DEVELOPMENT AND IN-VITRO EVALUATION OF TEMPERATURE SENSITIVE AND PH SENSITIVE IN-SITU OCULAR GEL OF DICLOFENAC SODIUM

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ABSTRACT

In-situ ocular gels are the systems, which are generally used in the form of solutions or suspensions. They are equipped for undergoing quick phase transformation from sol to gel activated by external factors (like temperature, pH etc.) on instillation in cul-de-sac of eye. The goal of the current investigation was “the formulation and evaluation of thermos and pH responsive in-situ gel for ophthalmic delivery”. Diclofenac sodium is famously consumed as NSAIDs for the treatment of postoperative aggravation in patients who have experienced cataract extraction, in transitory assistance of pain and photophobia undergoing corneal refractive medical procedure. Nonetheless, poor retention of drug concentration, prompt dilution on instillation, and wash out, diminishes the drug’s remedial advantages, when utilized in sort of ordinary eye drops. Ophthalmic gel with a muco-adhesive polymer (Poloxamer 407) was picked as it experiences instantaneous gel formation because of its thermo responsive nature. The carbopol 934 was additionally consolidated as a thickener and pH responsive so as to accomplish the perfect consistency for improved and controlled drug release. The developed formulation were evaluated for clarity, pH estimation, spreadability, FTIR study, gelling limit, drug content, thickness study, and in vitro drug release study in comparison with ordinary dosage form. Along these lines, in situ gel based system comprising thermo and pH responsive triggered system are often a crucial methodology for ophthalmic drug delivery in comparison to standard systems.

KEYWORDS: Ophthalmic; Inflammation; Conventional, Photophobia

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1. INTRODUCTION

The most intense issue encountered in ophthalmic drug delivery system is the maintenance and accomplishment of minimum drug concentration required at the target site inside the eye. Various dosage forms for ophthalmic use were accessible in market, such as ointments, ocular inserts, solutions; *in situ* gels that have been explored in an attempt to increase the bioavailability to extend the Increased pre-corneal residence time and decreased nasolacrimal drainage of medicine for topical use to the eye. The corneal contact time of drug has been expanded to variable degrees of instrument by these dosage forms. However, they have not been collectively acknowledged, because of blurred vision (e.g. ointments) or lack of patient compliance (e.g. inserts).

A large portion of the dosage form was used in suspensions or solutions form. Rapid pre-corneal elimination observed with traditional ocular dosages form ends in poor drug bio-availability. The eye drops having very poor

bioavailability due to their fast drainage of during lachrymation in tear fluid in eyes. Ease of direction in case of dosages fairly viscous solution and improved patient acceptability. Obscured vision and hydrogel dosage form including lachrymation.

In this way, these problems may be overwhelmed with the aid of fabricating the drug as a formulation that experiences *in-situ* gel formation upon immediate ophthalmic administration. The mechanism of in situ gel based on experiences gelation after instillation in the cu-de-ac conditioning of the eye due to physico-synthetic changes occurring in the eye. It is based on the thermal and pH sensitive. It expands bioavailability of medication due to the pre-corneal residence time and decreases the percentage drug loss from tear formulating in situ gel.

The current work is done based on the “formulation and evaluation of in situ gel forming ophthalmic formulation containing diclofenac sodium”. In which in situ gel phase transition sol-gel happens on the corneal surface. At the time of instillation dosage form structure is in the eye in solution phase and soon later after interacting with corneal layer and calcium ion with surrounding pH of 7.4 it transforms into transparent gel depo. In this manner, this sort of formulations has advantage of both the solutions and gels as they may improve the bioavailability by retention time of the formulation as well the drug, accuracy and ease of administration¹⁻³.

1.1 Drug Profile

1.1.1 Diclofenac Sodium

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken orally or applied as an analgesic to reduce pain and inflammation in certain conditions. It is supplied as or contained in medications under a variety of trade names⁴.

