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# Bigel-Based Transdermal Delivery Of Ketoprofen And Tulsi Oil: A Synergistic Approach For Effective Inflammation Control

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***Abstract:***
*This study investigates the development of ketoprofen bigel for transdermal route to reduce the inflammation by using HPMC K100 (hydroxypropyl methyl cellulose) based hydrogel and carbopol 930 based oleogel with Tulsi oil. Tulsi oil has analgesic and anti-inflammatory activity, menthol is also added in the formulation to give a cooling sensation, increasing blood flow and pain reduction. Upon exhaustive research, the transdermal drug delivery system (TDDS) has appeared as a potential, widely accepted, and popular approach to a novel drug delivery system. Ease of administration, easy handling, minimum systemic exposure, least discomfort, prolonged therapeutic effect; make it a promising approach for drug delivery. All prepared formulations were evaluated for In-vitro diffusion study using cellulose acetate membrane. Ex-vivo study is carried out using rat's abdominal skin. The desired drug release was obtained by optimized preparation, which contains 2.5% ketoprofen. All the prepared formulations showed good apperance. The spreadability results obtained were in correlation to the amount of polymers being added. Higher polymer concentration resulted in higher viscosity, resulting in poor spreadability and extrudability. Drug release from the bigel was 70.68 – 95.72% after 4 hours of study. Different batches were having the PH 5.11– 6.50.*
***Key words:*** *Osteoarthritis, Spreadability, bigel, thermogram, hydrogel,*

## INTRODUCTION:

Ketoprofen is chemically a propionic acid derivative, non steroidal anti-inflammatory drug (NSAID). Its anti-inflammatory action is due to inhibitory effect on cyclooxygenase-2, an enzyme involved in prostaglandin synthesis that is responsible for inflammation. Ketoprofen possesses analgesic, antipyretic, and anti-inflammatory properties, making it effective in managing muscle and joint inflammation, osteoarthritis, and joint stiffness. However, when administered orally, it is commonly linked with systemic side effects, particularly gastrointestinal disturbances, which occur more frequently than with many other NSAIDs. These drawbacks can be overcome by employing topical or transdermal formulations, as they bypass gastrointestinal irritation and help minimize systemic adverse effects.

Transdermal delivery of NSAIDs provides several benefits, including protection of the drug from gastric degradation, elimination of first-pass metabolism, and a lower risk of gastrointestinal complications such as ulcers, bleeding, and perforations. Among the newer dosage forms, bigels have attracted considerable attention. These are biphasic semisolid systems created by blending two distinct gel phases under high shear, resulting in a visually uniform gel. Bigels are considered a promising drug delivery platform, offering potential for controlled drug release.

This Bigel formulation contains tulsi oil, tulsi oil exhibits significant anti-inflammatory and analgesic activity, primarily attributed to its rich content of bioactive compounds such as eugenol, ursolic acid, and rosmarinic acid. These constituents help reduce inflammation by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) pathways, thereby decreasing the synthesis of pro-inflammatory mediators like prostaglandins and leukotrienes. Additionally, tulsi oil modulates cytokine production and scavenges free radicals, which further alleviates oxidative stress and tissue damage. Its analgesic effect is linked to the suppression of pain mediators and modulation of central and peripheral nociceptive pathways, making it a natural therapeutic agent for pain and inflammation management.

## MATERIALS AND METHODS:

Ketoprofen, Carbopol 934, HPMC K100, Tri-ethanolmine and ethanol was purchased from swaroop pharmaceuticals. (Chhatrapati Sambhajinagar, India). All chemicals used during research were of analytical grade.

**Pre- formulation studies:**

**Characterization of Ketoprofen:**

**Appearance:**

The sample of Ketoprofen was tested for its colour, odour and taste.

**Melting point:**

Thiel's tube apparatus was used to determine melting point of the ketoprofen.

**Solubility:**

An excess amount of ketoprofen was added to 100 ml of different chemicals like methanol, ethanol, phosphate buffer and acetate buffer. These solutions were kept on a rotary shaker for about 48 hours at100 rpm. After 48 hours these solutions were filtered using whatman's filter paper. The filtrates were diluted with respective chemicals ie methanol, ethanol, phosphate buffer, acetate buffer and quantified by using U.v spectrophotometer at 256nm.

**Uv spectrophotometric evaluation:**

For determining absorption maxima, ketoprofen was dissolved in sufficient quantity of ethanol and volume was make up with phosphate buffer (pH-6.8) to make stock solution and from this stocksolution different concentrations were prepared by further diluting these solutions with phosphate buffer. From these solutions one solution was taken and scanned from 200- 400nm. Absorption maxima was found at 256nm. The absorption maxima and calibration curve was given in a figure no.(1,2).

