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# FORMULATION AND EVALUATION OF FLURBIPROFEN OCULAR *IN-SITU* GEL

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**Keywords:**

*In-situ* gelling systems, Flurbiprofen, Carbopol 934, Carbopol 940, Carbopol 971 and HPMC E15, HPMC K4M, and HPMC K100, pH sensitive systems, Ocular delivery

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**ABSTRACT:** Conventional ophthalmic preparations exhibit poor bioavailability due to the rapid precorneal elimination of the drug, and the physiological constraints imposed by the protective mechanisms of the eye lead to the low absorption of the drugs resulting in a short duration of the therapeutic effect. In order to increase the residence time of the drug *in-situ* gelling systems were prepared and instilled as drops into the eye which undergo a sol-gel transition in the cul-de-sac. The present work describes the formulation and evaluation of flurbiprofen ocular *in-situ* gel, based on the concept of pH - triggered *in-situ* gelation. polyacrylic acid (carbopol) was used as the gelling agent in combination with hydroxy-propyl methyl cellulose (HPMC) which acted as a viscosity enhancing agent. The formulations were evaluated for clarity, pH measurement, gelling capacity, gelling temperature, drug content estimation, rheological study, *in-vitro* drug release study, sterility testing and stability studies. The physicochemical interactions between drug and polymers were investigated by fourier transform infrared (FTIR) spectroscopy. FTIR studies did not show any evidence of interaction between the drug and the polymers. The Formulation F22 (containing 1% HPMC E15, 0.3% carbopol 971) showed sustained release over a period of 8 h follows, first order mechanism.

**INTRODUCTION:** Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjunctiva, inflammation, eye flu *etc*. The protective mechanisms of the eye such as blinking, baseline and reflex lachrymation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles, including drugs, from the surface of the eye [1].

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Topically applied drugs do not reach the posterior segment of the eye (retina, vitreous, choroid); therefore systemic administration, per ocular or intraocular injections of drugs are normally applied in clinical therapeutics [2.] The unique anatomy and physiology of the eye and its protective barriers prevent the administered drugs from protecting into the target tissues.

There are many eye diseases which can affect the eye and also eye vision. Therefore marketed ophthalmic formulations are classified as conventional and non-conventional (novel) drug delivery systems [3]. There are most commonly available ophthalmic preparations such as drops and ointments which render 70% of the eye dosage formulations in the market.

But these preparations when installed into the eye are rapidly drained away from the ocular surface due to blinking tear flow and lachrymal nasal drainage of the eye. Only a small amount of the drug is available for its therapeutic effect resulting in need for frequent application to the eye [4]. So to overcome these problems novel pharmaceutical ophthalmic formulations such as *in-situ* gel, nanoparticle [5, 6] liposome, nano suspension [7, 8], micro emulsion [9], intophoresis and ocular inserts have been developed in last three decades to increase the bioavailability of the drug in a sustained and controlled manner.

Conventional ocular drug delivery systems like eye drops require frequent instillations to maintain a therapeutic drug level at the site of action, whereas, gels have difficulty in instillation into the eye. An alternative approach has been the application of *in-situ* gelling systems which are instilled in a liquid form and shift to a gel form in the cul-de-sac [11, 12]. The phase transition is triggered by the pH of the tears, the temperature at the eye surface or the electrolytes present in the tear film. Ophthalmic use of non-steroidal anti-inflammatory drugs (NSAIDs) offers several benefits after intraocular and refractive surgery [13]. NSAIDs also can reduce patients' intra - and postoperative pain; help maintain pupillary dilation, control inflammation after surgery. Flurbiprofen is a non-steriodal anti- inflammatory drug used to treat eye infections such as corneal ulcers, seasonal allergic conjunctivitis and reduce inflammation following cataract surgery.

**MATERIALS AND METHODS:** Flurbiprofen, carbopol (934, 940 and 971), HPMC (E15, K4M, K100) and ethanol.

**Preparation of *in-situ* Gels of Flurbiprofen:** Aqueous solutions of varying concentrations of different polymers and drug were prepared and evaluated for gelling capacity and viscosity in order to identify the compositions suitable for use as in situ gelling systems.

