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Development and Characterization of novel bigel of loxoprofen for topical drug delivery

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Abstract

Bigels are unique two-phase systems that have recently been presented as a structured method for active ingredient application. The purposes of the current study were to develop and characterize bigel formulations containing loxoprofen. They have the benefits of both hydrogel and organo-gel. In order to enhance penetration, pluronic lecithin was added to form the organo-gel, and HPMC was added to form the hydrogel, which properly hydrates the stratum corneum. Bigels were produced by mixing hydrogel with organo-gel in the appropriate ratio. pH, viscosity, extrudability, spreadability, and Gel-sol transition temperature were assessed for organo-gel and hydrogel. For the preparation of bigel, formulations O3 from organo-gel and H3 from hydrogel were characterized as optimum formulations. pH, viscosity, extrudability, spreadability, Gel-sol transition temperature, and other properties of the produced bigel were assessed. An 8-hour invitro drug release investigation yielded B1's results, which were 84.77%. B2 demonstrated 92.35 % release, B3 demonstrated 99.18% release, and bigel demonstrated extended-release. Based on evaluation characteristics, formulation B3 was chosen as the optimal formulation. Loxoprofen bigel release kinetics according to the Higuchi model. You can utilize loxoprofen bigel as an extended-release system.

Keywords: Loxoprofen, (B)Bigel Pluronic F127, (O)Organo-gel, HPMC, Gel-sol, (H)Hydrogel

INTRODUCTION:

Topical routes of administration are a prominent class of drug delivery mechanisms, and the therapeutic application of these approaches is beneficial for better development. The use of the skin as a substitute for systemic and localized therapy goes back to the beginning of time, and even stable topical preparations to treat conditions have existed for ages. These more recent developments are known as "skin substitutes."[1] Topical drug delivery focuses on applying active ingredients directly to the skin to treat a wide range of diseases, including local pain, skin infections, and cosmetic problems.[2] There are three types of typical dosage forms for topical delivery systems: liquid, semi-solid, and solid systems. Topical formulations, lotions, and suspensions all belong to the category of liquids. Pastes, creams, gels, and ointments are examples of semi-solids. Sticks and powders are examples of solid formulations.[3,4] Topical drug delivery has many benefits when it comes to the administration of drugs for both local and systemic therapy.

The outer layer of the skin has a multi-layered wall-like structure that forms a strong barrier to most substances, including drugs. One method for delivering drugs through Using a penetration enhancer, the skin will reversibly reduce its barrier function.[5] For a long time, A effective technique has been topical drug delivery through the skin. because skin is easily accessible, has a wide surface with considerable stimulation to the vascular and lymphatic networks, and the delivery is non-invasive. Drugs with systemic side effects, including nonsteroidal anti-inflammatory drugs, require transdermal administration.[6]

Gels are semisolid mixtures that typically contain two ingredients: liquid and solid. where the solid element is known as a gelling agent or gelator and the liquid element is known as a solvent.[7] In the pharma industry, gels are 3D networked systems with several applications. They can be separated into two main categories: hydrogels & organo-gels.[8,9] Organogels are rather simple to make, and their lipophilic character will improve the drug's ability to penetrate the stratum corneum. When applied to the skin, [10]Organogel's oily nature makes it tough to remove. & Hydrogels can hold a significant volume of water without becoming dissolved.[11,12]

Topical drug delivery systems are the center of attention for all recent advancements in the pharmaceutical industry.[13] The various kinds of topical preparations that are frequently utilized include gels, creams, pastes, lotions, ointments, dusting powder, etc.

