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Formulation And Evaluation Of Occular In Situ Gel

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Abstract

In-situ gel technology is a promising drug delivery strategy that undergoes a 'sol to gel' transition upon administration, providing controlled and prolonged drug release. These gels are composed of cross-linked 3D networks of polymers, with hydrogels being a specific type of absorbing water while retaining their shape. Gelation can be triggered by various stimuli, such as temperature, pH, ions, and light. They offer several advantages like improved patient compliance, extended drug residence time, localized drug delivery, etc, but also have some disadvantages like drug degradation and limited mechanical strength. In-situ gel falls into three categories: temperature-sensitive, ion-sensitive, and pH-sensitive, but multi-responsive gels that respond to multiple stimuli have better drug release characteristics. The mechanism of in-situ gel formation involves physical and chemical mechanisms. There are various applications of in-situ gel, like ocular drug delivery, nose-to-brain delivery, etc. In this review, we have discussed the types, and mechanisms of in-situ gel & use of in-situ gel in the treatment of different diseases through various routes like buccal, vaginal, ocular, nasal, etc., along with its use in targeted drug delivery.

Keywords: In situ gel, Thermosensitive nature, bioavailability, Natural Polymer, Antifungal activity

Introduction

Gel

A gel is a semi-solid dosage form that can have properties ranging from soft and weak to hard and tough. Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when it is present in the steady-state. A gel is defined as a soft, solid or semi-solid-like material consisting of two or more components, one of which is a liquid, present in substantial quantity.

By weight, gels are mostly liquid, yet they behave like solids because of a three-dimensional cross-linking network within the liquid. It is the cross-linking within the fluid that gives a gel its structure (hardness) and contributes to the adhesive stick (tack). In this way, gels are a dispersion of molecules of a liquid within a solid medium. The process of forming a gel is called gelation. [1]

Composition of gel:

Gels consist of a solid three-dimensional network that spans the volume of a liquid medium and ensnares it through surface tension effects. This internal network structure is made up of physical bonds (physical gels) or chemical bonds (chemical gels), as well as crystallites or other junctions that remain intact within the extending fluid. Virtually any fluid can be used as an extender including water (hydrogels), oil, and air (aerogel). Both by weight and volume, gels are mostly fluid in composition and thus exhibit densities similar to those of their constituent liquids. Edible jelly is a common example of a hydrogel and has approximately the density of water.[1]

1.3 Types of gel:

Hydrogel

A hydrogel is a network of polymer chains that are hydrophilic in nature which are sometimes found as a colloidal gel in which water is the dispersion medium. A three-dimensional solid is produced from the hydrophilic polymer chains being held together by cross-links. Because of the inherent cross-links, the structural integrity of the hydrogel network does not dissolve from the high concentration of water. [1]

Hydrogels are highly absorbent in nature means they can absorb around 90% water along with natural or synthetic polymeric networks. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. As responsive "smart materials," hydrogels can encapsulate chemical systems which upon stimulation by external factors such as a change of pH may cause specific compounds such as glucose to be liberated to the environment, in most cases by a gel-sol transition to the liquid state. [1]

Organogel

An organogel is a non-crystalline, non-glassy thermo reversible solid material which is composed of a liquid organic phase entrapped in a three-dimensionally cross-linked network.

The liquid can be an organic solvent, mineral oil or vegetable oil. The solubility and particle dimensions of the structure are important characteristics for the elastic properties and firmness of the organogel. Often, these systems are based on self-assembly of the ingredient molecules. Organogel have potential for use in a number of applications such as in pharmaceuticals, cosmetics, art conservation and food. [1]

Xerogel

A xerogel is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15–50%) and enormous surface area (150–900 m2/g), along with very small pore size (1–10 nm). When solvent removal occurs under supercritical conditions, the network does not shrink and a highly porous, low-density material known as an *aerogel* is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering which results in a denser and more robust solid, the density and porosity achieved depend on the sintering conditions.[1]

Nanocomposite Hydrogels

Nanocomposite hydrogels or hybrid hydrogel, are highly hydrated polymeric networks, either physically or covalently cross linked with each other and/or with nanoparticles or nanostructures. [1]

Nanocomposite hydrogels can mimic native tissue properties, structure and microenvironment due to their hydrated and interconnected porous structure. A wide range of nanoparticles, such as carbon-based, polymeric, ceramic, and metallic nanomaterials can be incorporated within the hydrogel structure to obtain nanocomposites with tailored functionality. Nanocomposite hydrogels can be engineered to possess superior physical, chemical, electrical, thermal, and biological properties.