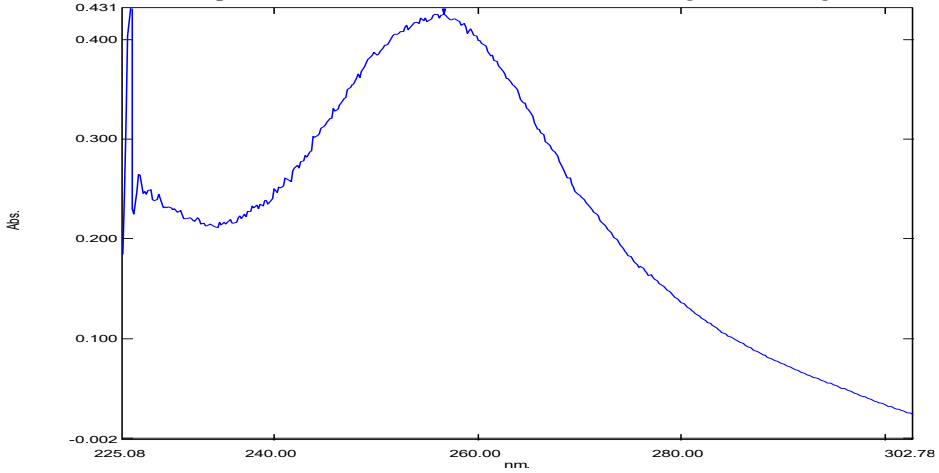


**Figure no. 1. Absorption maxima of ketoprofen**

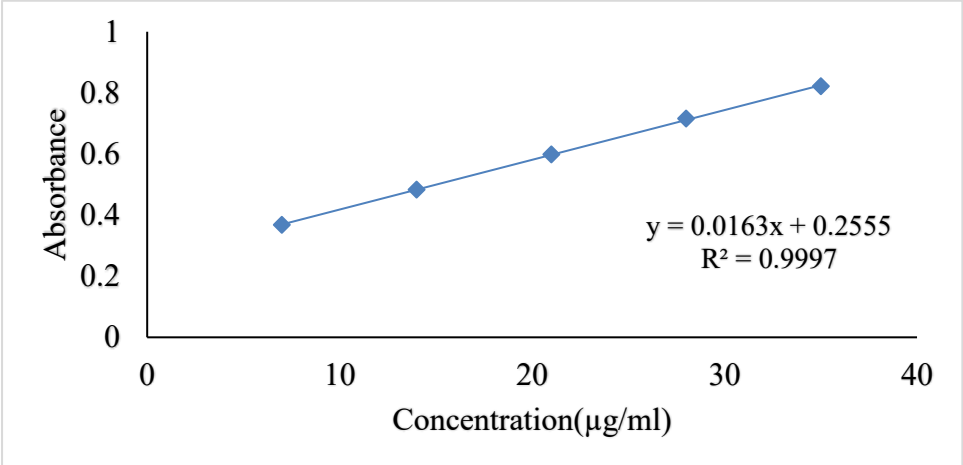


**Figure no.2. Calibration curve and linear regression equation of ketoprofen at 256nm**

**FT-IR Spectrophotometric determination:**

The purity of the drug was verified using FT-IR spectroscopy, and drug–excipient compatibility was evaluated with an FT-IR spectrometer (Shimadzu 8400-S, Japan). For the analysis, a 1:1 ratio (w/w) sample was blended with dry potassium bromide (KBr) relative to the KBr disc. The mixture was finely powdered using an agate mortar and then compressed into a disc with a hydraulic press at 1000 psi. Each disc was subsequently scanned 16 times at a speed of 2 mm/sec, with a resolution of 4 $cm^{-1}$, employing cosine apodization. The characteristic peaks were obtained, and FT-IR spectra were analyzed for the pure drug, the drug–polymer combination, and the optimized bigel and they are presented in Figures 3, 4, and 5.

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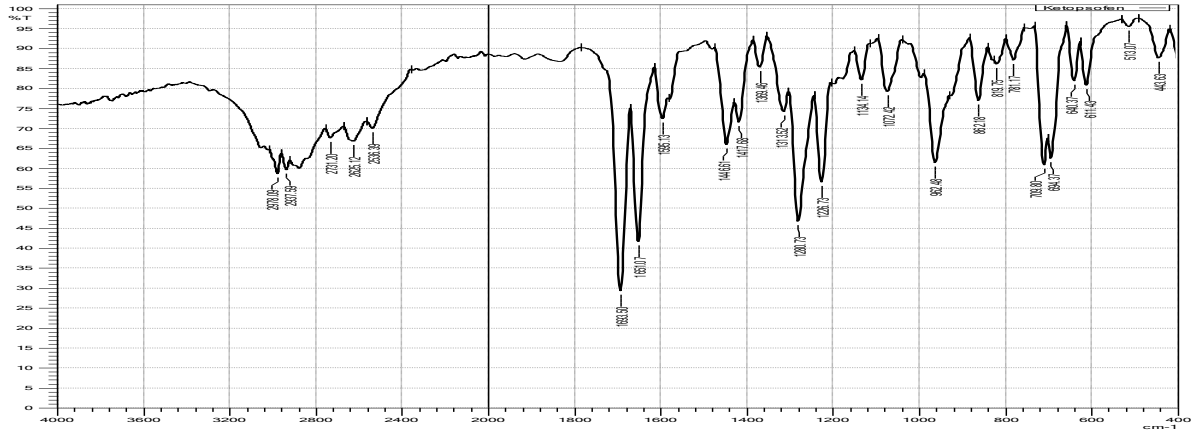