Gels are 3D networked systems with a focus on the pharmaceutical industry. Both hydrogel and organogel are frequently employed gels Polymers like carbopol and HPMC are mixed with water to form transparent, water-based hydrogels. They hydrate the stratum corneum by having a good amount of water in their structure. Organic solvents and polymers like pluronic are used to make organogel with proper proportions and ratios. Proper stratum corneum

hydration is provided by the hydrogel in bigel, and improved penetration is provided by the organogel in bigel.[14]

The drug used in the formulation is loxoprofen, a traditional NSAID. When used continuously, the administration of loxoprofen orally for pain management caused several problems, such as gastric irritation, ulceration, bleeding, and so on. The drug had to be administered through a different method and the proper vehicle as a result, which was performed by formulating the drug into bigel. Bigel will provide to effective pain relief because of its greater penetration and gradual release.[15,16] Additionally, the bigel shows great contact time and area, as well as easy washability. Additionally, the bigel offers the combined advantages of both hydrogel and organogel while reducing the drawbacks of individual gels.[17]

MATERIALS AND METHODS:

Received loxoprofen as a gift sample from Anlon Healthcare Gujarat. The following ingredients came from Central Drug House in New Delhi: Pluronic F127, HPMC K15, soy lecithin, isopropyl palmitate, sorbic acid, potassium sorbate, and ethanol. The materials were all of an analytical calibrated.

Research methodology of bigel

Because bigel is made of two separate gels, there are three phases involved in its preparation.[18]

1. Preparing a hydrogel.
2. Preparing an organogel.
3. Hydrogel and Organogel are combined to produce bigel.

Hydrogel preparation

The polymer used to make the hydrogel was HPMC. The needed amount of HPMC was combined with distilled water and left to soak. The dispersion was continuously stirred for an hour to develop a homogeneous gel.The formula for making hydrogel is given in Table 1.

Organogel preparation

The organogel is divided into two phases: the aqueous phase and the oil phase.

Oil phase preparation

The needed amount of soya lecithin was weighed & kept in a beaker, where it was dissolved in the needed amount of isopropyl palmitate while continuously stirring & then Sorbic acid was included in the mixture as a preservative, and it was left at room temperature for 24 hours. shown in Table 2

Table 1: Formulation of Hydrogel.

Formulations	HPMC (gm)	Distilled water (in ml)
H1	1	25
H2	1.5	25
H3	2	25
H4	2.5	25
H5	3	25

Table 2: The oil phase's formulation.

Formulation	Soy lecithin (gm)	Isopropyl palmitate (q.s)	Sorbic acid (gm)
O1	1.25	12.50	0.05
O2	1.25	12.50	0.05
O3	1.25	12.50	0.05
O4	1.25	12.50	0.05
O5	1.25	12.50	0.05

Aqueous phase preparation

The addition of pluronic F127 to cold water, where it was left to soak for an hour at a cold temperature. The sample was then taken, the mixture was continually mixed, and it was placed in the refrigerator for 24 hours to produce a clear solution. As a preservative, potassium sorbate was added in the necessary amount shown in Table 3.

Table 3: The aqueous phase's formulation.

Formulation	Pluronic F127 (gm)	Potassium sorbate (gm)	Distilled water (q.s. to 50ml)
O1	1.25	0.05	12.50
O2	2.50	0.05	12.50
O3	3.75	0.05	12.50
O4	5.00	0.05	12.50
O5	6.25	0.05	12.50

Preparing organogel by combining the oil and aqueous phases

The aqueous phase was mixed with the oil phase. in small volumes. while being continuously stirred until the entire volume was added, which is how organogel is made. contains the preparation formulas for pluronic lecithin organogel.

Hydrogel & organogel characterization[19,20]

Physical appearance of hydrogel & organogel

Visual inspection was used to assess the gels' physical appearance. Consistency, color, and transparency were examined as parameters.

pH determination of hydrogel & organogel

To calculate the pH of each formulation, an electrode from a digital pH meter was placed on the surface of the formulated gel. after one minute of equilibration, the reading was collected.

Viscosity determination of hydrogel & organogel

Brookfield viscometer (Brookfield DV-II+ Pro) was used to determine the viscosity of the formulated gels. In a 25 ml beaker, the samples were collected for examination. Using spindle numbers 96 for hydrogel and 64 for organogel, the viscosity of the samples was determined. On each sample, the test was conducted six times, and the average result was calculated. The angular velocity was 10 rpm, and the experiment was conducted at room temperature.

