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Research Article

Formulation and Evaluation of Indomethacin-Loaded Bigel for Enhanced Topical Drug Delivery

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Abstract

Indomethacin, a non-steroidal anti-inflammatory drug, is associated with gastrointestinal side effects upon oral administration. This study aimed to formulate and evaluate an indomethacin-loaded bigel for improved topical delivery and sustained drug release. Bigels were prepared by combining Carbopol 934-based hydrogel and lecithin–isopropyl palmitate organogel in varying ratios (B1-B5). The formulations were evaluated for physicochemical properties, drug content, in vitro drug release, and stability. All formulations showed acceptable pH (5.8–6.4), good homogeneity, and suitable viscosity (5600-6900 cps). Drug content ranged from 93.10% to 99.00%. In vitro release studies demonstrated sustained drug release over 8 hours, with formulation B3 showing optimal performance (99.90% release). Release kinetics of B3 followed the Higuchi model (R^2 = 0.9727), indicating diffusion-controlled release. Stability studies confirmed no significant changes in pH, viscosity, or drug content under storage conditions. In conclusion, the optimized bigel formulation (B3) offers effective topical delivery of indomethacin with improved stability and sustained release characteristics, making it a promising alternative to conventional formulations.

Keywords: Indomethacin, Bigel, Topical drug delivery, Biphasic system, Drug release kinetics

INTRODUCTION

Indomethacin is a potent non-steroidal anti-inflammatory drug (NSAID) widely used in the management of pain, inflammation, and musculoskeletal disorders such as arthritis, gout, and tendonitis. It exerts its pharmacological action by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes, thereby reducing prostaglandin synthesis responsible for pain and inflammation. Despite its strong therapeutic efficacy, indomethacin is associated with significant gastrointestinal side effects when administered orally, including gastric irritation, ulceration, and bleeding, which limits its long-term use[1].

To overcome these limitations, topical drug delivery systems have gained considerable attention as they provide localized action at the site of inflammation while minimizing systemic exposure and adverse effects[2]. However, conventional topical formulations such as creams and gels often suffer from poor drug penetration through the stratum corneum, low retention time on the skin, and limited controlled release behaviour, which reduces their overall therapeutic efficiency[3].

In recent years, novel semi-solid systems such as bigels have emerged as promising carriers for topical and transdermal drug delivery. Bigels are biphasic systems composed of both hydrogel and oleogel networks, offering the advantages of both systems in a single formulation. The hydrogel phase provides good hydrophilicity[4], ease of application, and cooling sensation, whereas the oleogel phase enhances lipophilicity, occlusiveness, and skin permeation of hydrophobic drugs like indomethacin. This dual nature of bigels improves drug loading capacity, stability, and controlled release characteristics compared to conventional formulations.

Therefore, the present study focuses on the formulation and evaluation of indomethacin-loaded bigel systems with the aim of enhancing topical drug delivery, improving skin permeation, and achieving sustained therapeutic action while minimizing systemic side effects.

MATERIALS AND METHODS

Indomethacin was kindly provided as a gift sample. Carbopol 934, Pluronic F-127, soy lecithin, isopropyl

palmitate, sorbic acid, potassium sorbate, ethanol, and other formulation excipients were procured from Hyderabad , India. All chemicals and reagents used in the study were of analytical grade and Distilled water was utilized throughout the experiment for formulation preparation and evaluation studies.

Preparation of Bigel

Since bigel is a biphasic system composed of two distinct gel networks, its preparation involves three main stages:

(i) preparation of hydrogel

(ii) preparation of organogel

(iii) combination of hydrogel and organogel to form the final bigel formulation.

Preparation of Hydrogel

The hydrogel was prepared using Carbopol 934 as the gelling polymer. The required quantity of Carbopol 934 was dispersed in distilled water and allowed to swell completely for 12 hr. The dispersion was continuously stirred for approximately one hour to obtain a uniform and homogeneous gel system[5].