**Figure no.3. FT-IR spectrum of ketoprofen**

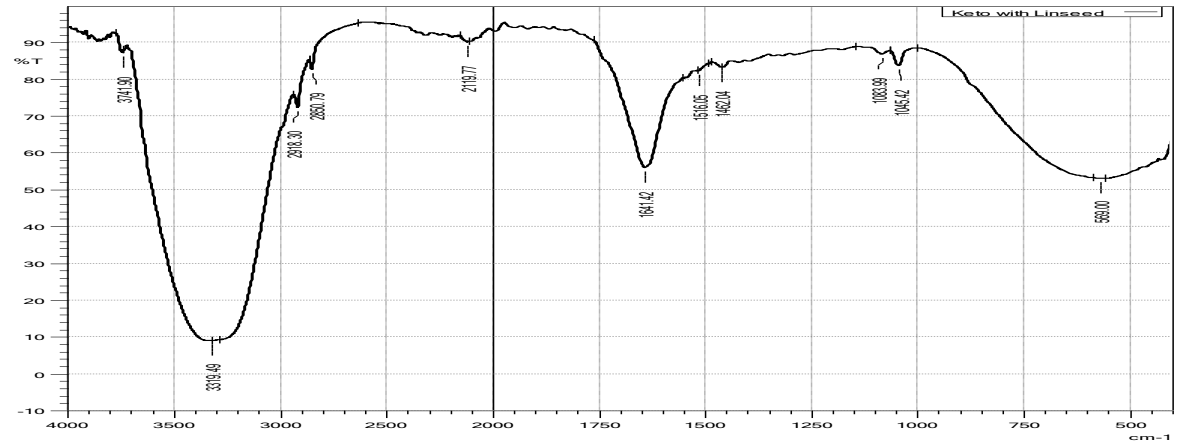



**Figure no.4. FT-IR spectrum of optimized KT2 Bigelformulation**

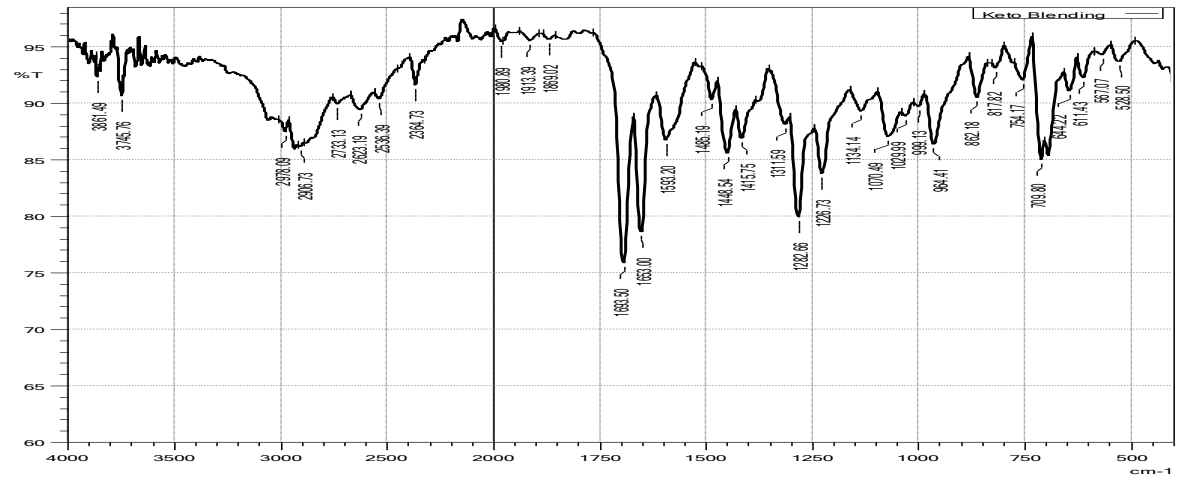



**Figure no.5. FT-IR spectrum of ketoprofen with blend of excipients**

**DSC thermal analysis of the drug:**

Thermal analysis was carried out to assess the purity of the drug sample. The results showed a distinct endothermic peak at 92.99 °C, corresponding to the melting point of the drug, thereby confirming its purity. The thermograms of both the pure drug and the drug–polymer mixture are presented in Figure no.(6, 7)

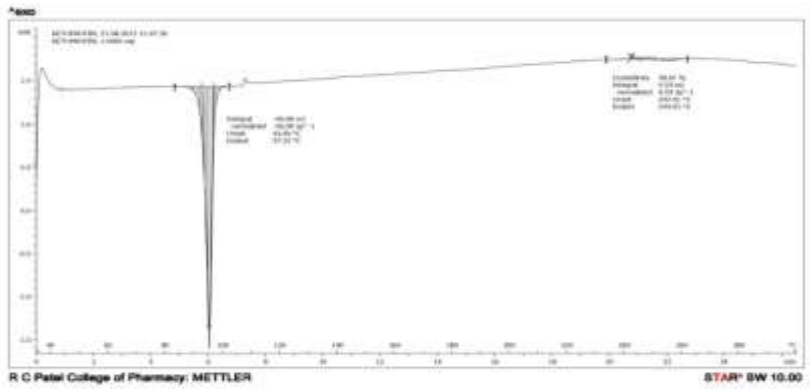



**Figure no. 6. DSC thermogram of Ketoprofen**

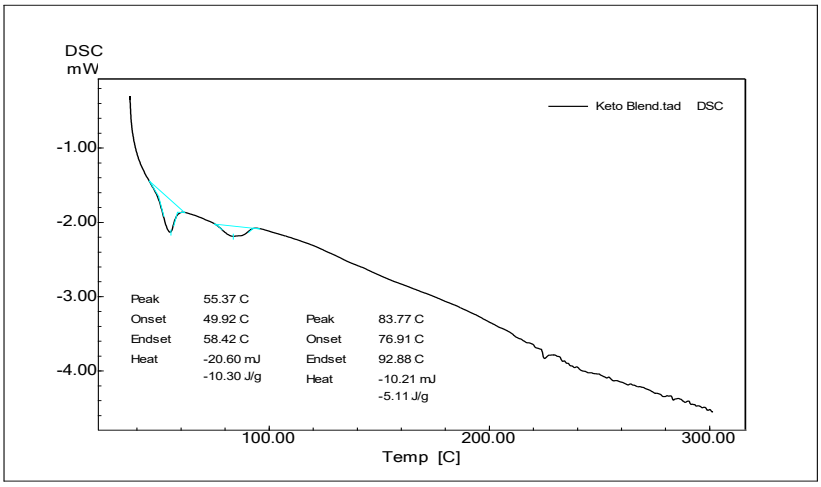



**Figure no. 7. DSC thermogram of ketoprofen with blend of excipients**

**Formulation of ketoprofen bigel with tulsi oil:**

The bigel of ketoprofen was formulated using polymers such as carbopol 934, HPMC K100, and span 60, with tulsi oil serving as the organogelator. The preparation involved two gel systems—oleogel and hydrogel—combined through a three-step process.

For oleogel preparation, carbopol 934 was dissolved in an adequate amount of water and stirred on a magnetic stirrer at 500 rpm for 2 hours. Separately, span 60 was dissolved in a beaker placed on a water bath, followed by the addition of Tulsi oil. The previously prepared carbopol 934 solution was then incorporated into this mixture, and triethanolamine was added to obtain a smooth oleogel.

For the hydrogel, HPMC K100 was dispersed in sufficient water and stirred magnetically at 500 rpm for 2 hours. The drug was dissolved in ethanol, to which menthol was added. After 2 hours, HPMC K100 was incorporated into this mixture to form the hydrogel.

Finally, the bigel was prepared by gradually adding the hydrogel into the oleogel under mechanical stirring at 1000 rpm, resulting in a homogeneous formulation.

Different formulations were prepared(KT1, KT2, KT3, KT4, KT5, KT6, KT7, KT8) and evaluated for different parameters.Polymer concentrations were given in table. (1).