1.4 In situ Gel

The formulations of *in situ* gels possibly possess characteristics of a pseudo plastic behavior. The developed formulations were therapeutically efficacious, stable, non -irritant and provide sustained release of the drug up to eight hours. [1]

1.5 Mechanism Of *In- Situ* Gelation -

They are aqueous liquid solutions before administration, but get converted into gel under physiological conditions. Several possible mechanisms lead to in-situ gel formation some are as follows: -

- ❖ Ionic cross-linkage
- ❖ pH change
- ❖ Temperature modulation.

Polymer solutions of Gellan gum, pectin & Sodium alginate etc are used for formulation of in-situ gels. [1]

1.6 Ophthalmic Drug Delivery System

Ophthalmic drug delivery system is one of the most widely used areas for around several years. It is one of the most widely researched areas in the field of medicines. The young generation of scientist has a very keen interest

in this ophthalmic field nowadays. The main reason of continuous strong interest of scientists in this drug delivery system is the problem of a low bioavailability of drug after the application to the eyeball.

Gelling capacity and gelling temperature both play an important role in formulation of *In-situ* gel. Both the parameters are determined to check the ability of the formulation to form a gel due to interaction with different environmental conditions like temperature, pH, humidity etc.

The formulation should undergo rapid conversion between sol to gel transition at the site of application due to change in pH and temperature by maintaining its integrity without erosion or dissolution. On experimentation it was found that as the concentration of polymers increases, the integrity of formed gel also increases. As a result it remains in gel form for a prolonged period of time ensuring proper drug release from the formed gel.

The viscosities of all the formulations at cold temperature and at 37°C were in the range between 980 to 1839 and 6032 to 8907 centipoises respectively. These *in situ* solutions are liquid at room temperature but undergo gelation when it comes in contact with body fluids or change in pH. [2]

Materials and methods:

Drug Gatifloxacin was obtained as a gift sample from Cipla Indore Carbopol, HPMC, Polaxomer, Ethanol, Methyl Paraben and Propyl Paraben were obtained from Oxford Laboratory Mumbai

Preformulation Studies:

6.3.0 Organoleptic evaluation

6.3.1. Colour / Odour

A small quantity of drug was taken on butter paper and it was analyzed visually for analyzing colour and odour.

6.3.2. Melting Point

Melting point is defined as temperature at which drug gets converted from solid to liquefied form. It is determined mainly by two methods: Capillary tube Method (Fusion Method) and through Melting point apparatus (Navyug, India). The melting point was determined by fusion method. A capillary tube was sealed at one end, and then filled with small amount of drug (Gatifloxacin) sample. The capillary tube was inserted into melting point apparatus along with thermometer till drug sample gets melted and temperature was recorded.

6.3.3. Solubility Profile of Drug

Solubility is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous solvent. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and presence of other chemical (including charge to the pH) of the solution.

Table No.3 Solubility Profile according To B.P.

S.NO.	Description term	Part of solvent required for part of solute
1.	Very Soluble	Less than 1ml
2.	Freely Soluble	From 1ml to 10ml
3.	Soluble	From 10ml to 30ml
4.	Sparingly Soluble	From 30ml to 100ml
5.	Slightly Soluble	From 100ml to 1000ml
6.	Very Slightly Soluble	From 1000 to 10000
7.	Practically in soluble	From 10000 or more

Take a small of drug in a test tube. Then check its solubility in different solvents like distilled water, 0.1N HCl, 0.1N NaOH, ethanol, methanol, phosphate buffer pH 7.2 & 6.8.

6.3.4. Determination of Absorption Maxima of Gatifloxacin

6.3.4.1 Preparation of Phosphate buffer pH 7.2:

34 gm of potassium dihydrogen phosphate were dissolved in 1000ml to produce phosphate buffer of pH 7.4.

6.3.4.2 Spectrophotometric estimation of Levofloxacin

Gatifloxacin was analyzed quantitatively by UV spectrophotometer (Systronics 2202) in Phosphate buffer pH 7.2. Standard calibration curve was plotted between concentration and absorbance.

