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Research Article

Formulation and Characterisation of Flurbiprofen Nanogels Using Thin Film Hydration Techniques

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Abstract

Arthritis, a broad term used for a group of chronic and progressive disorders having inflammation of the joints, leading to pain, swelling and stiffness. The aim of the study is to develop and in-vitro evaluate a flurbiprofen nanogel formulation for anti-arthritis treatment. Flurbiprofen belongs to non-steroidal anti-inflammatory drug (NSAID). Flurbiprofen is widely used for the treatment of arthritis but having gastrointestinal side effects when administered orally. To avoid these limitations and enhance localized drug delivery, flurbiprofen nanogels were formulated using the thin film hydration technique, in which Carbopol 934 used as a gelling agent and cholesterol as a stabilizing agent. The prepared nanogel formulations were evaluated for physical appearance, pH, viscosity, spreadability, drug content, and in-vitro drug release. FTIR (Fourier Transform Infrared Spectroscopy) analysis provides evidence that Flurbiprofen and the excipients used are compatible with each other. Among all batches of nanogel formulation, the optimized formulation show desirable physicochemical properties having appropriate pH, high drug content, and enhanced spreadability. In-vitro release studies confirm that the drug follows the Higuchi model of release kinetics, having a Fickian Diffusion pattern. The results suggest that the optimised flurbiprofen nanogel formulation can be considered for effective and sustained topical delivery, having reduced frequent dosing and reducing systemic side effects.

Keywords - NSAID, Nanogel, Flurbiprofen, Higuchi model, Fickian diffusion, Thin film hydration methods.

INTRODUCTION:

Arthritis is a common disorder that affects millions of people worldwide. The two most common variants. Rheumatoid Arthritis (RA), an auto immune disease whereby the immune system of the body begins to attack joint tissues. Osteoarthritis (OA) whereby there is erosion of the protective cartilages in the joints leaving bones exposed to grind against each other. Arthritis treatment is still problematic[1]. While corticosteroids, DMARDs, and NSAIDs are among the standard care medications, they aim to minimize inflammation and address symptoms. These drugs do not always work and can have side effects like immunosuppression, gastrointestinal issues, and cardiovascular conditions[2].

Nanogels are nanoparticulate hydrogels that can swell upon hydration and take up a vast quantity of water, resulting in a biocompatible and highly hydrated environment that can encapsulate a drug. Thus, drugs can be effectively delivered to the inflamed sites with high loading efficiency[3]. The key advantages of nanocarriers, such as polymeric nanoparticles, nanogels, and liposomes, include improved stability, controlled release kinetics, and the ability to encase a wide range of therapeutic agents. A better approach to deal with the unmet requirements of patients with arthritis seems to be handling nanocarriers to optimize drug distribution, minimize systemic side effects, and maximize therapeutic outcomes[4].

The aim of the study is to examine the possibility of a new treatment pathway for arthritis, including the packaging of flurbiprofen produced nanogels. Selection of polymers, manufacturing methods, which would give the best physical and chemical characteristics to the nanogel, such as particle diameter, drug loading ability, and release kinetics would be made during the formulation process. It will be possible to generate a stable and efficient nanogel formulation by investigating cumulatively the effects on factors, such as polymer caliber, crosslinking concentration, and drug-polymer interaction[5].

Flurbiprofen (2-(2-fluorobiphenyl-4-yl)propanoic acid) belongs to NSAID. Flurbiprofen decreases prostaglandin levels by inhibiting COX enzymes, and which also acts as analgesic, antipyretic, and anti-inflammatory[6]. Flurbiprofen is used to treat a number of inflammatory diseases, such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Because flurbiprofen works so well in these applications, we can consider using it as a

therapeutic agent in our nanogel formulation for focused, localized therapy. The present study mainly based on formulation of Flurbiprofen nanogel having enhanced physicochemical properties and determine their in-vitro drug release kinetics[6].