**Table no.1: Polymer concentration used in bigel**

| Formulation code | Carbopol 934 (gm) | HPMC K100 (gm) | Span 60 (gm) |
|---|---|---|---|
| KT1 | 0.08 | 0.08 | 2 |
| KT2 | 0.06 | 0.06 | 2 |
| KT3 | 0.06 | 0.06 | 1 |
| KT4 | 0.08 | 0.06 | 1 |

| | | | |
|---|---|---|---|
| KT5 | 0.08 | 0.06 | 2 |
| KT6 | 0.06 | 0.08 | 2 |
| KT7 | 0.08 | 0.08 | 1 |
| KT8 | 0.06 | 0.08 | 1 |

**Characterization of bigels**

**Appearance:**The prepared bigels were visually examined for their appearance. Each batch was inspected for the presence of any lumps after being set in containers. The observations are presented in Table no. (2).

**PH measurement:**The pH of the bigels was determined using a digital pH meter. All batches showed pH values ranging between 5.11 and 6.50, which does not causes skin irritation. The results are provided in Table no. (2).

**Spreadability:** To evaluate the spreadability of the formulated bigel, a simple apparatus consisting of two glass slides was used, with the upper slide connected to a pulley system. The slides were positioned on a wooden block, and a measured quantity of bigel was placed on the lower slide. A 200 g weight was then added to the pan attached to the pulley, causing the upper slide to move over the lower one and spreading the bigel by the slip and drag method. The time taken for the two slides to separate was recorded. The formula used to calculate spreadability is provided below:

$S = M. L / T$

Where M = weight tied to upper slide, L = length of glass slides, T = time taken to separate the slides.
Spreadability results were given in a table no. (2).

**Extrudability:** The extrudability of the formulation was determined using a Pfizer hardness tester. A 20 g sample of the prepared bigel was filled into an aluminum collapsible tube fitted with a plunger. A force of 1 kg/cm$^2$ was applied to the tube to expel the bigel, and the amount extruded was weighed. This procedure was repeated three times at different points on the same tube. The results are presented in Table no. (2).

**Viscosity determination:**Viscosity was evaluated on Brookfield viscometer with spindle no. S63 using 4 rpm and torque 84%. The formulation was evaluated for viscosity at a temperature (25- 27°C).The results of viscosity was given in a table no. (3).

***In-vitro* drug release evaluation:**Phosphate buffer (pH 6.8) was used as a medium in a franz diffusion cell for checking *In-vitro* drug release of the drug. Cellulose acetate membrane was used on which 1 gm of bigel was placed and this membrane was attached in between donor and receptor compartments. The assembly was placed on a magnetic stirrer at 500 rpm. The temperature of the medium was thermostatically controlled at 37 ± 0.5°C which resembles to body temperature. 1 ml of the sample was removed from the sampling port at predetermined intervals and same volume was replaced by phosphate buffer. These removed samples were scanned under U.v spectroscopy at 256 nm and %*In-vitro* drug release was calculated. The results are shown in a table no. (3) and figure no.(9).

**Drug content determination:** A 100 mg sample of the formulated bigel was dissolved in methanol and sonicated for 15 minutes. The solution was then placed on a mechanical shaker for approximately 2 hours, after which it was filtered using a 0.45 µm syringe filter. An appropriate volume of the filtrate was collected, diluted with methanol, and analyzed using a UV spectrophotometer at 256 nm to determine the percentage drug content. The results are presented in Table no. (2).

***Ex-vivo* skin permeation study using rat abdominal skin:**

The percentage drug permeation from the bigel formulation was evaluated using rat abdominal skin in a Franz diffusion cell. A 2–3 cm section of skin was excised from the abdomen after hair removal with a depilatory cream. One gram of bigel was applied onto the skin, which was then positioned between the donor and receptor compartments of the diffusion cell. The receptor compartment was filled with phosphate buffer (pH 6.8), and the temperature was maintained at 37 ± 0.5 °C using a water jacket. The setup was placed on a magnetic stirrer operating at 500 rpm. At predetermined time intervals, samples were withdrawn from the receptor medium and replaced with an equal volume of fresh phosphate buffer (pH 6.8). The absorbance of the collected samples was analyzed using UV spectroscopy, and the percentage drug permeation was calculated. The results are presented in Table no. (4) and Figure no. (10).

**Stability studies:**

According to ICH Q1A(R2) guidelines stability studies of the optimized KT2bigelformulation was done. The bigel was filled into aluminium collapsible tubes and store at controlled temperature and humidity condition. The stability study was done for a period of six months. The temperatures and humidity conditions are 30˚±2˚C/65±5% RH.

The results shows that optimized bigel formulation does not show any change in colour, pH, viscosity, extrudability, spreadability, % drug release. The results are given in a table no. (5).

**Animals:**

Albino Wistar rats of either sex, weighing between 250–300 g, were obtained from Wockhardt Pvt. Ltd., D-4, Chikalthana MIDC, Chhatrapati Sambhajinagar, Maharashtra. The experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC) under registration no. CPCSEA/IAEC/P'Ceutics/56/2023-24/181, in accordance with the Animal Welfare guidelines of the CPCSEA, Government of India.

Before initiating the study, the animals were acclimatized to laboratory conditions for 4–5 days. They were housed in standard wire mesh plastic cages under controlled environmental settings, maintaining a room temperature of 28 ± 5°C and relative humidity of 55 ± 5%. Throughout the study, the animals were provided with unrestricted access to standard pellet chow and water. All experimental procedures on animals were conducted in compliance with the ethical guidelines approved by the IAEC.

**Evaluation of anti-inflammatory activity:**

**Carrageenan-induced paw oedema model:**

The anti-inflammatory effect of the ketoprofen bigel was assessed following the procedure reported by Prof. Dr. S.K. Gupta et al. (13) and Hongxing Zhang et al. (15). Twenty Albino Wistar rats were randomly allocated into four groups, each consisting of five animals. Group I served as the control and was treated with gel base, Group II was administered with carrageenan (1%) without treatment, Group III received a marketed ketoprofen gel (Ketotopic), and Group IV was treated with the prepared ketoprofen–tulsi oil bigel formulation.