Spreadability determination of hydrogel & organogel

The spreadability of the organogel & hydrogel that had been determined was assessed using two glass plates and constant weight. On the glass plate, which held the 0.5 mg of gel, a circle drawn with a 1 cm diameter was already marked. A second glass plate was positioned on top of this one. The upper glass plate with the 1000 g weight was left there for 5 minutes. It is measured how much the diameter has grown as a result of the gel spreading.

Extrudability determination of hydrogel & organogel

Using a Monsanto hardness tester, all created formulations had their extrudability tested. The plunger tester was set to securely grasp the test tube. For 30 seconds, 1 kg/cm2 of pressure was applied. The weighing was done on the formulation that was extruded.

Hydrogel and Organogel are combined to produce bigel.

The combining of hydrogel with organogel is the most vital phase in the formation of bigel. Bigel was prepared using an optimized formulation of organogel and hydrogel & then transferred and mixed together. A creamy white, homogeneous gel was produced by repeating the process. After that, the appropriate quantity of the drug was dissolved in a very slight amount of ethanol, and the combination was well stirred for homogeneous dispersion. As shown in Table 4.

Table 4: Hydrogel and Organogel are combined to produce bigel

Formulation	Loxoprofen (%)	Hydrogel (%)	Organogel (%)
B1	1	5	14
B2	1	7	12
B3	1	9	10
B4	1	11	8
B5	1	13	6

Bigel characterization

Bigel physical appearance

Visual inspection was used to assess the gels' physical appearance. Consistency, color, and transparency were examined as parameters.

Bigel pH determination

To calculate the pH of each formulation, an electrode from a digital pH meter was placed on the surface of the prepared gel. After one minute of equilibration, the reading was collected.

Bigel viscosity determination

Brookfield viscometer (Brookfield DV-II+ Pro) was used to determine the viscosity of the formulated gels. In a 25 ml beaker, the samples were collected for examination. Using spindle number 62 used for bigel formulation, the viscosity of the samples was determined. For each sample the test was repeated six times, and the result was determined. The angular velocity was 10 rpm, and the experiment was conducted at room temperature.

Bigel spreadability determination

The spreadability of the bigel that had been determined was assessed using two glass plates and constant weight. On the glass plate, which held the 0.5 mg of gel, a circle with a 1 cm diameter was already marked. A second glass plate was positioned on top of this one. The upper glass plate with the 1000 g weight was left there for 5 minutes. It is measured how much the diameter has grown as a result of the gel spreading.

Bigel

extrudability determination

Using a Monsanto hardness tester, all created formulations had their extrudability tested. The plunger tester's was set to securely grasp the test tube. For 30 seconds, 1 kg/cm2 of pressure was applied. The weighing was done on the formulation that was extruded.

The temperature of gel-sol transition of bigel[21]

By allowing the gels to develop at a constant temperature between 25 and 60 degrees Celsius, the temperature of the

gel-sol transition each gel was established. Over the duration of five minutes, the water bath's temperature increased by 5.0C. It was possible to record the temperature at which the gel began to flow when the beaker was turned upside down.

Figure 1: Preparation of loxoprofen bigel.

In vitro drug release from the Bigel formulation [22]

A modified Franz diffusion cell apparatus and a cellophane membrane are used for in-vitro drug release studies were conducted. The dissolving medium used in the analysis is (PBS) phosphate buffer pH 7.4. The cellophane membrane used in the study was soaked in (Pbs)pH 7.4 for the rest of the night. Bigel was properly weighed and then kept over the cellophane membrane centerpiece. This cellophane membrane was then connected to one of the opening ends of the particularly made hollow glass cylinder. A 50 ml beaker of pH 7.4 phosphate buffer solution was used to dip the glass cylinder into after it had been attached to the metal shaft, allowing the membrane to barely touch the surface. Throughout the testing, the dissolution medium was maintained at 37+0.5 oC and continuously stirred at 50 rpm with the help of magnetic stirrer. The experiment continued under these parameters until it was over. The 3 ml sample of receptor media was divided into aliquots and filtered for a specified amount of time. After dilution, each sample's absorbance was determined using a UV spectrophotometer at 221.5 nm.