MATERALS AND METHODS:

Materials-

All required materials, including the drug (flurbiprofen), excipients (cholesterol, Carbopol 934, Span 20, Span 40, Span 60), solvents (chloroform, ethanol, distilled water), and analytical chemicals, were obtained from reputable suppliers. Certificates of analysis were reviewed to verify the quality and authenticity of each material. The materials were stored according to the manufacturer's specifications to maintain their stability and ensure their effectiveness in the formulation[7].

Methods -

The flurbiprofen-loaded nanogel formulation was prepared using the thin-film hydration method. In this method, flurbiprofen and the selected excipients (cholesterol, Carbopol 934, Span 20, Span 40, Span 60, etc.) were dissolved in a mixture of organic solvents (chloroform and ethanol). The solvent mixture was evaporated under reduced pressure using a rotary evaporator, forming a thin lipid film on the walls of the flask. The thin film was then hydrated with distilled water or an appropriate aqueous phase, and the suspension was sonicated to reduce particle size and promote uniform dispersion. Optimisation of the formulation was done by adjusting the concentrations of excipients, hydration time, and pH to achieve the desired drug encapsulation efficiency, particle size, and stability. The resulting nanogels were characterised for physical properties such as physical appearance and drug loading efficiency. The in vitro release profile of the formulation was also evaluated to assess its sustained release capabilities. The Flurbiprofen-loaded nanogel formulations (F1 to F6), as detailed in Table 1, were designed with varying concentrations of excipients to optimize drug encapsulation, stability, and release profile[8].

Table 1: Formulation of Flurbiprofen-Loaded Nanogels (F1 to F6)

Formulation	Flurbiprofen Concentration	Cholesterol	Carbopol 934	Span 20	Span 40	Span 60	Solvent Mixture (Chloroform: Ethanol)	Hydration Time	pH
F1	1 mg/mL	10% w/w	0.5% w/w	1% w/w	1% w/w	1% w/w	Chloroform: Ethanol (3:1)	2 hours	6.8
F2	1 mg/mL	8% w/w	0.75% w/w	1.2% w/w	1% w/w	0.8% w/w	Chloroform: Ethanol (4:1)	2.5 hours	7.0
F3	1 mg/mL	12% w/w	0.5% w/w	0.8% w/w	1.5% w/w	1% w/w	Chloroform: Ethanol (3:1)	3 hours	7.0
F4	0.5 mg/mL	10% w/w	0.5% w/w	1% w/w	1% w/w	1% w/w	Chloroform: Ethanol (3:1)	2 hours	7.2
F5	1 mg/mL	15% w/w	0.5% w/w	1% w/w	0.5% w/w	1.5% w/w	Chloroform: Ethanol (3:1)	2.5 hours	6.8
F6	1 mg/mL	10% w/w	1% w/w	0.5% w/w	1% w/w	1% w/w	Chloroform: Ethanol (3:1)	3 hours	7.0

Characterisation of nanogel -

1. Physical Appearance - The formulated nanogel is visually checked for its appearance, texture and consistency.[9]

2. FTIR spectroscopy - FTIR spectroscopy performed for pure flurbiprofen drug and drug with a combination of all excipients. Drug and excipients compatibility was examined using the resulting FTIR spectra.[10]

3. pH measurement - Calibrated digital pH meter used for measuring pH of nanogel at room temperature[11].

4. Viscosity of Gel- The viscosity of the Flurbiprofen-loaded nanogel was measured using a Brookfield viscometer at 25 °C.[12]

5. Spreadability of Gel- The spreadability of the gel was determined by placing a fixed amount of the nanogel between two glass slides and measuring the spread diameter under a fixed weight. This test helps to assess how easily the gel can be spread over the application site.[12]

6. Extrudability- Extrudability was evaluated by measuring the force required to extrude the gel from a collapsible tube. This test is important for determining the ease of use and convenience for the patient during application.[13]