Table 1: Hydrogel Preparation

Formulation	Carbopol 934 (g)	Distilled Water (mL)
H1	1.0	50
H2	1.25	50
H3	1.5	50
H4	1.75	50
H5	2.0	50

Preparation of Organogel

The organogel was prepared through two phases: oil phase and aqueous phase.

A. Oil Phase Preparation

A measured quantity of soy lecithin was accurately weighed and dissolved in isopropyl palmitate under continuous stirring to ensure uniform mixing. Sorbic acid was added as a preservative. The mixture was maintained at room temperature for 24 hours to allow proper gel stabilization[6].

Table 2: Oil Phase Preparation

Formulation	Soy Lecithin (g)	Isopropyl Palmitate (q.s.)	Sorbic Acid (g)
O1	1.50	10.50	0.10
O2	1.50	10.50	0.10
O3	1.50	10.50	0.10
O4	1.50	10.50	0.10
O5	1.50	10.50	0.10

B. Aqueous Phase Preparation

Pluronic F127 was added to cold distilled water and allowed to hydrate for one hour under low-temperature conditions. The mixture was then stirred continuously and stored under refrigeration for 24 hours to obtain a clear and stable solution. Potassium sorbate was incorporated as a preservative to enhance formulation stability.

Table 3: Aqueous Phase Preparation

Formulation	Pluronic F127 (g)	Potassium Sorbate (g)	Distilled Water (mL, q.s. to 50 mL)
O1	1.00	0.10	10.50
O2	1.50	0.10	10.50
O3	1.75	0.10	10.50
O4	2.00	0.10	10.50
O5	2.25	0.10	10.50

Preparation of Bigel

The prepared hydrogel and organogel phases were mixed in appropriate ratios under continuous stirring to form a homogeneous bigel system. Gentle mixing was performed to ensure uniform dispersion of both gel phases and to avoid phase separation, resulting in a stable biphasic bigel formulation suitable for topical application[7].

Table 4: Bigel Preparation

Formulation	Indomethacin (%)	Hydrogel (%)	Organogel (%)
B1	1	13	7
B2	1	11	9
B3	1	9	11
B4	1	7	13
B5	1	5	15

Method for Calibration Curve of Indomethacin in Methanol

A standard stock solution of indomethacin was prepared in methanol and further diluted to obtain a series of working standard solutions of known concentrations. The absorbance of each solution was measured using a UV-Visible spectrophotometer against methanol as blank under fixed analytical conditions[8].

A calibration curve was constructed by plotting absorbance versus concentration. Linear regression analysis was performed to obtain the equation of the line and correlation coefficient (R^2), which confirmed good linearity. The calibration curve was used for quantification of indomethacin in unknown samples.

Hydrogel and Organogel Characterization

Physical Appearance

The physical characteristics of both hydrogel and organogel formulations were evaluated by visual inspection. Parameters such as color, consistency, and transparency were carefully examined to ensure uniformity and absence of phase separation or particulate matter[9].

pH Determination

The pH of each formulation was measured using a calibrated digital pH meter. The electrode was placed directly on the surface of the gel and allowed to equilibrate for approximately one minute before recording the reading. The pH values were assessed to ensure compatibility with skin application[10].

Viscosity Determination

The viscosity of the prepared hydrogel and organogel systems was determined using a Brookfield DV-II+ Pro viscometer. Samples were placed in a 25 mL beaker and analyzed using spindle number 96 for hydrogel and spindle number 64 for organogel. Measurements were performed at 10 rpm under room temperature conditions. Each sample was tested six times, and the average value was recorded to ensure accuracy and reproducibility[11].

Spreadability Study

Spreadability of the hydrogel and organogel formulations was evaluated using the glass slide method. A fixed quantity of gel (0.5 g) was placed within a circular area of 1 cm diameter marked on a glass slide. A second glass plate was carefully placed over it, followed by application of a 1000 g weight for 5 minutes. The increase in diameter of the spread gel was measured and used as an indicator of spreadability[12].