Bigel Stability studies determination[23]

According to ICH guidelines, the stability studies were conducted for a month. The goal of stability studies is to gather information on how the active pharmaceutical ingredient changes over time when exposed to different

Figure 2: Standard graph plot of Loxoprofen in Distilled Water at 221.5(nm)

environmental factors such as humidity, temperature, and light. 45oC±2oC and 25oC±2oC (60 % RH) were the study's operating temperatures (75% RH). An aluminium collapsible tube was filled with all the prepared formulation The packaged gels are then maintained in various temperature and weather conditions mentioned above. The gels (%) drug content, viscosity, and pH were evaluated after the trial.

BIGEL'S RESULTS AND DISCUSSION:

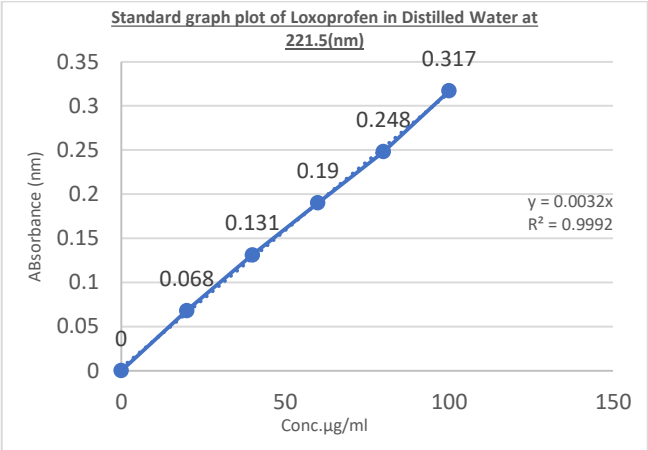
Standard graph plot of Loxoprofen in distilled water

The Standard graph plot of loxoprofen shows linearity & good regression coefficient given in Table 5.

Table 5: UV Absorbance & conc. of loxoprofen using distilled water.

S.no.	Conc. (µg/ml)	Abs. (nm)
1	0	0
2	20	0.060
3	40	0.131
4	60	0.190
5	80	0.248
6	100	0.317