6.3.4.3 Procedure for preparation of standard curve of Gatifloxacin in phosphate buffer pH 7.2

Weigh 100 mg of drug and dissolve in 100ml of phosphate buffer solution pH 7.2. Pipette out 1ml of stock solution and dilute to 100ml of phosphate buffer solution (Sub stock solution). Then pipette out 0.1ml, 0.2ml, 0.3ml, 0.4ml, 0.5ml from sub stock solution and dilute up to 10ml to prepare 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml and 5 µg/ml solution. Then absorbance is recorded using UV spectrophotometer at ƛ max 286nm.

6.3.5. Determination of Drug Excipients Incompatibility by FT-IR Spectroscopy

Infra red spectra were recorded by mixing powdered drug with dry powder potassium bromide. FT-IR spectra of the selected formulations were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were obtained by scanning in the range of 400-4000 cm-1 by using the spectrometer (Bruker-α-T, Germany). FT-IR is a technique used to determine the chemical interaction between drug and polymers**.**

6.3.6. Formulation Batch In situ gel: [34]

Table no.4 Formulation Batch In situ gel

Formulation batch	Drug	Carbopol 934 (%)	HPMC (%)	Chitosan (%)	Sodium alginate (%)
F1	0.4	1	-	-	-
F2	0.4	-	2	-	-
F3	0.4	-	-	0.25	-
F4	0.4	-	-	-	8

6.3.7. Formulation of in situ gel

6.3.7.1. Carbopol 934 - The weighed quantities of polymers were kept for swelling overnight in distilled water and dissolved (heated, if necessary) using a magnetic stirrer. Aqueous solution of Gatifloxacin was added in to the polymeric solution with continuous agitation for 20 min. Benzalkonium chloride was added to the resulting solution. The pH of the formulation was adjusted to 7.2 using 0.1 N NaoH/0.1 N HCl. Dispersion was allowed to hydrate for 60 min. Keep the gel for 24 hrs at room temperature.

6.3.7.2. HPMC (E15) - The weighed quantities of polymers were kept for swelling overnight in distilled water and dissolved (heated, if necessary) using a magnetic stirrer. Aqueous solution of Gatifloxacin was added in to the polymeric solution with continuous agitation for 20 min. Benzalkonium chloride was added to the resulting solution. The pH of the formulation was adjusted to 7.2 using 0.1 N NaoH/0.1 N HCl. Dispersion was allowed to hydrate for 60 min. Keep the gel for 24 hrs at room temperature.

6.3.7.3. Chitosan - The weighed quantities of polymers were kept for swelling overnight in mix of 0.25% glacial acetic acid and distilled water and dissolved (heated, if necessary) using a magnetic stirrer. Aqueous solution of Gatifloxacin was added in to the polymeric solution with continuous agitation for 20 min. Benzalkonium chloride was added to the resulting solution. The pH of the formulation was adjusted to 7.2 using 0.1 N NaoH/0.1 N HCl. Dispersion was allowed to hydrate for 60 min. Keep the gel for 24 hrs at room temperature.

6.3.7.4. Sodium Alginate - The weighed quantities of polymers were kept for swelling overnight in distilled water and dissolved (heated, if necessary) using a magnetic stirrer. Aqueous solution of Gatifloxacin was added in to the polymeric solution with continuous agitation for 20 min. Benzalkonium chloride was added to the resulting solution. The pH of the formulation was adjusted to 7.2 using 0.1 N NaoH/0.1 N HCl. Dispersion was allowed to hydrate for 60 min. Keep the gel for 24 hrs at room temperature.

6.4.0 Evaluation Parameter[35,36,37,38]

6.4.1. Clarity Test: Clarity test was observed by visual inspection under a good light, viewed against a black and white background, with the contents set in motion with a swirling action. Also it was observed for formation of turbidity or any unwanted particles dispersed in the solution

6.4.2 Determination of pH:

pH of each formulation was determined immediately after preparation by using digital pH meter (EI Instrument, Parwanoo H.P.) which was previously calibrated by pH 4 and pH 7 standard buffers.

6.4.3. Gelling Capacity:

The gelling capacity of the prepared formulation was determined by placing a drop of the formulation in a beaker containing 50 ml of freshly prepared concentrated calcium chloride solution and was visually observed for gelling time.