Bigel Characterization

Physical Appearance

The physical characteristics of the prepared bigel formulations were evaluated by visual inspection. Parameters such as colour, homogeneity, consistency, and transparency were observed to ensure uniformity and absence of phase separation[9].

pH Determination

The pH of each bigel formulation was measured using a calibrated digital pH meter. The electrode was placed on the surface of the gel and allowed to equilibrate for one minute before recording the final reading. The pH was evaluated to ensure suitability for topical application[10].

Viscosity Determination

The viscosity of the bigel formulations was determined using a Brookfield DV-II+ Pro viscometer. Samples were placed in a 25 mL beaker and analysed using spindle number 62. Measurements were performed at 10 rpm under room temperature conditions. Each formulation was tested six times, and the average value was recorded to ensure accuracy and reproducibility[11].

Spreadability Study

Spreadability was evaluated using the glass slide method under a fixed load. A known quantity of bigel (0.5 g) was placed within a 1 cm diameter circular area marked on a glass slide. A second glass plate was placed over it, and a 1000 g weight was applied for 5 minutes. The increase in diameter due to gel spreading was measured as an indicator of spreadability[12].

In Vitro Drug Release Study

In vitro drug release studies were performed using a modified Franz diffusion cell apparatus with a cellophane membrane. Phosphate buffer solution (PBS, pH 7.4) was used as the dissolution medium. The membrane was pre-soaked in PBS overnight prior to use. A weighed amount of bigel was placed on the cellophane membrane and mounted between the donor and receptor compartments. The receptor compartment was filled with 50 mL of PBS (pH 7.4) and maintained at 37 ± 0.5°C with continuous stirring at 50 rpm using a magnetic stirrer. At predetermined time intervals, 3 mL samples were withdrawn, filtered, and replaced with fresh medium to maintain sink conditions. The samples were analysed spectrophotometrically at 318 nm after suitable dilution to determine drug release[13].

Stability Studies

Stability studies were conducted in accordance with ICH guidelines over a period of one month to evaluate the effect of environmental conditions such as temperature, humidity, and light on the stability of the formulated bigels. The prepared bigel formulations were filled into aluminium collapsible tubes and stored under two different conditions, namely 25 ± 2°C/60% RH and 45 ± 2°C/75% RH. At the end of the study period, the formulations were assessed for any changes in pH, viscosity, and drug content in order to determine their physical and chemical stability[14].

RESULT

The calibration curve of indomethacin in methanol was established using absorbance data of standard solutions at different concentrations, as presented in Table 5. A calibration curve was constructed by plotting the absorbance values against the corresponding concentrations of indomethacin. The resulting data showed a linear relationship within the studied range. The regression equation for the straight line was found to be $y = 0.0107 + 0.0168x$, with a correlation coefficient ($R^2 = 0.9971$), indicating good linearity. This calibration curve was further used for the determination of indomethacin concentration in unknown samples.

Table 5: UV Absorbance & conc. of Indomethacin using Methanol.

Concentration (µg/ml)	Absorbance (mean±SD)
10	0.109
20	0.228
30	0.343
40	0.444
50	0.564
60	0.693
70	0.754
80	0.876
90	0.963

