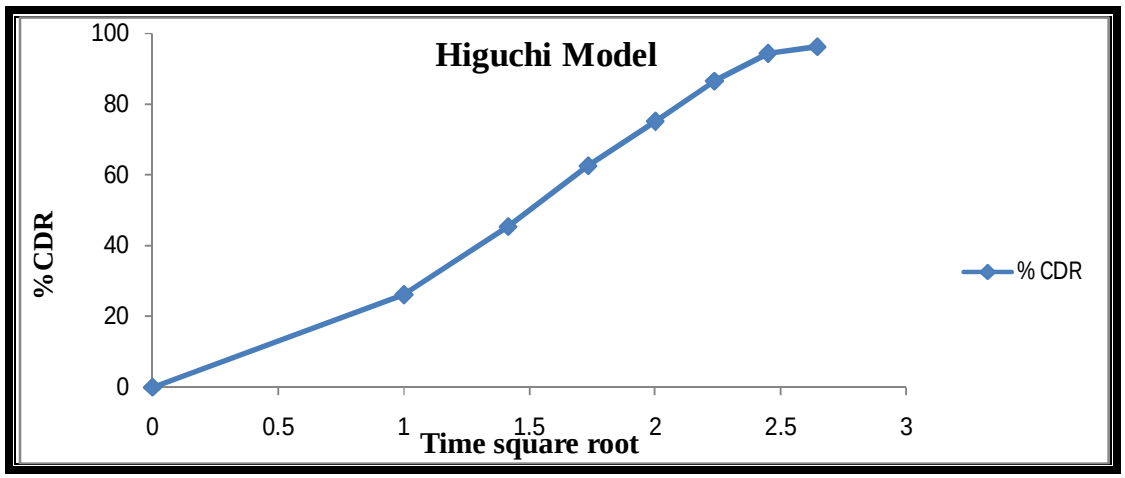

Figure 10 Higuchi model plot for drug release kinetics for fluconazole *in situ* ocular gel (F27).

Korsmeyer-peppas

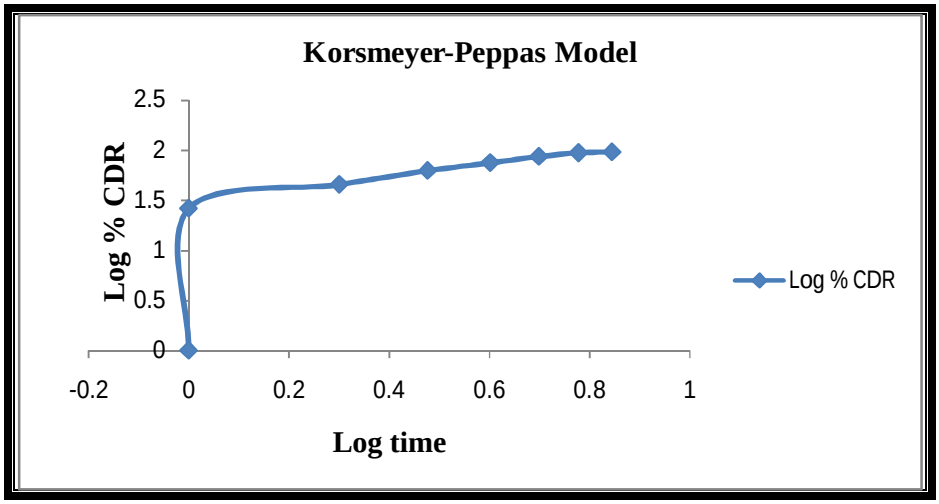

Figure 11 Korsmeyer-Peppas Model plot for drug release kinetics for fluconazole *in situ* ocular gel (F27).

Table 9 Drug release kinetic equation parameter of fluconazole *in situ* ocular gel (F27).

Formulation	Zero order		First order		Higuchi		Korsmeyer - peppas	
	R^2	K_O	R^2	K_f	R^2	K_h	R^2	N
F27	0.939	13.70	0.968	-0.48363	0.982	39.46	0.597	1.548

The data obtained for *in vitro* release shown in Table 9 were fitted into equation for the zero order, first order and higuchi and korsmeyer peppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

The calculated regression coefficients for zero order, first order and higuchi models and korsmeyer were shown in Table no. 9. It was found that the *in vitro* drug release fluconazole pH sensitive *in situ* ocular gel was best explained by higuchi equation as the plot showed the highest linearity. Therefore the release pattern seems to fit higuchi model.

DISCUSSION

Beside ophthalmic ointments have the advantages of increased contact time. By utilizing these advantages of different dosage forms the newer approach, *in situ* gelling system was developed. These gels exhibit a unique property of sol-to-gel transition when a change in their physicochemical property takes places. This type of novel ocular drug delivery can provide increased bioavailability by increasing residence time of gel formed and better patient compliance due to ease of administration.

The aim of the present work envisaged “design, development and evaluation of in situ ph sensitive ocular gel containing fluconazole” for the treatment of various fungal diseases of eye by providing comfortness, compliance to the patients and improved therapeutic performance of the drug over conventional

Ocular dosage forms.

From the above results, it shows that it is possible to formulate *in situ* ophthalmic gels of Fluconazole using Carbopol and polycarbophil for treatment of ocular fungal infections.

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