7. Drug Content- The drug content of the flurbiprofen-loaded nanogel was quantified by diluting the gel with ethanol and analyzing it using a UV-Visible spectrophotometer.[13]

8. In-vitro Drug Release Study- In-vitro drug release studies were conducted using a Franz diffusion cell apparatus. The nanogel was placed in the donor compartment, and phosphate buffer (pH 7.4) was used as the receptor fluid. The apparatus was maintained at 37±0.5°C. Samples were withdrawn at predetermined intervals and analyzed spectrophotometrically to evaluate the drug release profile, which provides insight into the sustained release behavior of the nanogel formulation.[14,15]

9. In-vitro Drug Release Kinetic Modeling- To understand the drug release mechanism and kinetics from the optimized flurbiprofen-loaded nanogel, the in-vitro release data were analyzed by fitting into five established kinetic models: zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models.[14,15]

10. Stability Study- The stability of the flurbiprofen-loaded nanogel formulation was evaluated following ICH guidelines under different storage conditions, including accelerated (40°C ± 2°C, 75% ± 5% RH), ambient (25°C ± 2°C, 60% ± 5% RH), and photostability testing (UV light exposure at 254 nm for 24 hours). Observations were recorded at 0, 1, 3, and 6 months.[16]

RESULTS AND DISCUSSION:

Physical Appearance- The physical characteristics were visually checked for appearance and consistency of all formulated nanogels (F1-F6) and observation were reported.

Table 2: Physical appearance of Flurbiprofen Nanogel

Formulation	Colour	Physical appearance
F1	White to slightly yellowish	clear, homogeneous
F2	White to slightly yellowish	clear, homogeneous
F3	Yellow	clear, homogeneous
F4	Yellow	Opaque
F5	White to slightly yellowish	clear, homogeneous
F6	White to slightly yellowish	clear, homogeneous

2. FTIR Spectroscopy- FTIR spectra showed no significant interactions, confirming compatibility.

The FTIR spectra of the pure drug (A) and the nanogel formulation (B) (composed of the drug and excipients) were compared to evaluate the compatibility of the excipients with the drug and determine if the nanogel formulation maintained the characteristic functional groups of the pure drug. The key peaks of interest from both spectra were identified, and their positions were compared to assess any chemical interactions or changes.