All ingredients were weighed accurately and the formulations were prepared by dispersing different grades of polymers carbopol (934, 940 and 971) solutions in different concentrations (0.1% w/v, 0.3% w/v, and 0.5% w/v) and HPMC (E15, K4M and K100) solutions in different concentrations (1% w/v and 1.5% w/v) in distilled water with continuous stirring until completely dispersed and allowed to hydrate overnight. Flurbiprofen (0.03%) was dissolved in 0.5 ml of ethanol and then added to the above polymeric solutions under constant stirring to obtain a uniform solution.

**TABLE 1: COMPOSITION OF *IN-SITU* GELLING SYSTEMS BY pH SENSITIVE SYSTEMS**

| Formulation code | Drug (%w/v) | Carbopol 934 (% w/v) | Carbopol 940 (% w/v) | Carbopol 971 (% w/v) | HPMC E15 (% w/v) | HPMC K4M (% w/v) | HPMC K100 (% w/v) | Benzalkonium chloride (% w/v) | Distilled water (% w/v) |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 0.03 | 0.1 | - | - | - | - | - | 0.02 | qs |
| F2 | 0.03 | 0.3 | - | - | - | - | - | 0.02 | qs |
| F3 | 0.03 | 0.5 | - | - | - | - | - | 0.02 | qs |
| F4 | 0.03 | - | 0.3 | - | - | - | - | 0.02 | qs |
| F5 | 0.03 | - | 0.5 | - | - | - | - | 0.02 | qs |
| F6 | 0.03 | - | - | 0.3 | - | - | - | 0.02 | qs |
| F7 | 0.03 | - | - | 0.5 | - | - | - | 0.02 | qs |
| F8 | 0.03 | - | - | - | 1 | - | - | 0.02 | qs |
| F9 | 0.03 | - | - | - | 1.5 | | - | 0.02 | qs |
| F10 | 0.03 | - | - | - | - | 1 | - | 0.02 | qs |
| F11 | 0.03 | - | - | - | - | 1.5 | - | 0.02 | qs |
| F12 | 0.03 | - | - | - | - | - | 1 | 0.02 | qs |
| F13 | 0.03 | - | - | - | - | - | 1.5 | 0.02 | qs |
| F14 | 0.03 | 0.3 | - | - | 1 | - | - | 0.02 | qs |
| F15 | 0.03 | - | 0.3 | - | - | 1 | - | 0.02 | qs |
| F16 | 0.03 | - | - | 0.3 | - | - | 1 | 0.02 | qs |
| F17 | 0.03 | - | 0.3 | - | - | - | 1 | 0.02 | qs |
| F18 | 0.03 | - | - | 0.3 | - | 1 | - | 0.02 | qs |
| F19 | 0.03 | 0.3 | - | - | - | 1 | - | 0.02 | qs |
| F20 | 0.03 | 0.3 | - | - | - | - | 1 | 0.02 | qs |
| F21 | 0.03 | - | 0.3 | - | 1 | - | - | 0.02 | qs |
| F22 | 0.03 | - | - | 0.3 | 1 | - | - | 0.02 | qs |

*qs to 100 ml

The pH of the solution was adjusted to 7.4 using 0.1N NaOH solution. Benzalkonium chloride (BKC) was then added to the above solution and mixing was confirmed until uniform and clear obtained. Final volume was made up by adding required amount of distilled water. All the formulations were terminally sterilized by auto-claving at 121 °C and 15 lb for 15 min.

**Evaluation of Ocular *in-situ* Gels:**

**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.

**pH:** The developed ophthalmic formulations were evaluated for pH using digital pH meter. Ophthalmic formulations should have a pH range in between 4.0 - 7.4.

**Drug Content:** Ocular *in-situ* gel of flurbiprofen was assayed by spectrophotometric analysis. The formulation (1 ml) was taken in a 100 ml volumetric flask diluted with simulated tear fluid (STF) pH 7.4 and was shaken to dissolve the drug in STF pH 7.4. The solution was filtered through Whatman filter paper; this filtrate was further diluted if necessary with PBS pH 7.4. Drug content was determined using a shimadzu UV 1800 double beam spectrophotometer at 247 nm. [5]

**Measurement of Gelling Capacity:** The prepared *in-situ* gelling system was evaluated for gelling capacity in order to identify the composition suitable for use as *in-situ* gelling systems. The *in-situ* gelling system was mixed with simulated tear fluid (in the proportion of 25:7 which means the application volume of 25 µl and normal volume of tear fluid in the eye is 7 µl) to find out the gelling capacity of the ophthalmic product. The gelation was then visually assessed by noting the time for gelation and time taken for the gel formed to dissolve.