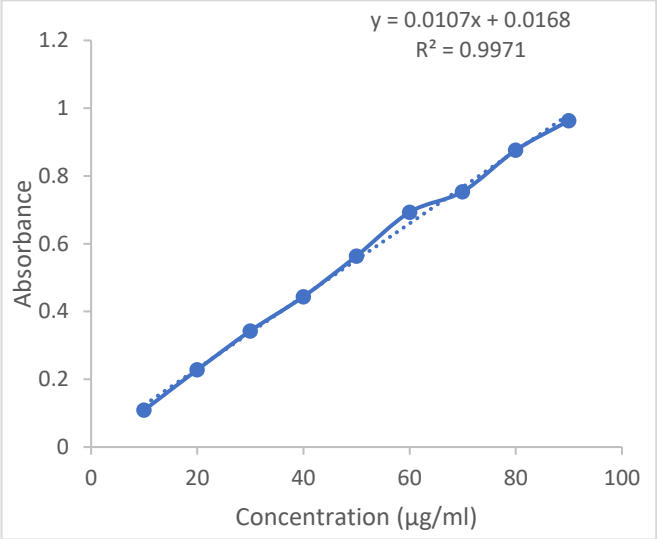

Figure 1: Calibration Curve of Indomethacin

Hydrogel and organo-gel physical appearance

Hydrogel Physical Appearance

The visual appearance of hydrogel formulations is an important parameter for topical drug delivery, as it directly affects patient acceptability and compliance. All prepared hydrogel batches were evaluated through visual inspection for clarity, colour, and homogeneity. The formulations were found to be transparent, colourless, and uniformly consistent without any visible particulate matter, as summarized in Table 6.

Organogel Physical Appearance

All organogel formulations were examined visually for appearance, texture, and uniformity. The prepared organogels were observed to be opaque, off-white in colour, and exhibited a smooth, creamy consistency. No phase separation or aggregation was observed in any formulation batch, as shown in Table 6.

Table 6: Physical Appearance Hydrogel & Organogel

Formulation	Hydrogel Physical Appearance	Formulation	Organogel Physical Appearance
H1	Clear, colourless, homogeneous	O1	Opaque, off-white, creamy
H2	Clear, colourless, homogeneous	O2	Opaque, off-white, creamy
H3	Clear, colourless, homogeneous	O3	Opaque, off-white, creamy
H4	Clear, colourless, homogeneous	O4	Opaque, off-white, creamy
H5	Clear, colourless, homogeneous	O5	Opaque, off-white, creamy

pH Determination of Hydrogel and Organogel

The pH of all prepared hydrogel and organogel formulations was found to be within the acceptable range for topical application. The observed pH values were close to the physiological skin pH, indicating that the formulations are unlikely to cause skin irritation and are suitable for dermal delivery. The pH results of both systems are presented in Table 7.

Table 7: pH Determination Hydrogel & Organogel

Formulation	Hydrogel pH	Formulation	Organogel pH
H1	6.3	O1	6.9
H2	6.7	O2	5.1
H3	6.3	O3	6.8
H4	6.8	O4	6.3
H5	5.2	O5	6.7

Viscosity Determination of Hydrogel and Organogel

Hydrogel Viscosity

The viscosity of hydrogel formulations was measured using a Brookfield viscometer. A gradual increase in viscosity was observed from formulation H1 to H5, which can be attributed to the increasing concentration of Carbopol 934. Higher polymer concentration leads to enhanced chain entanglement and gel strength, resulting in increased viscosity.

Organogel Viscosity

The viscosity of organogel formulations was also determined using a Brookfield viscometer. A steady increase in viscosity from O1 to O5 was observed, which may be due to higher concentration of Pluronic F127 and lecithin, leading to stronger gel network formation and improved structural rigidity.

Table 8: Viscosity of Hydrogel & Organogel

Formulation	Hydrogel Viscosity (cps)	Formulation	Organogel Viscosity (cps)
H1	3100	O1	3800
H2	3350	O2	4100
H3	3600	O3	4400
H4	3850	O4	4700
H5	4100	O5	5000

Spreadability Determination of Hydrogel and Organogel

The spreadability of hydrogel and organogel formulations was evaluated using the glass plate method. Formulations with lower viscosity exhibited higher spreadability, while those with higher viscosity showed reduced spreadability. An inverse relationship between viscosity and spreadability was clearly observed, which is desirable for topical formulations to ensure ease of application and adequate retention on the skin.