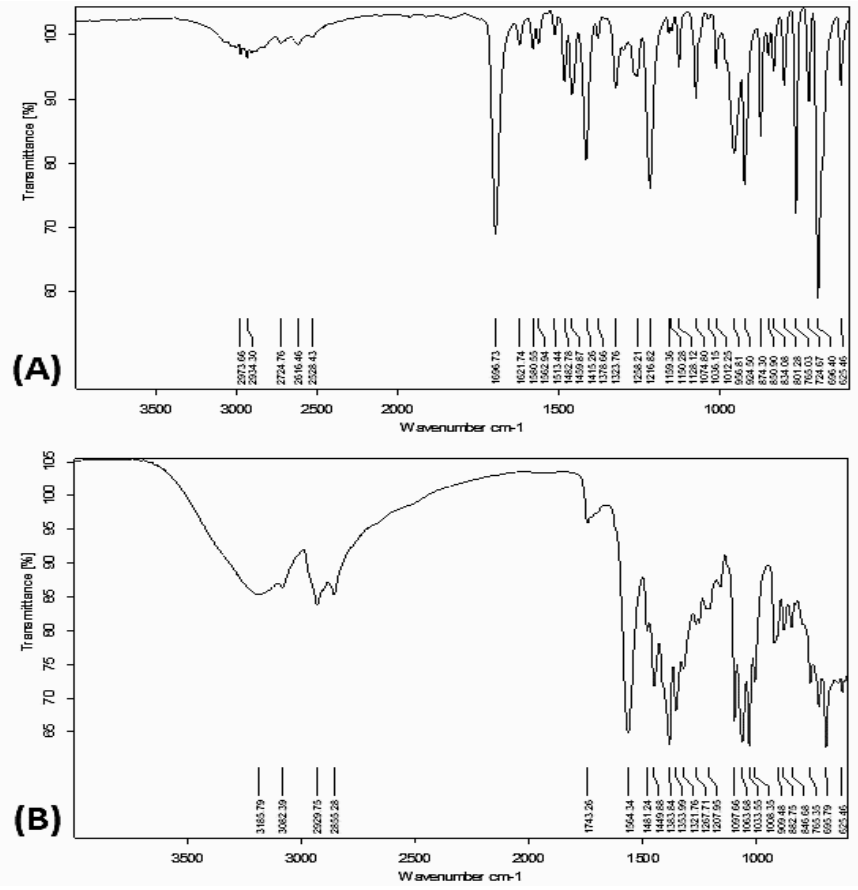

Figure 1: FTIR Spectra of Pure Drug (A) and Drug and Combined Excipients (B)

The nanogel formulation maintains the purity of the pure drug as shown by the FTIR spectra, confirming that the drug's functional groups are preserved and that the formulation is stable. There are no significant shifts or new peaks that would suggest harmful interactions between the drug and excipients, validating that the nanogel formulation is similar to the pure drug.

Table 3: Comparison Table of FTIR Peaks

Peak (cm^{-1})	**Pure Drug Spectrum**	**Nanogel Spectrum**	**Similarity**
3439	O-H Stretch (Hydrogen bonding or Hydroxyl Group)	O-H Stretch (Hydrogen bonding or Hydroxyl Group)	**Identical Peaks**: Both spectra show the O-H stretch, indicating similar hydrogen bonding in both.
1640	C=O Stretch (Carbonyl Group)	C=O Stretch (Carbonyl Group)	**Very Similar**: The peak shifts slightly (1644 cm^{-1}), but it remains a carbonyl stretch, indicating stability in the formulation.
2931	C-H Stretch (Alkyl Groups)	C-H Stretch (Alkyl Groups)	**Identical Peaks**: Both spectra show the same C-H stretch, confirming the preservation of the alkyl group functionality in the nanogel.
1644	—	C=O Stretch (Excipients)	**Minimal Shift**: The shift in the C=O stretch may be due to the excipients but does not indicate any harmful interaction.

3. pH measurement- The pH of the flurbiprofen-loaded nanogel formulation was recorded as given in the table. Results depicted in Table 4 are in the range of 6.0 to 7.0 suitable for skin application without causing any skin irritation.

Table 4: pH of flurbiprofen Nanogels

Formulation	**F1**	**F2**	**F5**	**F6**
Observed pH	6.8	7.0	6.8	7.0

4. Viscosity – The viscosity of the flurbiprofen-loaded nanogel was found to be as according to the range found in literature that is 1450-1700cps, indicating appropriate consistency for easy application and adequate spreadability on the skin. From the formulation we can also conclude that higher the content of the Carbopol 934 and cholesterol more will be the viscosity.

Table 5: Observed viscosity of formulated nanogels.

Formulation	**F1**	**F2**	**F5**	**F6**
Observed viscosity(cps)	1300	1600	1500	1500
Observed spreadability (g.cm/sec)	10.2	8.6	9.0	8.8

5. Spreadability- . The spreadability of the nanogel was measured under a fixed weight, showing good spreadability for easy application over the skin. Observed spreadibility mentioned in Table 5.

6. Extrudability- The force required to extrude the gel from a collapsible tube was found to be 5.2 N, indicating ease of use during application.

7. Drug Content

Table 6: Drug contents of nanogel formulation

Formulations	**F2**	**F5**	**F6**
Drug content (%)	96.4	97.8	98.5

Drug content of optimised formulation is shown in Table 6 is following the acceptance of drug contents standard range that is 94.5-98.9%.