**TABLE 2: EVALUATION OF CLARITY, pH, DRUG CONTENT AND GELLING CAPACITY OF ALL FORMULATIONS**

| Formulation code | Clarity | pH | Drug content | Gelling capacity |
|---|---|---|---|---|
| F1 | Clear | 7.2 | 98.3±1.1 | + |
| F2 | Clear | 7.0 | 99.7±1.2 | + |
| F3 | Clear | 7.3 | 101.3±0.9 | ++ |
| F4 | Clear | 7.0 | 97.9±1.3 | ++ |
| F5 | Clear | 7.0 | 99.9±1.1 | ++ |
| F6 | Clear | 7.1 | 99.3±0.9 | ++ |
| F7 | Clear | 7.2 | 99.5±0.5 | +++ |
| F8 | Clear | 7.0 | 98.5±0.6 | ++ |
| F9 | Clear | 7.1 | 99.1±0.1 | ++ |
| F10 | Clear | 6.9 | 98.7±1.1 | + |
| F11 | Clear | 6.7 | 99.1±0.3 | + |

**TABLE 3: EVALUATION OF CLARITY, pH, DRUG CONTENT AND GELLING CAPACITY OF ALL FORMULATIONS**

| Formulation code | Clarity | pH | Drug content | Gelling capacity |
|---|---|---|---|---|
| F12 | Cloudy | 6.5 | 102.3±0.2 | S |
| F13 | Cloudy | 6.6 | 98.7±0.6 | S |
| F14 | Clear | 7.3 | 98.7±1.1 | ++ |
| F15 | Clear | 7.1 | 98.5±0.7 | ++ |
| F16 | Cloudy | 6.8 | 96.5±0.5 | S |
| F17 | Cloudy | 6.7 | 97.5±1.1 | S |
| F18 | Clear | 7.0 | 99.1±1.3 | + |
| F19 | Clear | 7.1 | 98.4±1.3 | + |
| F20 | Cloudy | 6.9 | 99.5±1.0 | S |
| F21 | Clear | 7.2 | 99.6±1.0 | + |
| F22 | Clear | 7.4 | 99.5±0.5 | +++ |

*Mean ± SD, n = 3, ‘‘+’’: gels after a few minutes, dissolves rapidly; ‘‘++’’: gelation immediate, remains for few hours; ‘‘+++’’: gelation immediate, remains for extended period; ‘‘s’’: gelation immediate, remains for extended period but gels are stiff

**TABLE 4: EVALUATION OF VISCOSITY OF ALL FORMULATIONS**

| Formulation code | Viscosity (cp) at 20 rpm | | Formulation code | Viscosity (cp) at 20 rpm | |
|---|---|---|---|---|---|
| | Before gelation (25 °C) | After gelation (37 °C) | | Before gelation (25 °C) | After gelation (37 °C) |
| F1 | 117 | 980 | F12 | 912 | 2166 |
| F2 | 192 | 1128 | F13 | 989 | 2331 |
| F3 | 675 | 2005 | F14 | 698 | 1433 |
| F4 | 586 | 2341 | F15 | 735 | 1554 |
| F5 | 600 | 1468 | F16 | 1003 | 2443 |
| F6 | 656 | 1669 | F17 | 1243 | 2256 |
| F7 | 768 | 1985 | F18 | 512 | 1992 |
| F8 | 832 | 1764 | F19 | 326 | 1008 |
| F9 | 884 | 2052 | F20 | 1126 | 2892 |
| F10 | 497 | 1296 | F21 | 776 | 2257 |
| F11 | 634 | 1945 | | | |

**Rheological Studies:** Rheological studies were conducted using a Brookfield synchroelectric viscometer (LVDV Pro II). The developed formulation was poured into the small sample adaptor of the brookfield synchroelectric viscometer [11] and the viscosity was measured at non-physiological (pH 4 and 25 °C) and physio-logical condition (pH 7.4 and 37 °C) respectively.

**TABLE 5: VISCOSITIES OF OPTIMIZED *IN-SITU GEL* FORMULATIONS AT DIFFERENT RPM**

| RPM | F22 | |
|---|---|---|
| | Viscosty (cp) | |
| | Before gelation (25 °C) | After gelation (37 °C) |
| 10 | 300 | 1026 |
| 20 | 274 | 980 |
| 30 | 215 | 880 |
| 50 | 192 | 653 |
| 100 | 145 | 540 |

***In-vitro* Diffusion Studies:** *In-vitro* drug release study of the formulation was carried out by diffusion process. It was performed on Franz diffusion cell using semi permeable membrane was soaked overnight in the receptor medium (STF, pH 7.4) and tied to one end of the glass diffusion cell.