Table 9: Spreadability of Hydrogel & Organogel

Formulation	Hydrogel Spreadability (g·cm/sec)	Formulation	Organogel Spreadability (g·cm/sec)
H1	18.10	O1	17.60
H2	16.85	O2	15.40
H3	14.20	O3	13.10
H4	12.95	O4	11.80
H5	11.60	O5	10.50

Indomethacin Bigel Characterization

For the development of bigel formulations, the optimized hydrogel (H3) and organogel (O3) were selected. These phases were combined in different ratios to obtain various bigel formulations (B1-B5). Indomethacin was dissolved in a small quantity of ethanol and incorporated into the gel under continuous stirring to ensure uniform drug distribution. A suitable preservative was also included in all formulations. All prepared bigels exhibited satisfactory consistency and homogeneity.

Physical Appearance of Bigel

The visual appearance of the bigel formulations is an important parameter for topical application, as it influences patient acceptability. All formulations were evaluated for color, consistency, and homogeneity. The prepared bigels were found to be off-white, smooth, and creamy in texture with uniform consistency, as shown in Table 10.

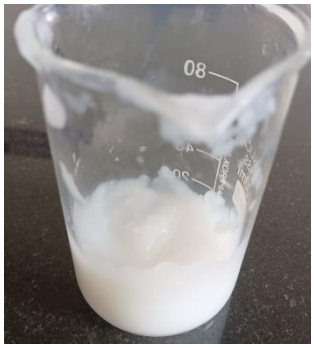

Figure 2: Physical Appearance of Bigel

Table 10: Physical Appearance of Indomethacin Bigel

Formulation	Bigel Physical Appearance
B1	Off-white, smooth, creamy
B2	Off-white, smooth, creamy
B3	Off-white, smooth, creamy
B4	Off-white, smooth, creamy
B5	Off-white, smooth, creamy

pH Determination of Bigel

The pH of all bigel formulations was found to be within the acceptable range for topical application (close to skin pH), indicating minimal risk of irritation.

Table 11: pH of Indomethacin Bigel

Formulation	Bigel pH
B1	6.3
B2	6.1
B3	6.4
B4	6.0
B5	5.8

Viscosity Determination of Bigel

The viscosity of the bigel formulations was determined using a Brookfield viscometer. It was observed that formulations containing a higher proportion of organogel exhibited higher viscosity due to the presence of a stronger oil-phase network. Conversely, formulations

with higher hydrogel content showed comparatively lower viscosity.

Table 12: Viscosity of Indomethacin Bigel

Formulation	Bigel Viscosity (cps)
B1	6800
B2	6500
B3	6900
B4	5900
B5	5600

Spreadability Determination of Indomethacin Bigel

The spreadability of bigel formulations was evaluated using the glass plate method. The results showed that spreadability decreased with an increase in organogel concentration and viscosity. Formulation B1, containing the highest proportion of organogel, exhibited the lowest spreadability due to its higher viscosity. In contrast, formulation B5, with a lower organogel content and reduced viscosity, demonstrated the highest spreadability. This confirms the inverse relationship between viscosity and spreadability, which is critical for topical application.

Table 13: Spreadability of Indomethacin Bigel

Formulation	Bigel Spreadability (g·cm/sec)
B1	45.20
B2	48.75
B3	62.10
B4	56.40
B5	60.30

Drug Content of Bigel

The drug content of the indomethacin-loaded bigel formulations was determined to evaluate the uniform distribution of the drug within the gel matrix. The results indicated that the drug content ranged from 93.10% to 99.00%, demonstrating satisfactory drug loading efficiency across all formulations. Formulation B1 showed the lowest drug content, which may be attributed to incomplete drug dispersion at higher organogel proportions. In contrast, formulation B3 exhibited the highest drug content, indicating uniform distribution and optimal formulation conditions.