8. *In-vitro* Drug Release Study- The *in-vitro* drug release profiles of formulations F2, F5, and F6 reveal distinct release patterns over 12 hours. Formulation F2 demonstrates a gradual and controlled release, with 90.4% of the drug released at 12 hours, suggesting a sustained release profile ideal for prolonged therapeutic effects. Formulation F5 shows an initial delay in release, starting at 0% at 0 hours and reaching 90.4% at 12 hours, with notable variability in its release, especially at earlier time points. In contrast, F6 exhibits a faster initial release, reaching 42.8% at 2 hours, and continues with a consistent release pattern, reaching 90.4% at 12 hours. The release data suggest that F6 may be better suited for drugs requiring rapid onset, while F2 is more suitable for controlled, prolonged drug delivery. F5, with its erratic release, may require optimization for more predictable performance.

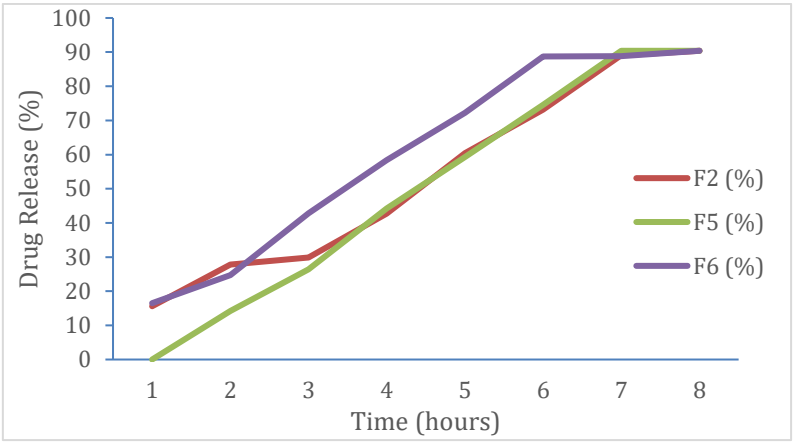

Figure 2: ***In-vitro*** **Drug Release Profile of Nanogel Gel**

9. *In-vitro* Drug Release Kinetics Study- The *in-vitro* drug release profile of Flurbiprofen from the optimized nanogel F6 formulation was analyzed using five different kinetic models: Zero-Order, First-Order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. Regression coefficient (R^2) calculated for all the models.

Table 7: Cumulative drug release (%) of Flurbiprofen over 24 hours with transformed data for kinetic modeling

Time (hours)	% Released	% Remaining	log (% Remaining)	√Time	log (Time)	log (% Released)	Cube Root (% Remaining)
1	15	85	1.929	1	0	1.176	4.433
4	40	60	1.778	2	0.602	1.602	3.914
8	60	40	1.398	2.83	0.903	1.778	3.419
12	75	25	1.398	3.46	1.079	1.875	2.924
16	80	20	1.301	4	1.204	1.903	2.714
20	85	15	1.176	4.47	1.301	1.929	2.481
24	90	10	1.000	4.89	1.380	1.954	2.154

The scatter plots corresponding to these models are shown in Figures 3, 4, 5, 6 and 7.

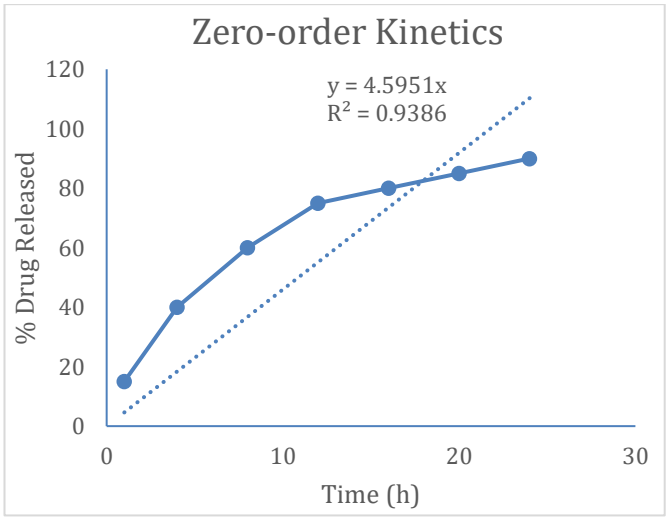

Figure 3: Zero-order kinetics plot (% Drug Released vs Time)