**TABLE 6: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F1 TO F4**

| Time-h | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| 1 | 3.20±1.150 | 9.61±2.423 | 14.5±2.995 | 18.9±1.885 |
| 2 | 4.81±2.000 | 13.9±2.905 | 18.2±3.756 | 27.1±4.108 |
| 3 | 7.11±2.189 | 18.4±3.196 | 25.1±1.015 | 32.5±3.392 |
| 4 | 10.8±2.469 | 23.2±3.007 | 30.6±2.027 | 37.2±3.407 |
| 5 | 14.3±2.852 | 28.2±4.467 | 35.6±2.955 | 42.6±4.107 |
| 6 | 18.9±3.569 | 32.1±3.049 | 41.6±3.307 | 48.8±4.657 |
| 7 | 23.2±4.400 | 34.4±3.881 | 46.5±3.968 | 54.2±3.510 |
| 8 | 28.2±4.914 | 36.8±4.883 | 51.9±4.086 | 60.0±2.885 |

**TABLE 7: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F5 TO F8**

| Time-h | F5 | F6 | F7 | F8 |
|---|---|---|---|---|
| 1 | 31.0±2.516 | 26.5±1.607 | 36.8±0.642 | 23.2±0.916 |
| 2 | 42.6±1.882 | 29.4±1.587 | 42.2±2.005 | 30.5±1.527 |
| 3 | 50.6±3.000 | 34.8±1.677 | 44.9±3.066 | 31.9±1.050 |
| 4 | 54.4±2.008 | 44.5±1.607 | 51.1±2.150 | 36.8±1.527 |
| 5 | 57.3±1.401 | 50.0±2.081 | 57.3±1.686 | 42.4±2.523 |
| 6 | 63.9±0.550 | 52.3±3.027 | 62.6±2.884 | 46.5±4.700 |
| 7 | 67.3±1.527 | 56.7±2.502 | 67.4±3.094 | 51.3±3.482 |
| 8 | 69.7±2.400 | 62.4±3.055 | 70.9±2.951 | 60.1±2.950 |

**TABLE 8: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F9 TO F12**

| Time-h | F9 | F10 | F11 | F12 |
|---|---|---|---|---|
| 1 | 8.10±1.185 | 12.5±1.054 | 8.10±2.042 | 11.2±1.442 |
| 2 | 11.2±1.845 | 18.6±2.950 | 11.4±2.081 | 16.6±3.353 |
| 3 | 13.5±1.755 | 25.1±1.648 | 17.7±2.451 | 25.1±2.478 |
| 4 | 18.4±1.379 | 33.5±1.250 | 23.8±1.594 | 36±2.605 |
| 5 | 24.8±1.267 | 40.6±2.100 | 32.3±2.370 | 46.8±3.686 |
| 6 | 29.8±3.511 | 48.4±2.708 | 36.6±3.931 | 52.3±4.005 |
| 7 | 34.4±2.500 | 56.2±4.574 | 45.7±1.824 | 57.7±2.930 |
| 8 | 44.5±4.273 | 68.9±1.606 | 50.7±2.605 | 65.8±2.461 |

The donar compartment was filled with 1 ml formulation and the receptor compartment was filled with 25 ml of simulated tear fluid, assuring that the membrane was just touched the receptor surface. The whole assembly was adjusted on a magnetic stirrer and the temperature was maintained at 34 ± 0.5 °C. Aliquots were diluted with the stimulated tear fluid and analyzed by UV-visible spectrophotometer at 247 nm.

**TABLE 9: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F13 TO F16**

| Time-h | F13 | F14 | F15 | F16 |
|---|---|---|---|---|
| 1 | 10.0±1.958 | 5.80±1.539 | 10.3±2.225 | 7.70±1.692 |
| 2 | 16.6±2.802 | 12.5±1.654 | 16.2±5.040 | 16.6±4.080 |
| 3 | 24.7±3.254 | 17.8±4.088 | 28.6±3.358 | 29.6±3.840 |
| 4 | 28.2±3.561 | 28.6±2.753 | 36.9±3.111 | 37.5±4.349 |
| 5 | 32.5±4.181 | 36.9±3.922 | 45.7±2.897 | 47.0±2.884 |
| 6 | 37.7±3.892 | 46.5±3.288 | 54.2±3.401 | 53.4±2.326 |
| 7 | 45.1±4.443 | 53.8±4.440 | 68.4±0.949 | 61.6±3.709 |
| 8 | 53.4±3.357 | 67.4±3.635 | 72.8±1.038 | 65.0±2.599 |