Standard graph plot of loxoprofen in distilled water



FTIR of loxoprofen

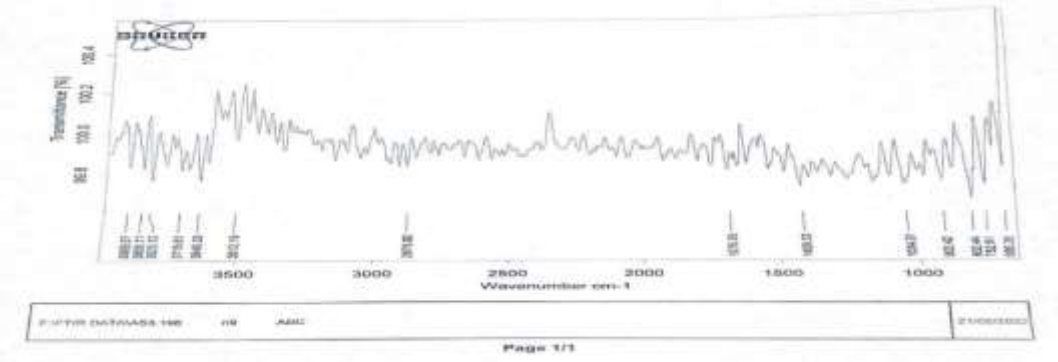


Figure 3: FTIR of loxoprofen

FTIR of loxoprofen bigel

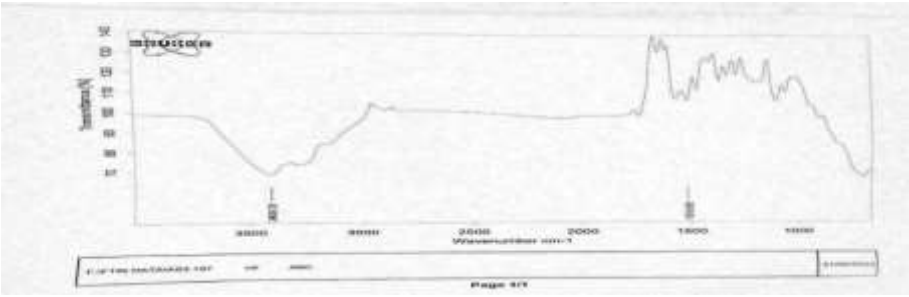


Figure 4: FTIR of loxoprofen bigel

Hydrogel and organo-gel physical appearance

Hydrogel physical appearance

The hydrogel visual appearance is a key point for topical delivery because it influences patient compliance. All hydrogel formulations were evaluated visually for crystal clear, color, and consistency. All hydrogels were determined to be clear, colorless, & of uniform consistency given in Table 6.

Table 6: Hydrogel's physical appearance

Formulation	Hydrogel physical appearance
H1	Crystal clear, colorless, homogenous
H2	Crystal clear, colorless, homogenous
H3	Crystal clear, colorless, homogenous
H4	Crystal clear, colorless, homogenous
H5	Crystal clear, colorless, homogenous

Organogel physical appearance

All organogel formulations were found to be cloudy, off-white in color, and creamy in texture given in Table 7.

Table 7: Organogel's physical appearance

Formulation	Organogel physical appearance
O1	Cloudy, off-white, creamy
O2	Cloudy off-white, creamy
O3	Cloudy, off-white, creamy
O4	Cloudy off-white, creamy
O5	Cloudy, off-white, creamy

pH determination of hydrogel & organogel

The acquired pH was within the range that was considered acceptable for topical usage, thus it would not irritate the skin. Table 8 & 9 shows the pH of the gel formulations.

Table 8: pH determination of hydrogel

Formulation	Hydrogel pH
H1	6.2
H2	5.9
H3	6.4
H4	6.0
H5	5.7

Table 9: pH determination of organogel

Formulation	Organogel pH
O1	6.2
O2	5.9
O3	6.4
O4	6.0
O5	5.7

Viscosity determination of hydrogel & organogel

Using a Brooksfield viscometer, the viscosity of the prepared hydrogel was determined. As the hydrogel formulation progressed from H1 to H5, its viscosity gradually increased. The growth depends upon the amount of HPMC The formulation's HPMC concentration was inversely correlated with its viscosity. shown in Table 10.

Table 10: Hydrogel viscosity measurement

Formulation	Hydrogel viscosity (cps)
H1	3200
H2	3300
H3	3500
H4	3500
H5	3600

Using a Brooksfield viscometer, the prepared organogel's viscosity was evaluated. From formulation O1 to O5, the viscosity of the pluronic lecithin organogel steadily increased. The amount of pluronic that was added to the formulation determined the improvement. The formulation's viscosity influenced how much pluronic was present. shown in Table 11.

Table 11: Organogel viscosity measurement

Formulation	Organogel viscosity (cps)
O1	4000
O2	4100
O3	4500
O4	4600
O5	4700

Spreadability determination of hydrogel & organogel

The formulated hydrogel and organogel's spreadability were evaluated. It was discovered that formulations H1 and O1 spreadability the best and formulations H5 and O5 spreadability the least. The formulation's integrity and viscosity are dependent on the proportion of polymer put into it. The preparations H1 & O1 with the lowest viscosity demonstrated higher spreadability, while the formulations H5 & O5 with the greatest viscosity showed the lowest spreadability shown in Tables 12 & 13.