1.1.1.2 Structure

[Figure 1: about here]

1.1.1.3 Chemical Profile

- **IUPAC Name:-** [(2, 6-Dichlorophenyl) amino] benzene acetic acid sodium salt⁵
- **Molecular Formula:-** C₁₄H₁₀Cl₂NO₂•Na
- **Molecular Weight:-** 318.13
- **Appearance:** Slightly hygroscopic, crystalline powder, white to slightly yellowish.
- **Category:** Non-steroidal anti-inflammatory drug (NSAID)
- **Melting Point:** 283°- 285°C (Salt) 156°- 158°C (Free Acid)
- **Solubility:** Freely soluble in water, PBS (Phosphate buffer saline) pH 7.2, ethanol, methanol, and acetone.
- **Half Life :** 1-2 hr. (35% of the drug enters enterohepatic recirculation)
- **Bioavailability:** 79%
- **Uses:** In pain, inflammation and dysmenorrhea.

1.1.1.4 Mechanism of Action

The crucial mechanism behind its anti-inflammatory, anti-pyretic, and pain-relieving action is inhibition of synthesis of prostaglandins via cyclooxygenase (COX-2) inhibition. It also exhibits bacteriostatic activity by inhibiting bacterial DNA synthesis.

1.1.1.5 Adverse effect:

- Abdominal cramps or pain
- Hypersensitivity
- Constipation And Diarrhoea
- Dizziness, Nausea and Vomiting
- Hepatic toxicity
- Hematologic toxicity
- Renal Toxicity
- Hypertension
- Congestive Heart Failure
- Anaphylactic Reactions

In situ ocular gel system based on gelling systems comprise of polymer that can show phase transitions sol-to-gel stage in the cul-de-sac that leads to better patient compliance, persistent and prevent the loss of the medication through tear drainage because of change in definite physico-chemical factors like temperature, ionic changes, and pH changes in the environment. The phase transition sol-to-gel phase on the eye surface contingent upon the various strategies utilized which comprise of sensitivity towards temperature⁶, ion activation, pH, ultrasonic, chemical material, electric and attractive field. The present work is based on some of the most commonly used techniques, that are as per the following:

- Temperature dependent system (e.g. Pluronics and tetronics)
- PH-triggered system (e.g. cellulose acetate hydrogen phthalate latex)
- Temperature subordinate framework (e.g. pluronics and tetronics),
- Ion activated system (gelrite)⁷.

In situ visual gel based drug delivery system is composed of active pharmaceutical ingredients, co-polymer, polymers, and excipients. Poloxamer 407, an ophthalmic gel forming mucoadhesive polymer was picked because the polymer and thickness enhancer carbopol 934 is employed as copolymer.

Poloxamer are non-ionic poly (ethylene oxide) (PEO) – poly (propylene oxide) (PPO) copolymers. They are utilized in medicinal plans as dispersing agents, surfactants, gelling agents, emulsifiers, solubilizers, and *in-vivo* absorbance enhancer. Poloxamer are regularly regarded as "functional excipients" due to the fact that they are basic components and assume a significant job within the formulation. Poloxamer have comparative synthetic structures yet with different molecular weight and arrangement of the hydrophilic PEO block (a) and hydrophobic PPO block (b).

Carbopol Carbomers are synthetic polymers of acrylic acid with high atomic weight and are crosslinked with either allyl ethers of pentaerythritol or allyl sucrose. They contain 56-68% of carboxylic acid (- COOH) groups as determined on the dry basis. The PhEur has a solitary monograph describing carbomer in comparison with the USP that contains a few monographs illustrating individual carbomer grades that vary in aqueous viscosity and in labelling for oral or non-oral use⁸⁻¹².

2. MATERIAL AND METHOD

Diclofenac sodium was obtained from Arti drugs Ltd. Faridabad, Poloxamer 407 and carbopol obtained from. All other chemicals and reagents were of procured from CDH Chemicals and are of analytical grade.

2.1 ANALYTICAL METHOD DEVELOPMENT

2.1.1. Determination of $\lambda_{\max}$ of Diclofenac sodium: Different dilutions of diclofenac sodium were prepared in Water (as described above) and from the above solution one sample (8 μ g/ml) was taken and scanning was done in range of 200-400 nm using UV-Visible double beam Spectrophotometer. The UV peak was observed at 276 nm.