Table 14: Drug Content of Indomethacin Bigel

Formulation	Bigel Drug Content (%)
B1	93.10
B2	96.80
B3	99.00
B4	95.50
B5	97.20

In Vitro Drug Release of Indomethacin Bigel (B1-B5)

In vitro drug release of indomethacin-loaded bigel formulations (B1-B5) was evaluated using a modified Franz diffusion cell apparatus across a cellophane membrane for 8 hours. The study demonstrated a sustained and controlled release pattern from all formulations. Among them, formulation B1 showed comparatively slower release due to higher organogel content, whereas formulation B3 exhibited the most optimized and complete drug release profile. An increase in hydrogel proportion resulted in a higher rate of drug diffusion. Overall, a decrease in drug release rate was observed with increasing organogel concentration, indicating its role in sustaining drug release.

Figure 3: In Vitro Drug Release of Indomethacin Bigel (B1-B5)

Table 15: In Vitro Drug Release of Indomethacin Bigel (B1-B5)

Time (min)	B1 (%)	B2 (%)	B3 (%)	B4 (%)	B5 (%)
0	0	0	0	0	0
15	10.12	12.85	14.20	18.45	22.10
30	18.30	22.40	26.75	30.90	36.25
60	28.65	33.10	38.90	44.20	50.15
120	38.40	45.60	52.80	58.75	65.30
180	47.90	58.20	75.40	70.85	76.10
240	58.25	69.80	86.90	72.40	88.30
300	66.10	78.50	95.60	91.20	94.10
360	74.80	86.30	92.50	91.40	96.20
420	81.50	91.20	99.80	93.10	97.60
480	86.90	94.80	99.90	96.80	97.90

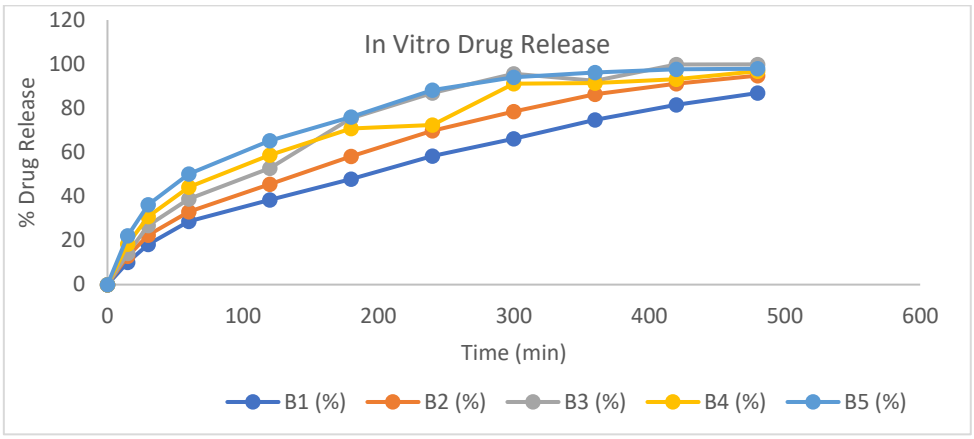

Figure 4: In Vitro Drug Release Profile of Indomethacin Bigel (B1-B5)

Kinetic models of bigel formulation (B3)

Drug Release Kinetics of Formulation B3 release kinetics were assessed using zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, with correlation coefficients (R^2) of 0.8678, 0.9436, 0.9727, and 0.9653, respectively, indicating that the drug release largely followed the Higuchi diffusion mechanism.