Table 12: Hydrogel spreadability determination

Formulation	Hydrogel Spreadability (g.cm/sec)
H1	17.24
H2	16.31
H3	12.49
H4	12.33
H5	11.82

Table 13: Organogel spreadability determination

Formulation	Organogel Spreadability (g.cm/sec)
O1	17.19
O2	14.53
O3	13.40
O4	11.04
O5	10.34

Extrudability determination of hydrogel & organogel

The formulated hydrogel and organogel's spreadability were evaluated. It was discovered that formulations H1 and O1 extrudability the best and formulations H5 and O5 extrudability the least. The formulation's integrity and viscosity are dependent on the proportion of polymer put into it. The preparations H1 & O1 with the lowest viscosity demonstrated higher extrudability, while the formulations H5 & O5 with the greatest viscosity showed the lowest extrudability shown in Tables 14 & 15.

Table 14: Hydrogel extrudability determination:

Formulation	Hydrogel extrudability (gm/sec)
H1	1.69
H2	1.54
H3	1.40
H4	1.26
H5	1.16

Table 15: Organogel extrudability determination:

Formulation	Organogel extrudability (gm/sec)
O1	1.49
O2	1.42
O3	1.32
O4	1.26
O5	1.12

Loxoprofen bigel characterization

For developing bigel, the optimal hydrogel (H3) and organogel (O3) formulations were used. To develop several bigel formulations, hydrogel and organogel were mixed at various ratios. 1 ml of ethanol was used to dissolve the loxoprofen drug before it was combined with the gel. Bigel's formulation also included a consistent component, a preservative. A fixed quantity of the drug was added to each formulation that was prepared. All of the developed formulations showed satisfactory consistency.

Bigel physical appearance

The formulation's visual appearance is a crucial step for topical delivery because it influences patient compliance. All hydrogel formulations were evaluated visually for crystal clear, color, and consistency. All organogel was determined to be cloudy, and off-white in color, and the consistency is milky shown in Table 16.

Table 16: Bigel physical appearance

Formulation	Bigel physical appearance
B1	Cloudy, off-white, creamy
B2	Cloudy off-white, creamy
B3	Cloudy, off-white, creamy
B4	Cloudy, off-white, creamy
B5	Cloudy, off-white, creamy

Bigel pH determination

The acquired pH was within the range that was considered acceptable for topical usage, thus it would not irritate the skin. shown in Table 17.

Table 17: Loxoprofen bigel pH

Formulation	Bigel pH
B1	6.2
B2	5.9
B3	6.4
B4	6.0
B5	5.7

Bigel Viscosity determination

The formulation of loxoprofen bigel B1 with 70% organogel had maximum viscosity, while formulation B5 with 30% organogel had the lowest viscosity. shown in Table:18.

Table 18: Loxoprofen bigel viscosity

Formulation	Bigel viscosity (cps)
B1	6200
B2	6400
B3	6500
B4	6600
B5	6600

The temperature of gel-sol transition of bigel

The amount of organogel present in the formulation obviously influences the gel sol transition temperature due to the fact that the B1 gel with 30% organogel showed the lowest gel sol transition temperature and the B5 with 70% organogel showed the highest shown in Table 19.

Table 19: Temperature of the gel-to-sol transition with loxoprofen bigel

Formulation	The temperature of gel-sol transition
B1	43
B2	48
B3	49
B4	53
B5	56

Bigel spreadability determination

The amount of additional organogel determines the formulation's consistency and viscosity. The formulation B1 having 70% organogel had the least spreadability, while formulation B5 includes 30% organogel. Similarly, formulation B5 with the lowest viscosity showed good spreadability formulation B1 with the highest viscosity showed the least spreadability. shown in Table 20.

Table 20: Spreadability determination Loxoprofen bigel

Formulation	Bigel spreadability (g.cm/sec)
B1	62.03
B2	60.45
B3	55.80
B4	51.92
B5	47.52

Bigel extrudability determination

As a result, formulation B1 with 70% organogel showed the lowest extrudability, & formulation B5 included 30% organogel. The maximum viscosity formulation B1 had the lowest extrudability, whereas the lowest viscosity formulation B5 had the best extrudability shown in Table 21.