To induce inflammation, all groups were injected with 0.1 ml of 1% w/v carrageenan (in normal saline) into the sub-plantar region of the left hind paw.One hour post-injection, 100 mg of the Ketoprofen with tulsi oil bigel formulation was applied transdermally onto the left hind paw in the treatment groups, by gently rubbing with the
index finger approximately 50 times.[33]

Paw volume was measured in all groups at regular intervals up to six hours after the application of the formulations, starting two hours post-application. A graduated Vernier caliper was used to assess changes in paw oedema before and after treatment. The percentage inhibition of oedema (protection) was then calculated using the formula given below.

% protection = 100 * (Vc – Vd) / Vc (1)

where Vc is paw volume without treatment of drug and Vd is paw volume following drug treatment.Results are given in table no.(6) and figure no.(11,12,13).

1. **Statistical Findings**

The results are expressed as mean ± SD. Data were analysed using Graphpad prism 10. Comparison between different groups was done by one-way ANOVA followed by Dunnette's multiple comparison test to compare difference between groups at the pre specified time intervals. p-value less than ($p$<0.001) indicates that data is statistically significant.

**Anti-nociceptive activity:**

Animals were divided into three groups 5 animals each. Albino Wistar rats were used for carrying out the studies. These groups were treated as follows:

Group I: Control

Group II: Applied with marketed gel

Group III: Treated with Ketoprofen Tulsi oil bigel formulation

**Hot plate analgesia test:**

A modified version of the Eddy and Leimbach method was employed to study the analgesic effects of the drugs. The hot plate analgesia meter was utilized as the instrument for this study. (Biocraft scientific systems pvt Ltd. AGRA-5 (India). The apparatus featured an electrically heated flat platform designed to prevent the animal from escaping. The temperature of the hot plate was adjustable and maintained at 50°C–55°C for this experiment. Food was withheld 12 hours prior to drug administration and was reintroduced after the experiment concluded. Individual mice were placed on the hot plate and promptly

removed upon observing responses such as jumping or paw licking. A cut-off time of 10 seconds was enforced to prevent thermal injury to the paws. The reaction time, defined as the duration (in seconds) for the animal to display reflexive pain behaviour, was recorded at 0, 30, 60, 90 and 120 minutes after treatment.:[34]Results are expressed in figure no. (14)

The percentage protection against paw licking response was used to assess the % analgesia and was calculated using the following formula:

$$Perentage\ Protection = \frac{(\text{Test Latency} - \text{Control Latency})}{(\text{Cut off time} - \text{Control Latency})} \text{x} 100$$

**Evaluation of analgesic activity using the tail-flick test in rats:**

Tail flick method was used to evaluate analgesic activity of optimized KT2 bigel formulation. The albino Wistar rats of either sex weighing between 250-300 gm were used during studies and they are divided into 3 groups of 5 animals (n=5), Group I Control group and were treated with vehicle, Group II treated with marketed ketoprofen gel (ketotopic 2.5%) Group III Treated with KT2 Bigel formulation(100 mg of ketoprofen 2.5%) applied to 3-5 cm portion of the rat's tail. After 30 minutes of application of gel, Bigel remaining on the surface of the skin was wiped off with help of piece of cotton. The distal 2-3 cm portion of rat's tail was immersed in hot water maintained at 55 ± 0.5 °C. The time taken by rat to withdraw the tail from hot water was noted as reaction time. The reaction time was recorded at 0, 30, 60, 90 and 120 min after the application of the treatments as explained above. The cut off time was considered as 15 sec to prevent tissue injury.The percentage protection against tail-flick response was used to assess the % analgesia and was calculated using the following formula:

$$Perentage\ Protection = \frac{(\text{Test Latency} - \text{Control Latency})}{(\text{Cut off time} - \text{Control Latency})} \text{x} 100$$

Results of tail flick method was given in figure no. (15)

**RESULTS AND DISCUSSION:**

Ketoprofen bigel was formulated by changing concentrations of polymers. Different batches were prepared and evaluated.

**Appearance:**

All formulated bigels were white in colour and smooth in texture.Formulated bigels were homogeneous, there is no grittiness present into the formulation. The results are given in table no. (2).

**Table no. 2: Appearance,Spreadability, Extrudability Parameters, PH, Drug content**

| Formulation code | Appearance | Spreadability | Extrudability | pH | Drug content (%) |
|---|---|---|---|---|---|
| KT1 | White color smooth texture | 68 ± 1.50 | 0.48± 0.03 | 6.50 ± 0.39 | 99.96 ± 1.05 |
| KT2 | White color smooth texture | 74.5 ± 1.26 | 0.64 ± 0.07 | 5.68 ± 0.34 | 98.59 ± 0.27 |
| KT3 | White color smooth texture | 75 ± 1.29 | 0.65 ± 0.04 | 6.23 ± 0.34 | 98.34 ± 0.21 |
| KT4 | White color smooth texture | 71 ± 1.28 | 0.56 ± 0.03 | 5.42 ± 0.22 | 97.11 ± 0.22 |
| KT5 | White color smooth texture | 70 ± 1.25 | 0.54 ± 0.07 | 6.26 ± 0.39 | 97.89 ± 0.37 |
| KT6 | White color smooth texture | 73 ± 1.14 | 0.6 ± 0.06 | 5.11 ± 0.17 | 99.48 ± 0.29 |
| KT7 | White color smooth texture | 68.5 ± 1.65 | 0.5 ± 0.03 | 5.31 ± 0.29 | 98.27 ± 0.42 |
| KT8 | White color smooth texture | 74 ± 1.75 | 0.62 ± 0.01 | 6.35 ± 0.16 | 99.72 ± 0.81 |

**pH measurement:**

pH of any formulation is important because a small change in pH can produce irritation or itchiness. The pH of all the prepared formulations are shown in table no. (2).

**Spreadability:**

The spreadability test results demonstrated that the bigel formulations could be easily spread with the application of minimal force. The prepared bigels (KT1 to KT8) exhibited spreadability values ranging between 68 and 75 g·cm/sec. Among these, KT2 was identified as the best formulation, showing a desirable spreadability value. The detailed results are presented in Table 2.