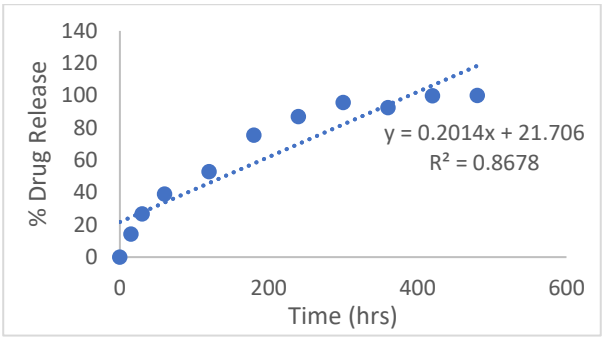

Figure 5: Zero order Kinetics

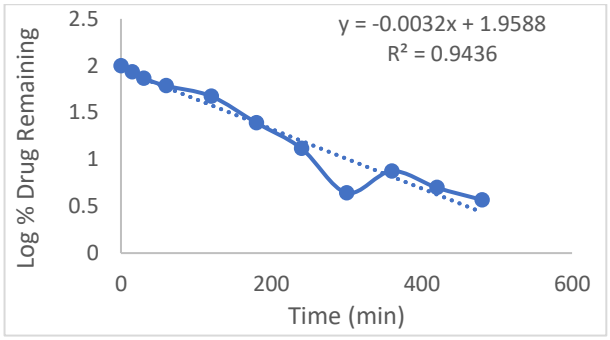

Figure 6: First order Kinetics

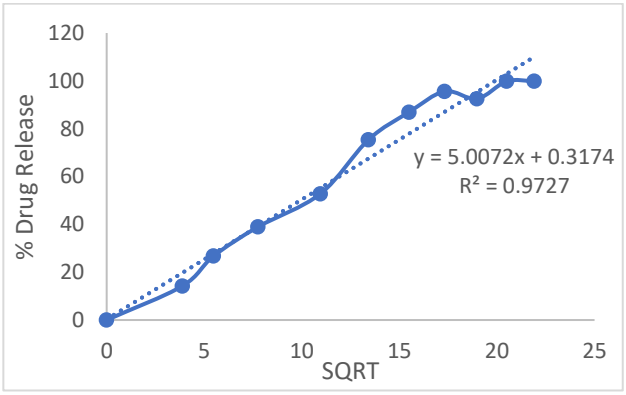

Figure 7: Higuchi's Model

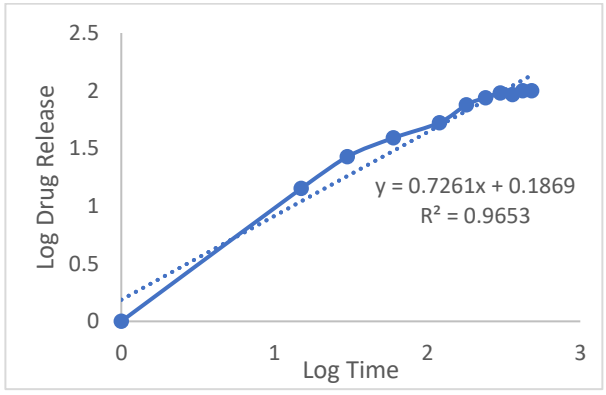

Figure 8: Korsmeyer-Peppas Model

Table 16: Kinetic Equation Parameter of B3

Formulation	Zero order	First Order	Higuchi model	Korsemeyer's model
B3	0.8678	0.9436	0.9727	0.9653

Stability Studies of Optimized Indomethacin Bigel (B3)

The results indicated that the optimized bigel formulation remained physically and chemically stable under the tested conditions, with no significant changes observed in pH, viscosity, or drug content compared to initial values. This confirms that the formulation maintains its integrity under normal storage conditions, suggesting good shelf-life stability.

CONCLUSION

The present study successfully developed and evaluated indomethacin-loaded bigel formulations for enhanced topical drug delivery. The results demonstrated that the combination of hydrogel and organogel systems effectively improved the physicochemical properties, drug loading, and controlled release behavior of the formulation. All prepared bigels exhibited acceptable pH, good homogeneity, viscosity, and satisfactory spreadability, indicating their suitability for dermal application.

Among all formulations, B3 showed optimal performance with maximum drug content (99.00%), balanced viscosity, good spreadability, and a controlled, sustained drug release profile following the Higuchi diffusion mechanism. Stability studies further confirmed that the optimized formulation (B3) remained stable under different storage conditions without significant changes in key parameters.

Overall, the indomethacin-loaded bigel system represents a promising and effective approach for topical delivery, offering improved therapeutic efficacy, prolonged drug release, and reduced systemic side effects compared to conventional formulations.

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