6.4.4. Measurement of Gelation Temperature:

About 10 ml of the formulation was transferred to a 50 ml beaker with a magnetic bead and placed on a magnetic stirrer (Jyoti Scientific Industries, Gwalior) with thermostatically controlled heater. The temperature of the stirrer was increased in increments of 1°C and the temperature of the formulation was recorded using a thermometer. The rotation of bead gradually slowed down as the viscosity increased. The temperature at which the magnetic bead stopped rotating was taken as gelation temperature.

6.4.5. Viscosity Measurement:

The viscosity was measured using a Brookfield viscometer (Brookfield engineering limited) and the angular velocity increased gradually from 2 to 50 rpm. The studies were performed using spindle no. 96 for gels at physiological temperature (37°C) and for sols at normal room temperature (28°C)

6.4.6. In-Vitro Release Studies:

The in-vitro drug release was studied by using a USP rotating paddle apparatus (Electro Lab, TDT 08L). Phosphate buffer 7.2 maintained at 37ºC was used as the medium. The paddle speed was set to 50 rpm. 3ml of the formulation was placed in a dialysis tube with cellophane membrane covered cells and it was placed such that it just touches the diffusion medium. The drug samples were withdrawn at the interval of one hour for a period of ten hours from the medium and were analyzed by U.V spectrophotometer at their respective wavelength using Phosphate buffer pH 7.2 as blank. The cumulative percentage drug release was evaluated.

Results and discussion:

7.0 RESULT AND DISCUSION

7.1. Preformulation of Gatifloxacin:

7.1.0 Organoleptic evaluation

7.1.1 Colour:

The drug was found to be creamish amorphous powder.

7.1.2 Melting point:

The melting point of drug was found to be 182^0C – 187^0C

7.1.3 Odour

The drug does not have any obnoxious odour.

7.1.4 Solubility:

Table no.5: Solubility of pure Gatifloxacin in given solvent

S.NO.	Solvent	Solubility
1	Water	Slightly soluble
2	Ethanol	Slightly soluble
3	Methanol	Slightly soluble
4	0.1 N HCL	Very Slightly soluble
5	0.1 N NaOH	Sparingly soluble
6	Phosphate buffer PH 6.8	Slightly soluble
7	Phosphate buffer PH 7.2	Soluble

Discussion – Gatifloxacin is soluble in phosphate buffer pH 7.2, it is slightly soluble in water, ethanol, and methanol. It is very slightly soluble in 0.1N HCl. It is sparingly soluble in 0.1 N NaOH.

7.1.5 Determination of Absorption Maxima of Gatifloxacin

Calibration curve of Gatifloxacin in phosphate buffer pH 7.2:

Table no.6 Concentration and absorbance data for calibration curve of Gatifloxacin