**TABLE 10: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F17 TO F21**

| Time-h | F17 | F18 | F19 | F20 | F21 |
|---|---|---|---|---|---|
| 1 | 8.43 ±2.851 | 12.5 ±3.151 | 10.4 ±3.511 | 7.30 ±0.862 | 11.2 ±1.442 |
| 2 | 14.8 ±4.132 | 18.9 ±4.279 | 16.2 ±3.991 | 14.3 ±1.950 | 15.5 ±2.753 |
| 3 | 21.3 ±2.321 | 26.7 ±4.955 | 28.6 ±3.597 | 22.4 ±2.951 | 24.8 ±4.233 |
| 4 | 25 ±3.908 | 33.3 ±4.755 | 35.4 ±4.009 | 27.5 ±2.876 | 29.8 ±2.882 |
| 5 | 32.5 ±3.774 | 43.6 ±5.118 | 41.6 ±4392 | 34.1 ±4.324 | 36.6 ±3.941 |
| 6 | 35.6 ±5.641 | 51.1 ±4.352 | 47.6 ±5.296 | 42.6 ±3.222 | 44.3 ±3.959 |
| 7 | 45.7 ±4.654 | 61.6 ±3.154 | 57.7 ±3.745 | 50.9 ±2.615 | 60.3 ±4.639 |
| 8 | 51.5 ±4.669 | 67.8 ±3.514 | 64.3 ±4.720 | 60.4 ±2.142 | 63.9 ±4.824 |

## Optimised Formula:

**TABLE 11: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F22**

| Time-h | % Drug release |
|---|---|
| 0 | 0±0.00 |
| 1 | 16.2±1.15 |
| 2 | 30.5±2.67 |
| 3 | 55.6±3.87 |
| 4 | 60.5±3.57 |
| 5 | 69.7±2.98 |
| 6 | 76.6±4.34 |
| 7 | 80.5±3.85 |
| 8 | 86.7±4.97 |

## Sterility Studies:

**TABLE 12: TEST OF STERILITY**

| Formulation code | Days of incubation | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| T5 | - | - | - | - | - | - | - |
| P8 | - | - | - | - | - | - | - |