Table 21: Extrudability determination Loxoprofen bigel

Formulation	Bigel extrudability (gm/sec)
B1	1.68
B2	1.52
B3	1.36
B4	1.15
B5	1.14

Drug content of bigel

A study of the loxoprofen bigel formulation showed its drug content. From 93.10% to 99.00% are considered in the measurement of drug content. The formulation B1 contains the least amount of drugs, according to the results, whereas formulation B3 contains the most shown in Table 22.

Table 22: drug content of Loxoprofen bigel

Formulation	Bigel drug content (%)
B1	93.10
B2	98.00
B3	99.00
B4	95.20
B5	97.40

In-Vitro (%) drug release of loxoprofen bigel B1-B5

In-vitro drug release data for all forms of loxoprofen bigel. Using modified in vitro Franz diffusion cell apparatus across a cellophane membrane, the study was performed for 8 hours. Formulation B1 showed a release of 84.77%, Formulation B2 demonstrated a release of 92.35%, and Formulation B3 showed a release of 99.18% up to an 8-hour period. Formulation B4 showed 99.89% release up to 7 hours, while formulation B5 showed 99.23% release up to 6 hours. Comparatively high amounts of organogel were added to formulations B4 and B5, compared to B1, B2, and B3. As the conc. of organogel in the formulation increased, a gradually reduced in the rate & amount of drug release is shown in Table 23 & Fig 7-8.

Table 23: In-Vitro (%) drug release of loxoprofen bigel B1–B5

TIME	B1	B2	B3	B4	B5
0	0	0	0	0	0
15	11.25	14.06	12.18	16.87	25.31
30	16.16	27.46	25.55	29.39	34.25
60	26.77	31.72	35.43	37.47	43.36
120	32.94	38.00	41.75	47.58	57.33
180	40.13	49.98	55.66	56.00	65.94
240	46.53	66.87	64.25	65.50	72.82
300	57.72	72.83	75.78	78.93	86.57
360	63.49	81.70	83.76	89.28	99.23
420	73.11	88.34	90.94	99.89	-
480	84.77	92.35	99.18	-	-

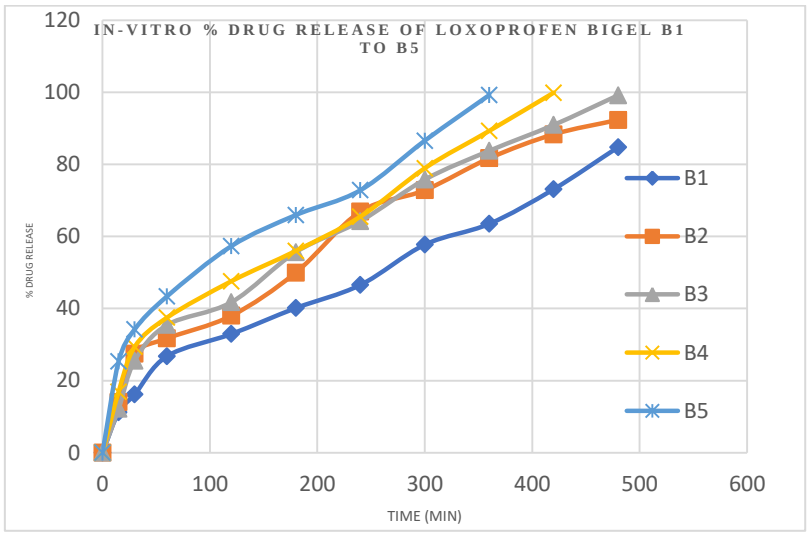


Figure 5: In-Vitro (%) drug release of loxoprofen bigel B1 – B5

Figure 6: bigel formulations of Loxoprofen

Kinetic models of three best bigel formulations B2, B3 & B5 shown in Table 24 & Fig 9.