S. No	Concentration (µg/ml)	Absorbance (at 286nm)
1	0	0
2	1	0.087
3	2	0.157
4	3	0.225
5	4	0.276
6	5	0.378

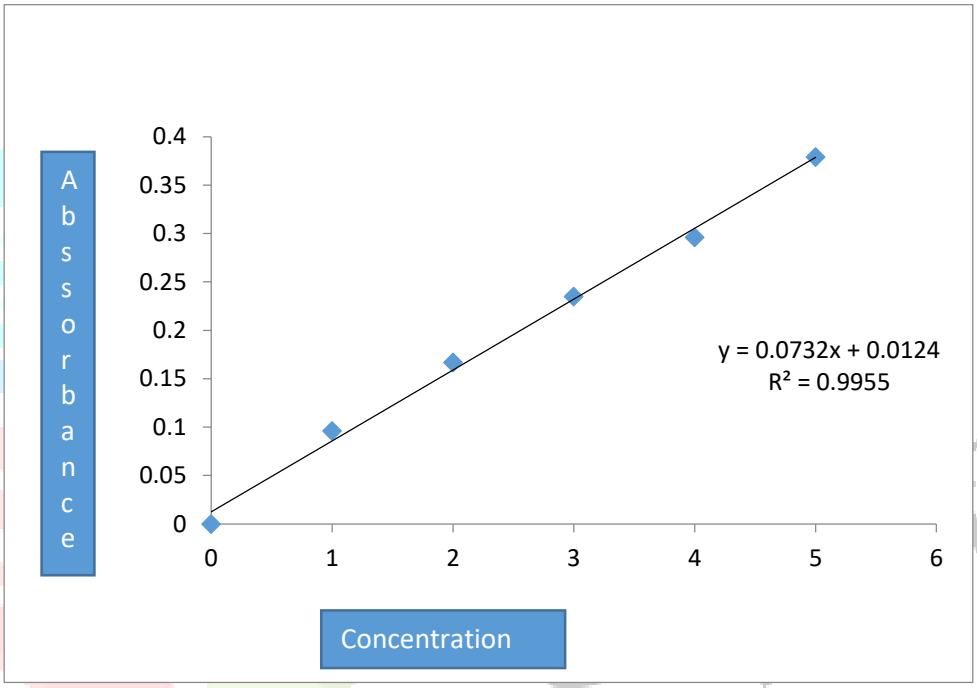

Figure no. 1 calibration curve of Gatifloxacin in phosphate buffer pH 7.2:

7.1.6 FT-IR studies

Drug-excipients compatibility study was performed by FTIR technique. The IR spectra of the solution were taken, which indicate no interaction between Gatifloxacin HCl and polymers [6,17]. FT-IR spectrum of drug and polymer mixture shows characteristic peaks at 3035cm–1 indicates the presence of carboxylic group, 1616cm–1 exhibits alkenes, 1450cm–1 indicates the presence of aromatic ring, 1355cm–1 exhibits carboxylic acids, 1288cm–1 indicates alkyl halides, 1239cm–1 indicate ester, 1196cm–1 indicates alkyl halide, and 1135cm–1 indicates amine oxide. From the spectral study it was observed that there was no significant change in the peaks of drug polymer mixture. Hence, no specific interaction was observed between the drug and the polymers used in the formulations

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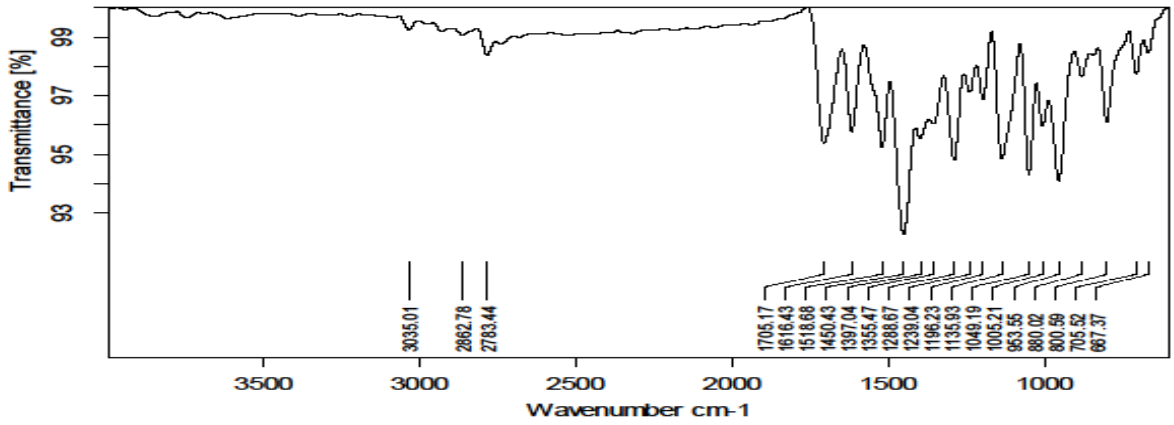

Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3849.6538	0.997	0.002	94.0046	2.012058	0
3746.0680	0.997	0.002	41.1927	2.317038	0
3615.6260	0.996	0.002	119.8053	2.205209	0
3035.0075	0.993	0.003	25.6157	3.963492	0
2862.7773	0.991	0.003	46.2211	3.076821	0
2783.4406	0.984	0.016	431.0785	21.033516	0
1705.1699	0.954	0.042	61.5132	43.290035	0
1616.4341	0.968	0.029	31.1496	36.314285	0
1518.6819	0.962	0.025	27.3886	29.133415	0
1450.4277	0.923	0.077	103.6757	99.885893	0
1397.0390	0.955	0.007	154.3935	4.718873	0
1355.4721	0.960	0.006	83.7364	2.010688	0
1288.6681	0.948	0.032	33.9197	37.226288	0
1239.0366	0.971	0.008	21.4384	8.271273	0
1196.2306	0.969	0.016	46.6146	14.827589	0
1135.9282	0.949	0.042	54.5730	50.744606	0
1049.1892	0.943	0.034	23.7792	40.506232	0
1005.2138	0.960	0.012	22.8882	11.649598	0
953.5545	0.941	0.054	54.3333	65.838097	0
880.0216	0.977	0.009	24.3020	11.261519	0
800.5867	0.961	0.027	29.3823	32.844292	0
705.5170	0.977	0.016	25.4678	19.045244	0
667.3691	0.965	0.006	30.0408	5.579518	0