**Extrudability:**

Extrudability is an essential characteristic of semisolid formulations, as it determines the ease with which the preparation can be dispensed from its container. Among the tested formulations, KT2 exhibited the best extrudability. The detailed results are presented in Table 2.

**Viscosity:**

The viscosity of all batches was measured using a Brookfield viscometer and was found to range between 47615 and 86,147 cps. The optimized KT2bigel formulation, showed a viscosity of 55950 cps. The viscosity results are presented in Table 3.

**Table no. 3. Viscosity & I*n-vitro* drug release**

| Formulation code | Viscosity (cps) | I*n-vitro* drug release (%) |
|---|---|---|
| KT1 | 86147 ± 431 | 70.68 ± 2.89 |
| KT2 | 55950 ± 168 | 94.46 ± 4.06 |
| KT3 | 47615 ± 238 | 95.72 ± 4.13 |
| KT4 | 64672 ± 194 | 82.32 ± 3.71 |
| KT5 | 67878 ± 339 | 79.09 ± 2.56 |
| KT6 | 73487 ± 220 | 90.21 ± 3.84 |
| KT7 | 85869 ± 429 | 70.81 ± 2.63 |
| KT8 | 71286 ± 214 | 90.6 ± 3.92 |

***In-vitro* drug release evaluation:**

Percent drug release of all the bigelsformulations was evaluated by using franz diffusion cell. The values of % drug release of batches KT1 TO KT8 is in the range of 70.68-95.72%. The KT2 Bigelformulation is optimized bigel which is having drug release 94.46%. The % release of the drug from formulation is given in a table no. (3)& drug release plot is shown in figure no. (8,9).