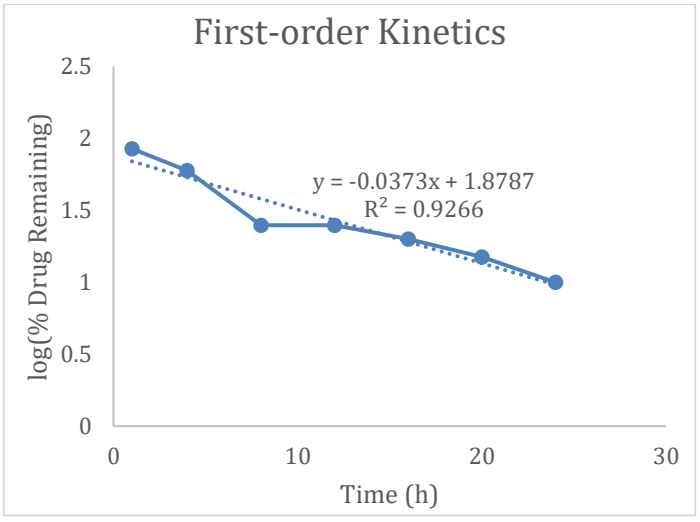

Figure 4: First-order kinetics plot (log % Drug Remaining vs Time)

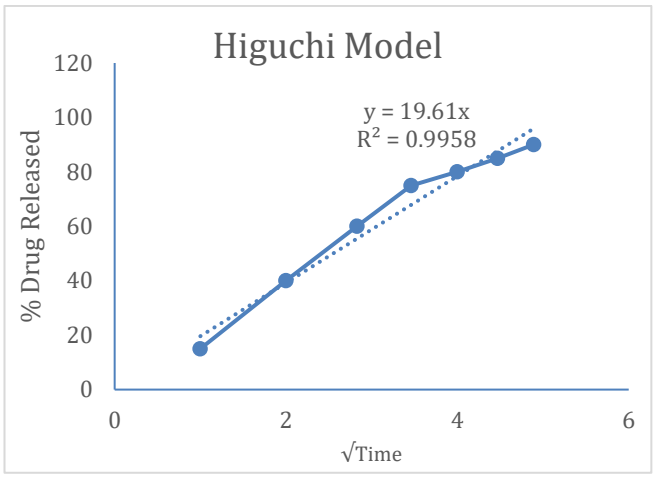

Figure 5: Higuchi model plot (% Drug Released vs √Time)

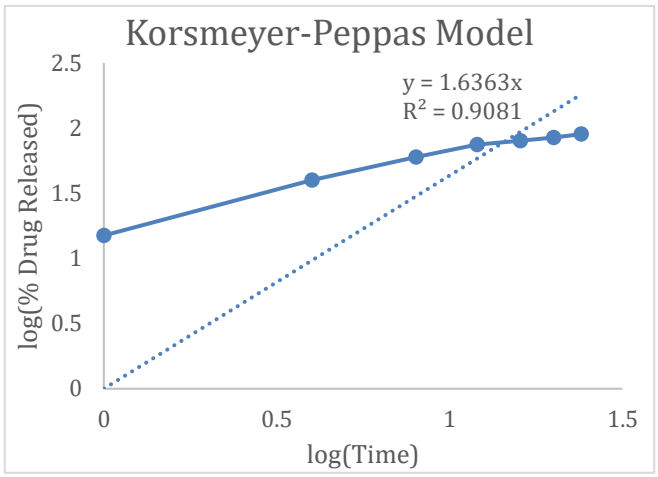

Figure 6: Korsmeyer-Peppas plot (log % Drug Released vs log Time)