Table 24: Kinetic models of B2, B3 & B4 bigel formulations

Formulation	Zero order	First order	Higuchi model	Korsmeyer-peppas Model
	R^2	R^2	R^2	R^2
B2	0.948	0.9705	0.9866	0.9708
B3	0.953	0.7924	0.9924	0.9771
B5	0.9508	0.6335	0.9863	0.9806

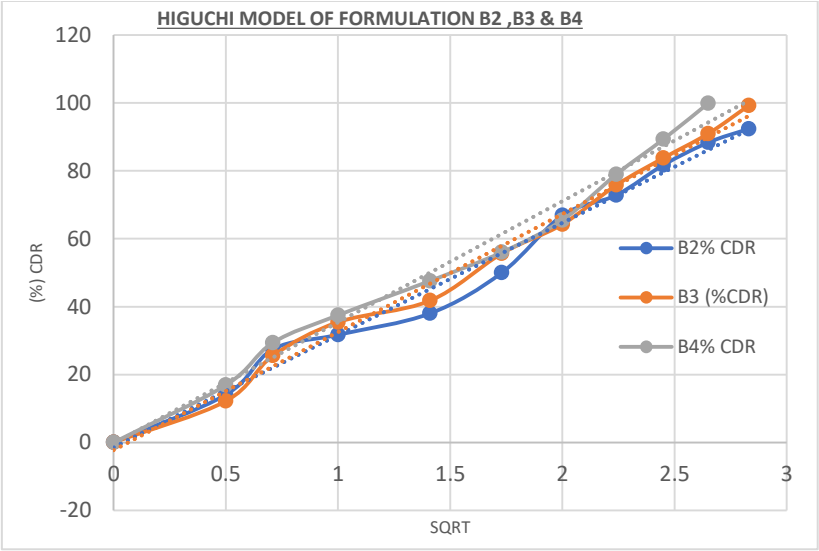


Figure 7: Higuchi model of formulation

Stability studies of bigel best formulation

The formulations' stability studies were completed, and they were stored at various temperatures and levels of humidity. A glass vial containing the formulation was sealed, and it was kept in a stability chamber for a month at 25°C and 40°C. The percentages of drug content, viscosity, and pH were all measured for the sample. In Table 23, the results from the formulation's evaluation are given. The prepared loxoprofen bigel was determined to be physically and chemically stable and did not exhibit any appreciable changes in pH, % drug content, or viscosity from the initial values. Evidently, in typical shelf conditions, all of the gels are stable shown in Table 25.

Table 25: Loxoprofen bigel stability study

Formulation	B3 (25±2ºC)
pH	7.4
Viscosity (cps)	6100
Drug content (%)	98.72

CONCLUSION:

Bigels are a relatively recent concept, and the last ten years have seen the most of the research in this field. The research into to the principles of bigels (hydrogels and organogels) and some of their combinations, such as emulsions, since dosage forms are already highly developed this makes the development and characterization of bigels extremely easy. development of drug delivery bigels and understanding of them have both benefited from research in other areas, like as cosmetics and food technology.. The purpose of the topical drug delivery system is to allow a therapeutic quantity of drug to correct place in the body and to achieve the desired effect of the drug for while. In the present study, we have designed Bigel with loxoprofen. The stratum corneum is properly hydrated because of the hydrogel and organogel in the bigel, which also promotes in greater penetration. Hydrogels and organogels combined for improved patient compliance and increased penetration. To increase the transdermal drug's penetration into the skin, pluronic lecithin organogel (PLO) was selected as the delivery platform. The developed gel's physicochemical properties were assessed in accordance with standards protocol called compliance following patient use. No chemical reaction of loxoprofen is found even after spectroscopical analysis. The gel's (physical appearance and FTIR) bigel concentration was uniform, and the kinetics of the drug release was well-ordered. Therefore, it can be said that Loxoprofen bigel allows controlled release of the drug, and those systems can be useful as drug delivery carriers.

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