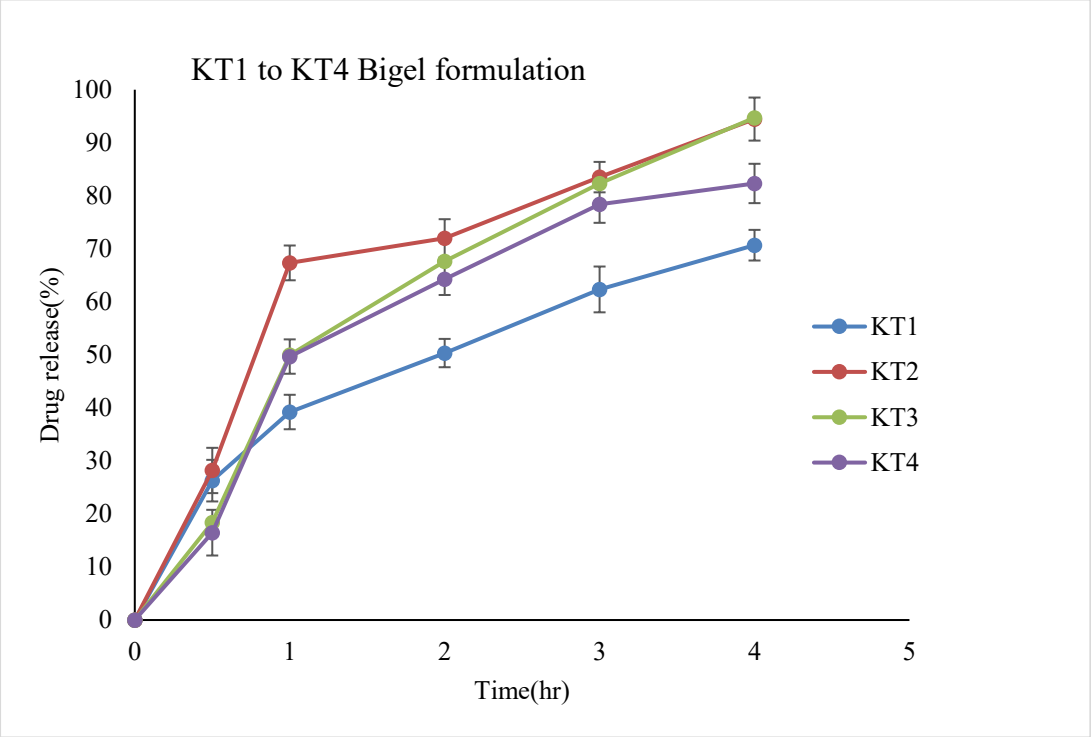



**Figure no. 8. *In-vitro* % drug release of KT1 to KT4 Bigl formulation**

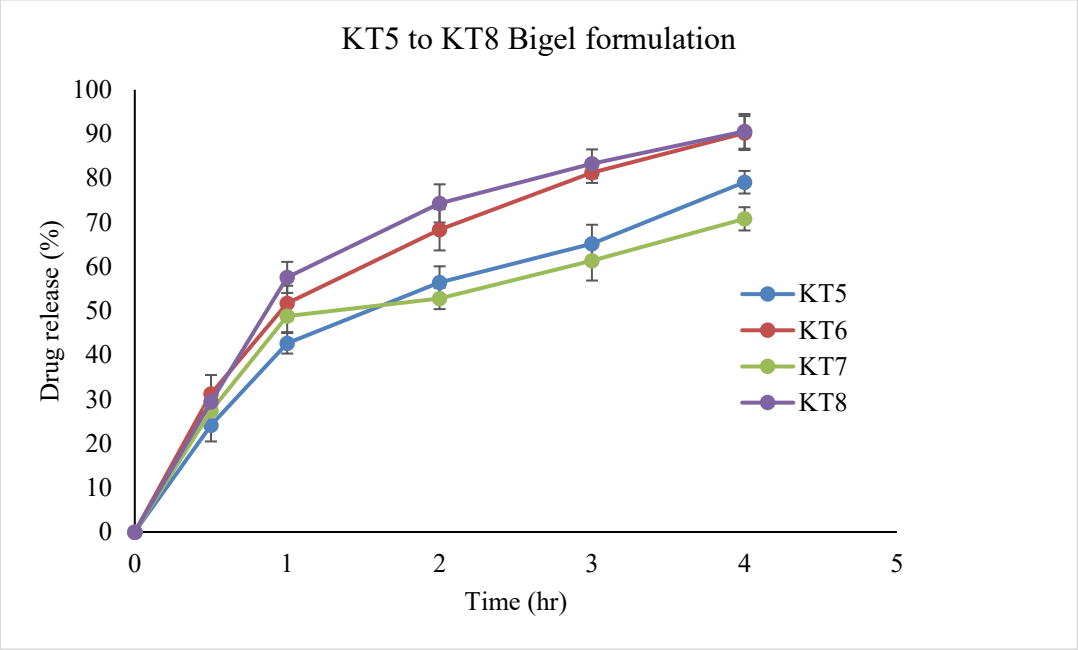



**Figure no. 9. *In-vitro* % drug release of KT5 to KT8 Bigl formulation**

**Drug content determination:**

The drug content of the formulated bigels was determined using UV spectroscopy. The percentage of drug content in the formulations ranged from 97.11% to 99.96%. The results are provided in Table 2.

***Ex-vivo* skin permeation study using rat abdominal skin:**

The % drug permeation of the optimized KT2bigel formulation was determined using rat's abdominal skin. The optimized KT2bigel formulation shows drug permeation85.34%. The plot of drug permeation is given in a figure no. (8) & values of % drug permeation is shown in a table no. (4).

**Table no. 4: *Ex-vivo* permeation of optimized KL8 bigel through rat's skin**

| Sr.no | Time | Drug permeation (%) |
|---|---|---|
| 1 | 0 | 0.000 |
| 2 | 0.5 | 22.24 ± 4.16 |
| 3 | 1 | 37.12 ± 2.34 |
| 4 | 2 | 44.96 ± 3.12 |
| 5 | 3 | 52.91 ± 2.63 |
| 6 | 4 | 62.32 ± 4.44 |
| 7 | 5 | 76.28 ± 3.12 |
| 8 | 6 | 85.34 ± 2.21 |

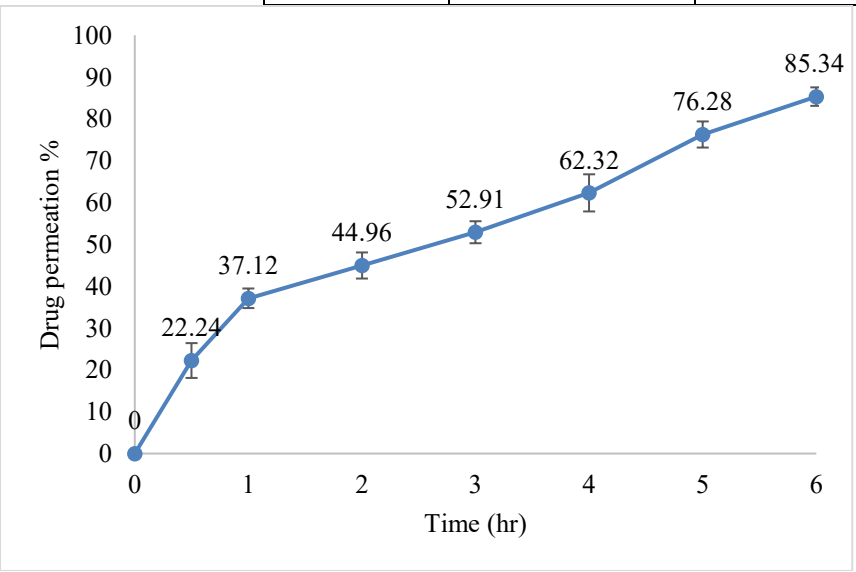



**Figure no. 10. *Ex-vivo* % drug permeation of ketoprofen through rat's abdominal skin**

**Stability studies:**

The optimize KT2 bigel formulation was studied for stability studies as per ICH guidelines. The formulation was kept at 30°±2°C/65±5% RH.

The results shows that KT2bigelformulation does not showssignificant change in colour, texture, viscosity, spreadability, extrudability, % drug release. The results are given in table no. (5).

**Table no. 5: Stability studies of optimized Ketoprofem with tulsi oil bigelformulation (KT2)**

| Parameters | 0 day | 90 days | 180 days |
|---|---|---|---|
| pH | 5.68 ± 0.35 | 5.61 ± 0.30 | 5.56 ± 0.28 |
| Drug content (%) | 98.59 ± 0.27 | 98.47 ± 0.23 | 97.41 ± 0.20 |
| *In-vitro* drug release (%) | 94.46 ± 4.06 | 94.32 ± 3.45 | 93.18 ± 3.13 |
| Spreadability (g.cm/sec) | 74.5 ± 1.26 | 73.28 ± 1.20 | 73.17 ± 1.14 |
| Extrudability(g/sec) | 0.64 ± 0.07 | 0.61 ± 0.04 | 0.57 ± 0.02 |

**Anti-inflammatory activity:**

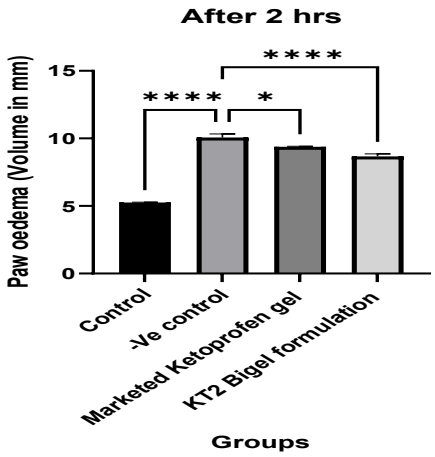
**Carrageenan-induced paw oedema model**

Transdermal application of the optimized ketoprofen bigel formulation significantly ($P < 0.0001$) reduced carrageenan-induced paw oedema in rats compared to the control group. The maximum inhibition of paw oedema was observed after 6 hours treatment with the optimized ketoprofen with tulsi oilbigel formulation (KT2). The results are given in table no. (6)