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Figure no. 2 FT-IR Studies

7.2.0 Evaluation Parameter

7.2.1 Clarity:

The formulations (F1–F4) were prepared by using various concentrations of sodium alginate along with HPMC in different ratios. All the formulations prepared were clear without any turbidity and suspended particles or impurities.

7.2.2 Determination of pH:

The pH of in situ gel solution was found to be around 6.49 to 7.40 for all the formulations. The pH of all formulations is in acceptable range. So they can be easily used in eyes for proper treatment.

Table no. 7 : Result for pH, Clarity Test, Gelling capacity, Gelation temperature

S.NO.	Formulation code	Clarity	pH	Gelling capacity	Gelation temperature	Viscosity (at 50 rpm)
1.	F1	Transparent	6.13 ± 0.15	+ + +	25 ± 0.59	77
2.	F2	Transparent	6.30 ± 0.132	+ +	26.5 ± 0.7	53
3.	F3	Transparent	6.29 ± 0.176	-	31 ± 0.12	42
4.	F4	Transparent	6.39 ± 0..62	+ +	28.5 ± 0.31	75

Table no. 8 Gelling Capacity

S. No	Gelling Capacity	Observation
1	No gelation	-
2	Gelation occurred in few minutes and remained for few hour	+
3	Gelation immediate, remained for few hour	+ +
4	Gelation immediate, and for extended period	+ + +
5	Very stiff gel	+ + + +

7.2.3 Gelling capacity

The gelling capacity of batches was found to be in the range of immediate gelation for extended period to gelation for few hours.

7.2.4 Gelation temperature

The gelation temperature of formulations was found to be in the range 25 to 31.

7.2.5. In-vitro release studies:

Table no. 9 In-vitro release studies

Time (hrs)	Cumulative % drug release			
	F1	F2	F3	F4
0.5	21 ± 0.84	19 ± 0.62	21 ± 0.98	18 ± 0.30
1	34 ± 0.61	27 ± 0.30	27 ± 0.58	25 ± 0.28
2	45 ± 0.89	38 ± 0.64	37 ± 0.97	34 ± 0.57
3	51 ± 0.96	46 ± 0.94	46 ± 0.87	43 ± 0.53
4	71 ± 0.96	57 ± 0.88	58 ± 0.92	55 ± 0.26
5	82 ± 0.98	61 ± 0.93	62 ± 0.45	58 ± 0.95