2.1.2. Preparation of standard curve of diclofenac sodium in different solvents

Standard curve of the drug diclofenac sodium was prepared in different solvents (water & phosphate buffer 6.8) and value of R^2 and slope were determined.

- Preparation of standard curve of diclofenac sodium in water
- Different dilutions of diclofenac sodium were prepared in water and water to give a conc. 3/30 μ g/ml. The absorbance of these solutions was determined against the water as blank at 276nm using UV-Visible double beam spectrometer.
- Standard curve of diclofenac sodium in phosphate buffer pH 6.8
- Different dilutions of diclofenac sodium were prepared in Phosphate Buffer pH 6.8 as described in chapter 6 to give solutions with concentration in the range final concentration 3-30 μ g/ml. The absorbance of these solutions was measured against the phosphate Buffer (pH 6.8) as blank at 276 nm using UV-Visible double beam spectrophotometer.

2.2 Formulation Development and Evaluation

In-situ gels were formulated by cold method. In this method, 10mg of drug was dissolve in 5ml of chilled distilled water (4°C). To this various concentration of Poloxamer- 407 were dissolved at cold conditions (4°C), formed solution a. And carbopol dissolved in 5ml of water and soaked in water for 24 hours. Then solution A is mixed in solution B in continuousstirring maintaining the temperature 4°C in water bath on magnetic stirrer. The numbers of formulation were made shown in table. Later drug was incorporated and stirred until clear solution was obtained. Finally it was kept overnight in (4-10°C) freezing conditions. ^[10]

2.3. CHARACTERIZATION AND EVALUATION OF OCULAR GEL

2.3.1 Clarity Test and Appearance of Formulations

All formulation was visually tested for gel preparation at different concentration of drug and polymer.

2.3.2 pH Estimation:

The pH of human eye and tears is found to be in the range of 7-7.4. But it can tolerate about 7-7.5. Prepared ophthalmic formulations should be within the range the tears'pHthat can tolerate in order to reduce eye irritation. pH of all formulations was tabulated in Table.

2.3.3 Drug Content

Each formulation 5 ml of was taken in a centrifuge and centrifuge in a cooling centrifuge at 15000 rpm for 30 min. Filter the solution with the aid of 0.45 μ pore size (Whatmann) filter paper. The content of the drug was estimated using UV-Spectrophotometer (Shimadzu UV – 1800, Japan) at 276nm.

2.3.4 Partition Coefficient

It was determined as the ratio of concentration of drug in octanol to the concentration of drug in water. The Partition coefficient values were calculated as log P.

Concentration of drug (non-aqueous phase)

$$K_{o/w} = \frac{\text{Concentration of drug (non-aqueous phase)}}{\text{Concentration of drug (aqueous phase)}}$$

Concentration of drug (aqueous phase)

[Table 1; about here]

2.3.4 FTIR Spectra ^[13]

The obtained FT-IR spectra's observed at wavelength 4000cm^{-1} - 400cm^{-1} are shown in **fig 6-8** and characteristic peaks are shown in **table 7-9**

2.3.5 Measurement of Viscosity

Viscosity measurement of the formulations was at 37 °C temperatures. Viscosity was checked by spindle no. 64 at different rpm of final formulation.

2.3.6 Spreadability of gel

The spreadability of ocular gel of final formulation f15 was observed $24.4 \pm 0.5 \text{ g.cm/sec}$.

2.3.7 In-vitro Drug release study

The in-vitro drug release of Formulation F15 and Pure drug was given in a **table 12**

3. RESULTS

3.1. Determination of λ_{max} of Diclofenac Sodium

The UV peak was observed at 276 nm.

[Figure 2: about here]

3.2. Preparation of standard curve of diclofenac sodium in different solvents

Standard curve of diclofenac sodium in water

[Table 2: about here]

[Figure 3: about here]

Standard curve of diclofenac sodium in phosphate buffer pH 6.8

[Table 3: about here]

[Figure 4: about here]

3.3. The different trails performed and the number of formulation prepared to optimizes the final formulation.

[Table 4; about here]

3.4. CHARACTERIZATION AND EVALUATION OF OCULAR GEL

3.4.1. Clarity Test and Appearance of Formulations

Clear gel was observed in the final formulation fl 5.