**Table no. 6. Evaluation of Anti-inflammatory activity using carrageenan-induced paw oedema in rats**

| Sr.no. | Groups | After 2 hrs | After 4 hrs | After 6 hrs | % Inhibition |
|---|---|---|---|---|---|
| 1 | Control | 5.26 ± 0.031 | 5.27 ± 0.03 | 5.27 ± 0.04 | - |
| 2 | Negative control | 10.07 ± 0.57 | 10.92 ± 0.52 | 12.40 ± 0.24 | - |
| 3 | Marketed ketoprofen | 9.38 ± 0.09 | 8.02 ± 0.64 | 7.85 ± 0.46 | 29.67 |
| 4 | Optimized ketoprofen bigel | 8.66 ± 0.43 | 7.72 ± 0.36 | 7.07 ± 0.50 | 47.36 |

ns- non significant**** $P < 0.0001$, ****$P < 0.05$, Values are Mean ± SEM, n = 5 when compared with inflammatory control by using one-way ANOVA followed by Dunnette's multiple comparison test.



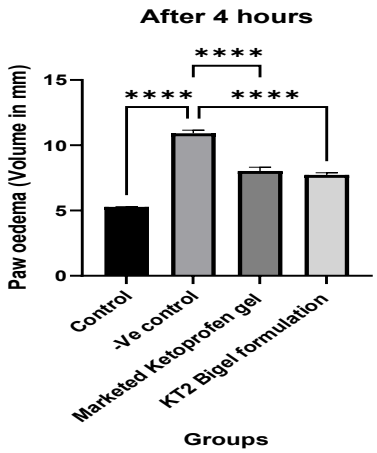




**Figure no. 11. Anti-inflammatory study after 2 hrs**

**Figure no. 12. Anti-inflammatory study after 4 hrs**

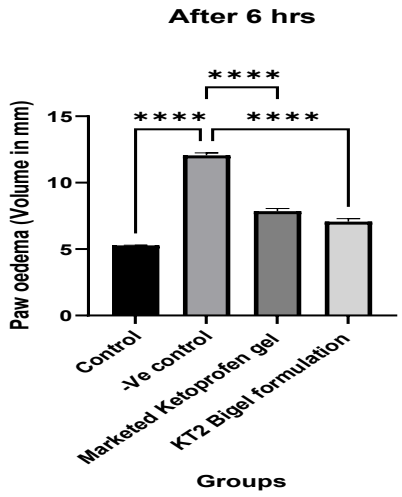



**Figure no. 13. Anti-inflammatory study after 6 hrs**

**Results of Hot plate analgesia test:**

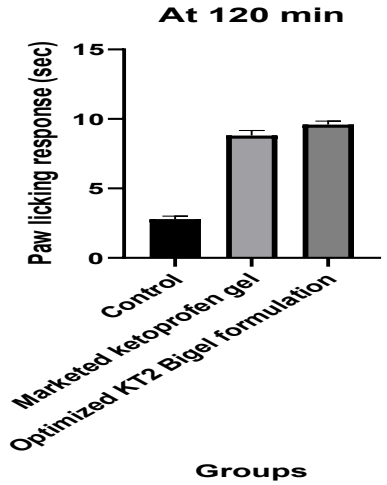



**Figure no. 14. Analgesic activity evaluation using Hot plate method for ketoprofen marketed gel and optimized KT2 Bigel formulation are compared with that of control group $p < 0.0001$. Results are expressed as Mean ± SD using Dunnettes multiple comparison test, (n=5).**

**Results of analgesic activity using the tail-flick test in rats:**

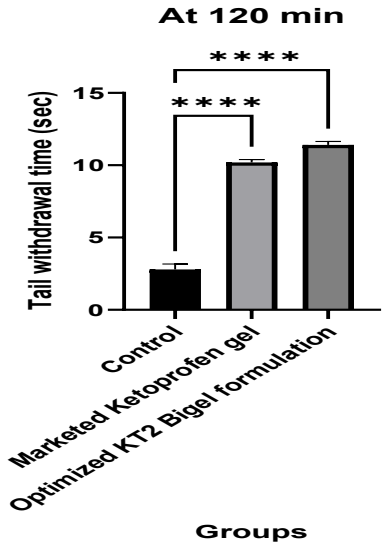



**Figure no. 15. Analgesic activityevaluation using tail flick method for Marketed formulation and optimized KT2 Bigel formulation after application of respective treatments. Results are expressed as**

**mean ± SD: p < 0.0001 vs control for marketed formulation and p < 0.0001 vs KT2 Bigel formulation (Dunnettes multiple comparison test)**

**Conclusion:**

Ketoprofen drug is characterized by Uv spectroscopy to check its purity. Different concentrations were made by diluting the stock solution with suitable solvent, λmax was found at 256nm. In FT-IR analysis ketoprofen shows C-H stretching at 2734.20cm$^{-1}$, O-H stretching was observed at 2978.09 cm$^{-1}$, C = O stretching was found at 1693.50 cm$^{-1}$, C=C (aromatic ring, stretching) was found at 1595.13 cm$^{-1}$. DSC thermogram shows an endothermic peak at 97.25 °c which indicates melting point of the ketoprofen. Bigel was prepared by using polymers like carbopol 934 and HPMC K100 these polymers,Tulsi oil and other excipients used in formulation does not causes a change in ketoprofen which was confirmed by FT-IR. Linseed oil increase anti-inflammatory and analgesic activity of the formulation. All the prepared bigel formulations are characterized by different tests. From these tests the best batch was chosen and further subjected for checking % drug permeation studies of the formulation. Rat's abdominal skin was used as a membrane in Franz diffusion cell, 85.34% drug was permeated in 6 hours from the optimized bigel formulation.

Carrageenan induced paw oedema method was used to evaluate anti-inflammatory studies of KT2Bigel formulation. KT2bigel formulation have inhibited paw oedema significantly compare to that of marketed ketoprofen gel. Analgesic activity wa evaluated using hot plate and tail flick method Where KT2 Bigel formulation shows significant percentage protection than marketed ketoprofen gel, p value was found to be <0.0001 using Dunnette's multiple comparion test.

**Conflict of interest:** No

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