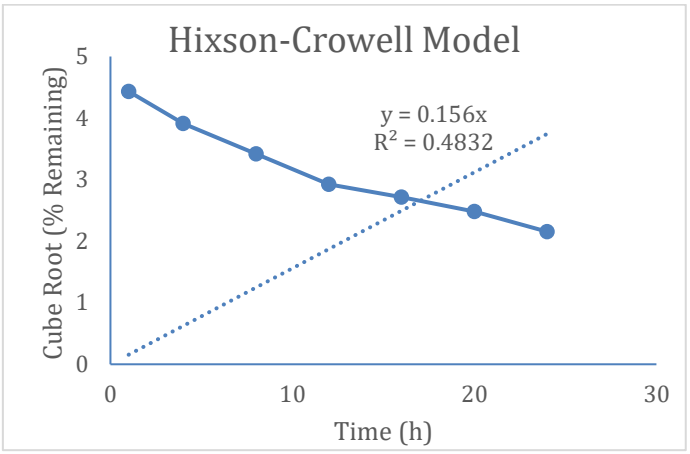

Figure 7: Hixson-Crowell plot (Cube root % Drug Remaining vs Time)

Table 8: R^2 value evaluated for in vitro drug release for kinetic modelling

Kinetic model	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	Hixson-Crowell model
R^2 value	0.5517	0.9266	0.9694	-3.31	-8.521

The R^2 value of Higuchi model is highest that is 0.9694 close to one confirming that Fickian diffusion controlled mechanism is followed by the optimized formulation F6. First order kinetics model has R^2 value 0.9266 showing good fit for release kinetics.

6.5. Stability Study

Table 9: Stability Data for Flurbiprofen Nanogel

Time (Months)	Appearance	pH	Viscosity (cps)	Drug Content (%)	Microbial Limits
0 (Initial)	Clear, homogenous	7.0 ± 0.2	1500	100% ± 1.5	Negative for bacteria and fungi
1 Month	No change	6.8 ± 0.2	1480	98% ± 1.5	Negative for bacteria and fungi
3 Months	Slight viscosity decrease	6.7 ± 0.2	1450	95% ± 2.0	Negative for bacteria and fungi
6 Months	No separation, slight viscosity decrease	6.6 ± 0.2	1400	90% ± 2.5	Negative for bacteria and fungi
12 Months	No separation, slight discoloration	6.4 ± 0.3	1350	85% ± 3.0	Negative for bacteria and fungi
UV Exposure (1 Month)	Slight discoloration	6.3 ± 0.2	1480	80% ± 3.5	Negative for bacteria and fungi

CONCLUSION:

The primary objective of the research is to develop Flurbiprofen loaded nanogel and evaluate its physiochemical properties. Flurbiprofen-loaded Nanogels (F1 to F6) were successfully developed and characterized to enhance the topical delivery of Flurbiprofen. The Flurbiprofen Nanogels were formulated using cholesterol, carbopol 934, and different concentrations of Span 20, Span 40, and Span 60, with a chloroform: ethanol solvent mixture, to optimize their physicochemical properties. The formulations were designed to provide sustained release, enhanced skin penetration, and long-term stability. The sustained release of 85% drug release over 12 hours following Higuchi model suggest that the drug release pattern follows Fickian diffusion. It confirms that the drug diffusion through the nanogel matrix occurs in a time dependent manner. As far as the stability is concerned, Formulation F6 exhibited 90 percent drug retention in 6 months under normal storage conditions, and it would be considered stable over a long period. The optimal pH (7.0) and viscosity (1500 cps) of Formulation F6 further contribute to its comfort and ease of application. The results of this study suggest that Flurbiprofen Nanogels, particularly Formulation F6, offer a more effective, stable, and patient-friendly alternative making it a promising option for prolonged pain relief and improved therapeutic outcomes.

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Informed Consent Statement: Not applicable

Ethical approval: This study does not involve experiments on animal or human subjects.

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