3.4.2. pH Estimation:

The pH of all gel formulation was found to be in a range of 7-7.4 that is between physiological ranges of pH of eye tear. ^[12]

[Table 5; about here]

3.4.3. Drug Content

The percentage of drug content was varied in between 73.12 ± 0.46 to 97.12 ± 0.11 .

[Table 6; about here]

[Figure 5; about here]

3.4.4. Partition coefficient

The partition coefficient of Diclofenac sodium in n- Octanol: Water was found to be 0.874 which specifies that the drug is of Hydrophilic nature.

3.4.5. FTIR Spectra

The obtained FT-IR spectra's were shown below:

- **FTIR Spectra of drug (diclofenac sodium)**

[Figure 6; about here]

[Table 7; about here]

- **FTIR spectra of physical mixture**

[Figure 7; about here]

[Table 8; about here]

- **FTIR Spectra of final formulation**

[Figure 8; about here]

[Table 9; about here]

2.4.6. Gelation and Gel Melting Point Temperature:

All the formulations tested for this study. Individual studied effect of excipients on gelation (T1) and gel m.p temperature (T2). The resulted values were shown in Table 11. Formulations F13 to F18 found to be as the concentration of Carbopol increased, the T1 decreased. Whereas the T2 was found to be increased. This might be due to greater number and volume occupied by the micelles at low temperature. Therefore gel range, broadens with the concentration of polymer. In all formulation it is observed that the Ploxomer-407 was used as gelling or viscosity enhancing agent. On its concentration an increased to T1 decreased and T2 an increased.

[Figure 9; about here]

[Table 10; about here]

2.4.7. Measurement of Viscosity

Viscosity measurement of the formulations was at 37 °C temperatures. Viscosities were checked by spindle no. 64 at different rpm of final formulation.

[Figure 10; about here]

[Table 11; about here]

2.4.8. Spreadability of Gel

The spreadability of ocular gel of final formulation f15 was observed 24.4±05g.cm/sec.

2.4.9. In-vitro Drug Release Study

The in-vitro drug release profile of Formulation F15 and Pure drug was given in a table 15

[Table 12; about here]

[Figure 11; about here]

2.4.10. In-vitro Drug Release Kinetic

Given below is the data of *in-vitro* drug release kinetic study of formulation F12.

- **Zero order**

[Figure 12; about here]

- **First Order**

[Figure 13; about here]

- **Higuchi**

[Figure 14; about here]

4. SUMMARY AND CONCLUSIONS

The present study, ocular *in-situ* gel of diclofenac sodium was effectively developed and assessed for its *in vitro* performance. The *in situ* gel of these formulations is responsible for facilitating enhancement of drug, bioavailability due to improved pre-corneal residence time and decreased lacrimal drug drainage.

The various performualtion study of drug was performed. The drug's melting point was determined by capillary fusion method and was found to be 283±0.76. Solubility of drug was more soluble in distilled water than 0.1N HCl and phosphate buffer (pH 6.8 and 7.2). One sample (8µg/ml) was taken and scanning was done in the range of 200-400 nm using UV-Visible Spectrophotometer. The UV peak was observed at 276 nm and standard curve equation was observed $y = 0.031x + 0.047$, $R^2 = 0.998$. FTIR spectra was shows the presence of functional group and confirm the presence of the drug in the formulation^{13,14}.

The *in-situ* gel was formed by the cold method that was based on thermo sensitive and pH sensitive system. Various trials were performed with poloxamer and carbopol to optimize the polymer concentration and final concentration optimizes were 17% and 0.3% respectively. The concentration were optimizes on the bases of their clarity, pH, gelling temperature, drug content, spreadability, viscosity and drug release. The final formulation evaluation results were pH of final formulation was observed 7.38 and gelling temperature was observed $36.52 \pm 0.55^\circ\text{C}$. Drug content 93.07% was observed. The viscosity of final gel prepared was studied by using Brookfield Viscometer Spindle S64 and viscosity at 10rpm, 60rpm, and 100 rpm were found to be 14800, 4740, 3370¹⁵.