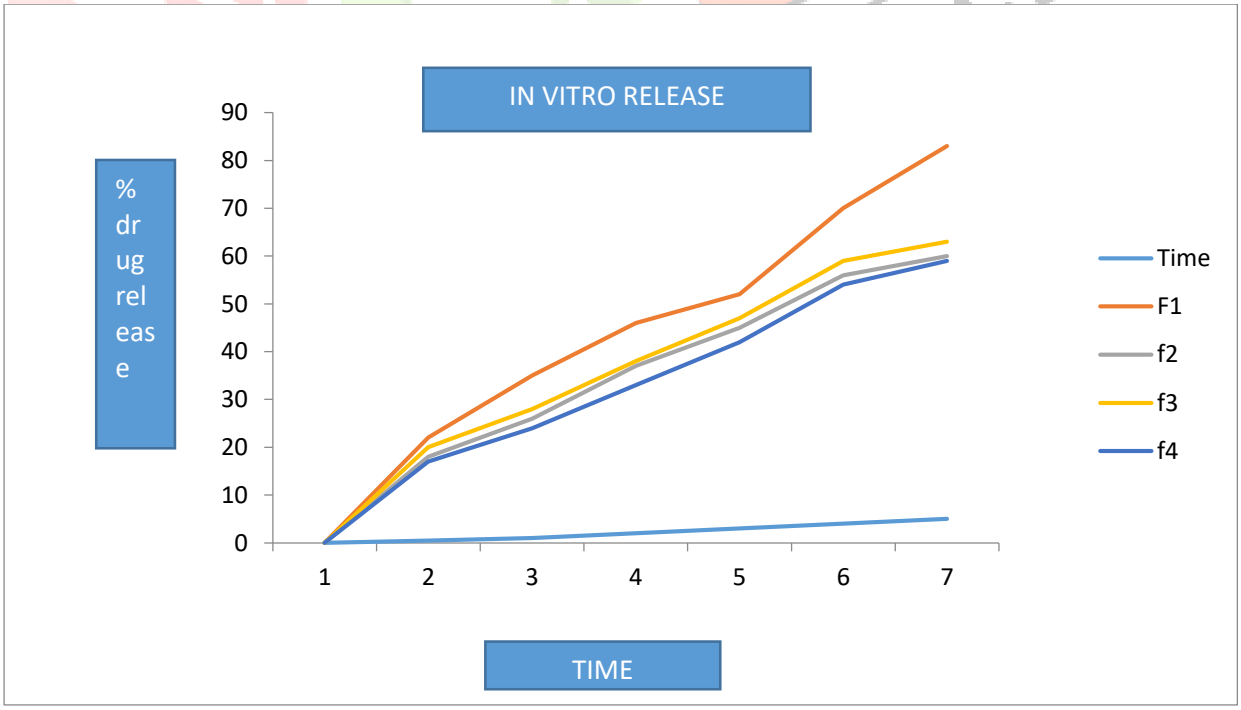

Figure No3 : In vitro release of drug Gatifloxacin

Summary

8.0. Summary and Conclusion:

The real challenge in the development of a controlled drug delivery system is not just to sustain the release but also to prolong the presence of the dosage form in the eye until all the drug is completely released in the desired period of time. Various approaches for preparation of in situ ophthalmic gels were designed.

The aim of the present investigation was to formulate and study ophthalmic in – situ gel of Gatifloxacin. Carbopol, Hydroxy Propyl methyl cellulose (HPMC), Chitosan, and Sodium alginate were used as polymers for the preparation of ophthalmic in-situ gel. All prepared formulations were evaluated for viscosity, determination of pH, clarity test, gelling capacity, measurement of gelation temperature, and in-vitro release studies etc.

FTIR spectra of the selected formulations were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were obtained by scanning in the range of 400-4000 cm-1 by using the spectrometer (Bruker-α-T, Germany). It was found that no incompatibility between drug and excipients was obtained.

Solubility is the property of a solid, liquid or gaseous chemical substance called solute to dissolve in a solid liquid or gaseous solvent. The drug was freely soluble in phosphate buffer pH 7.2.

The melting point was determined by the capillary method using melting point apparatus. The melting point of drug was found to be in the range 182^0C to 187^0C.

The viscosity of gel was determined by Brookfield viscometer. It was obtained in the range 50 to 72cps.

The pH of the in situ gel was found to be in the neutral range 7.2 to 7.82. The pH range of gel shows that any of the formulation can be used easily because it will not produce any irritation in eyes.

The formulations (F1–F4) were prepared by using various concentrations of sodium alginate along with HPMC in different ratios. All the formulations prepared were clear without any tur- bidity and suspended particles or impurities.

In in-vitro gelation study the formulations were evaluated for their in-vitro gelling capacity, accurately measured 10 mL of formulation was added to 100 mL of 0.1N (HCl, pH 7.2-7.8) at 37^0C in a beaker with mild agitation that avoids breaking of formed gel. The in vitro gelling capacity was graded in three categories on the basis of stiffness of formed gel, gelation time and time period for which the formed gel remains as such.(+) Gels after few minutes, dispersed rapidly, (++) Gelation immediate remains for few hours, (+++) Gelation immediate remains for an extended period

Conclusion:

The aim the present study is to develop Gatifloxacin *in-situ* gel for sustained ophthalmic preparation. Gatifloxacin is an antibiotic that is used to treat bacterial infections; it stops the multiplication of bacteria by inhibiting the reproduction and repair of their genetic material (DNA).

Marketed eye drop solution cleared very rapidly from the corneal region whereas, both in-situ gelling systems were cleared at a slow rate and retained at the corneal surface for a longer duration

Gatifloxacin can be targeted in treatment of the bacterial infection and also reduce dosing frequency, increase bioavailability of Gatifloxacin that will result in better patient compliance with minimum side effects.

Thus, this project is planned to develop in-situ gel formulation of Gatifloxacin

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