Where " - " sign indicate no growth

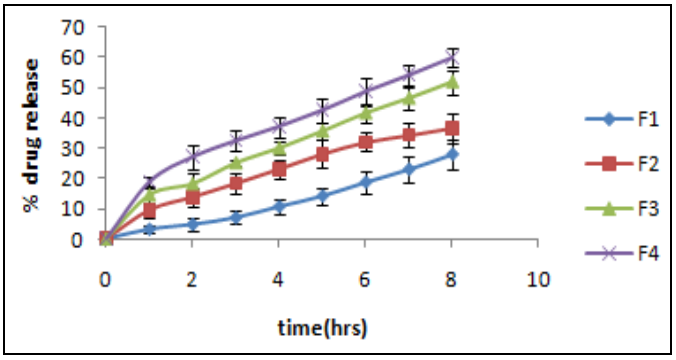


**FIG. 1: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F1 TO F4**

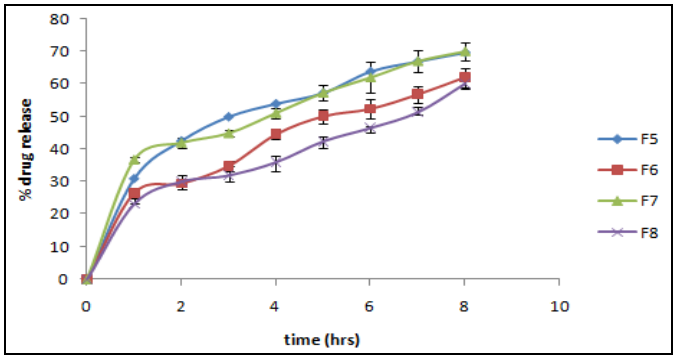


**FIG. 2: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F5 TO F8**

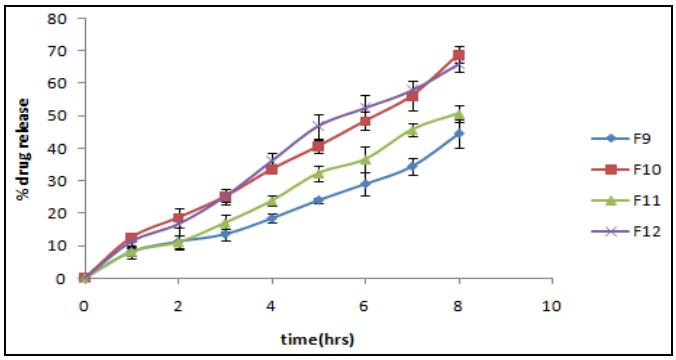


**FIG. 3: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F9 TO F12**

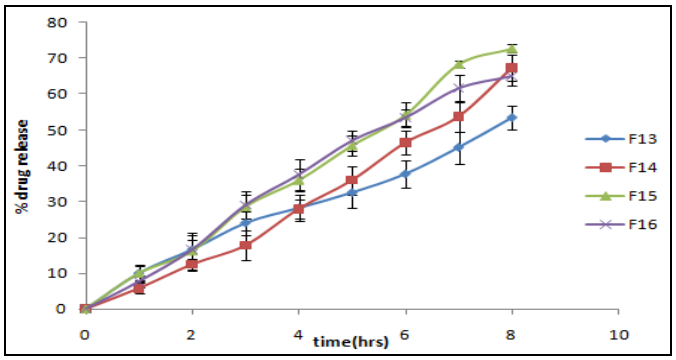


**FIG. 4: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F13 TO F16**

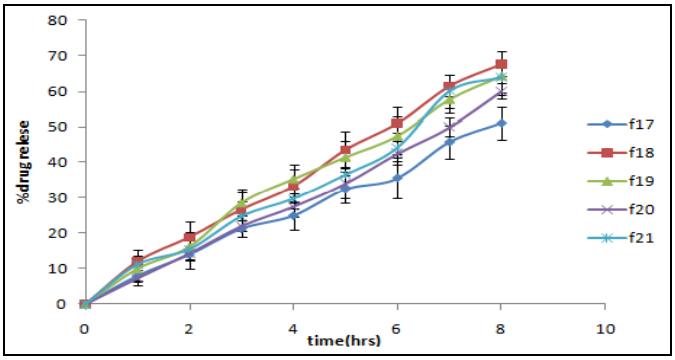


**FIG. 5: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F17 TO F21**

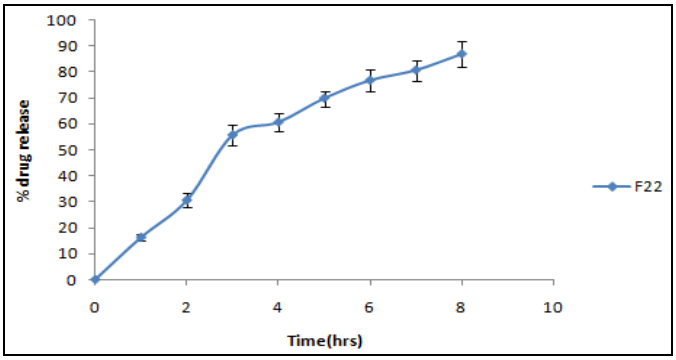


**FIG. 6: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATION F22**

The optimised formulation F22 were evaluated for the sterility. After 7 days of incubation the results showed no microbial growth in the formulation.

**CONCLUSION:** In this study, ophthalmic in situ gelling system of flurbiprofen was successfully formulated with polymers carbopol 934, carbopol 940, carbopol 971 and HPMC E15, HPMC K4M, HPMC K100 for pH- triggered *in-situ* gelling system. Flurbiprofen, is a non-steriodal anti-inflammatory agent used in the treatment of ocular inflammations. Optimized formulation F22, flurbiprofen (0.03% w/v %) using carbopol 971 (0.3% w/v %) as a gelling agent in combination with HPMC E15 (1% w/v) as a viscosity enhancing agent.

The formulation underwent gelation in the cul-de-sac upon instillation as drops into the eyes. The formulation was found to be clear, having good in situ gelling capacity. Optimized formulation was sterile and showed sustained drug release over 8 h period. The formulation showed sustained drug release with prolonged drug residence time, thereby increasing the effectiveness of the drug by localization at the site of action.

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