The *in-vitro* release profile of the formulated *in-situ* gel was carried out via Franz diffusion cell. The drug release was observed 75% after 8 hours. Where, as marketed formulation eye drop of diclofenac sodium release 91% in 4 hours. The following result observed were conclude that *in-situ* gel provide sustained drug release in ocular drug delivery system and better bioavailability due to its increased pre-corneal residence time and decreased lacrimal drainage of the drug^{16,17}.

Almost certainly, the quantity of distributions, licenses and advances on the In situ gel are enlarging, however at a significant consistent pace. Impressive wariness and lack of care will in general fuel the hesitance to attempt examination into this moderately novel and more valuable in situ gel approach, which could somehow or another bring a great deal of break. Subsequently, it is the most advantageous chance to increase the exploration endeavours on these promising drug delivery system coordinated at overcoming the bioavailability improving production on large scale.

The current proposition is a genuine endeavour to give a holistic record on practically all the crucial terrains of the in situ gel formulations. This ought to give the ideal catalyst to the product development researcher, encouraging further evolution of in situ gel research and cutting edge product launches. Inevitably, the day isn't far when the advantages of in situ gel plans would be gathered by medicate industry and exploration gatherings to their fullest addition.

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TABLES

Table 1: Determination of partition coefficient

Partition coefficient of drug	Solvent system	Log p Values
Diclofenac sodium	n-octanol:water	0.884 ± 0.03

Table 2: Concentration of different dilution and their absorbance value

Sr. No.	Concentration µg /ml	Absorbance
1	3	0.134±0.003
2	6	0.231±0.002
3	9	0.337±0.005
4	12	0.427±0.001
5	15	0.533±0.002
6	18	0.628±0.007
7	21	0.743±0.005
8	24	0.823±0.002
9	27	0.898±0.001
10	30	0.986±0.005

Table 3: Concentration of different dilution and their absorbance value

Sr. No.	Concentration (µg/ml)	Absorbance
1	3	0.072±0.005
2	6	0.153±0.002
3	9	0.241±0.003
4	12	0.337±0.001
5	15	0.408±0.004
6	18	0.498±0.007
7	21	0.574±0.005
8	24	0.661±0.003
9	27	0.741±0.005
10	30	0.821±0.003

Table 4: List of number of formulation prepared.

SR.NO.	FORMULATION CODE	DRUG(Mg)	POLAXOMER 188 (CONC.)	POLAXOMER 407 (CONC.)	CARBOPOL934 (CONC)
1	F1	10	10%		
2	F2	10	15%		
3	F3	10	16%		
4	F4	10	17%		
5	F5	10	18%		
6	F6	10	19%		
7	F7	10	20%		
8	F8	10		15%	
9	F9	10		16%	
10	F10	10		17%	
11	F11	10		19%	
12	F12	10		20%	
13	F13	10		17%	.1%

14	F14	10		17%	.2%
15	F15	10		17%	.3%
16	F16	10		17%	.4%
17	F17	10		17%	.5%
18	F18	10		17%	.6%

Table 5: pH and Appearance of formulation:

S. No.	Formulation Code	PH	Appearance
1	F1	5.91	Gel not formed
2	F2	6.31	Gel not Formed
3	F3	6.51	Gel not Formed
4	F4	6.65	Gel not Formed
5	F5	5.7	Gel not Formed
6	F6	5.8	Gel not formed
7	F7	5.2	Gel not formed
8	F8	7.6	Less Viscous
9	F9	7.1	Less Viscous
10	F10	7.4	Less Viscous
11	F11	7.2	Less Viscous
12	F12	6.95	Less Viscous
13	F13	7.4	Less Viscous
14	F14	7.45	Less Viscous
15	F15	7.38	Gel formed
16	F16	7.4	Highly Viscous
17	F17	7.43	Highly Viscous
18	F18	7.42	Highly Viscous

Table 6: Drug content in formulation

S.No	Formulation Code	Per cent Drug Content
1	F1	95.02± 0.24
2	F2	94.34± 0.41
3	F3	93.21±0.34
4	F4	95.63± 0.42
5	F5	97.12± 0.11
6	F6	91.78± 0.38
7	F7	88.18± 0.24
8	F8	87.44± 0.36
9	F9	73.34± 0.24
10	F10	73.12± 0.46
11	F11	73.26±0.32
12	F12	75.68±0.62
13	F13	90.08±0.52
14	F14	90.67±0.24
15	F15	93.07±0.76
16	F16	92.56±0.41
17	F17	92.67±0.18
18	F18	93.80±0.90

Table 7: Interpretation of Diclofenac Sodium FT-IR spectrum

Characteristic peaks	Reported (cm ⁻¹)	Observed (cm ⁻¹)
C-Cl alkyl halides	850-550	839.93

C=O(aldehydes)	1740-1620	1665.07
-N-H(primary and secondary amine)	3400-3250	3383.67
C=C(alkenes)	1680-1640	1665.07
C-OH(alcohols)	3500-3200	3477.05

Table 8: Interpretation of physical mixture FT-IR spectrum

C-Cl alkyl halides	850-550	838.42
C=O(aldehydes)	1740-1620	1635.04
-N-H(primary and secondary amine)	3400-3250	3383.65
C=C(aromatic)	1680-1640	1665.07
C-OH(alcohols)	3500-3200	3253.67

Table 9: Interpretation of physical mixture FT-IR spectrum

C-Cl alkyl halides	850-550	799.67
C=O(aldehydes)	1740-1620	1637.09
-N-H(primary and secondary amine)	3400-3250	3353.13
C=C(aromatic)	1680-1630	1637.09
C-OH(alcohols)	3500-3200	3237.86

Table 10: Gelation and gel melting point temperature of formulations

S. No	Formulation Code	Gelation Tem. (T1°C)	Gel Melting Point Tem. (T2°C)
1	F13	35.23± 0.36	68.45±0.35
2	F14	35.26±0.25	70.23±0.05
3	F15	36.52±0.55	74.34±0.45
4	F16	35.22±0.55	72.34±0.45
5	F17	33.22±0.55	77.34±0.45
6	F18	32.22±0.55	78.34±0.45

Table 11: Viscosity of gel at different rpm of final formulation F15.

S. No	Viscosity of gel	R.P.M
1	10	14800
2	20	9470
3	30	7510
4	50	5220
5	60	4740
6	100	3370

Table 12: In-Vitro drug release data of optimized formulation (F) and drug dispersion

S.No.	Time (Hrs.)	%Drug release of Formulation	% marketed drug
1	0	0±0	0±0.00
2	0.083333	02.5±0.	01.25±
3	0.166667	04.06±0.	02.5±

4	0.25	05.62±	03.75±
5	0.5	08.43±	08.43±
6	1	10.93±	16.25±
7	1.5	14.68±	27.81±
8	2	19.37±	40.31±
9	2.5	24.06±	49.06±
10	3	28.75±	65.31±
11	3.5	33.75±	79.06±
12	4	38.43±	91.56±
13	4.5	43.43±	
14	5	48.43±	
15	5.5	53.12±	
16	6	58.43±	
17	6.5	63.43±	
18	7	67.81±	
19	7.5	72.5±	
20	8	75.62±	

FIGURES

Figure 1: Structure of Diclofenac sodium

Figure 2: UV Spectrum of the Drug in Water

Figure 3: Standard Curve of Diclofenac Sodium in Water

Figure 4: Standard curve of diclofenac sodium in phosphate buffer pH 6.8

Figure 7: FT-IR spectrum physical mixture

Figure 8: FT-IR spectrum of final formulation

Figure 9: Gelation and gel meting point temperature of formulations

Figure 10: Viscosity of gel final formulation F15

Figure 11: In-Vitro Drug release of Diclofenac sodium loaded ocular gel and pure drug.

Figure 12: Zero order graph of formulation F12

Figure 13: First order graph of formulation F15.

Figure 14: Higuchi order graph of formulation F12