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Design and Testing of a Microemulsion Gel Transdermal Delivery System of Ibuprofen: Skin Permeation

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Abstract
Transdermal system has non-invasive method of drug delivery that has a lasting therapeutic effects and minimises a gastrointestinal side effects. This study was intended to design and test a microemulsion based gel containing ibuprofen as an agent to increase skin permeation and enrich the onset of action. Microemulsion formulation comprised 10% isopropyl myristate, 5% Tween 80, 5% ethanol and water populated in Carbopol 934 gel-base for increased viscosity and stability. The physicochemical characteristic of the gel was obtained, showing high (96.3%) drug-loading efficiency and appropriate viscosities that make it suitable to be used topically. Ex vivo skin permeation study in Franz diffusion cells indicated the highest 3.1-fold difference in the flux of the ibuprofen over conventional gel systems. In vivo studies on rats showed that the gel has a quick onset of effect and its ability to demonstrate a higher percentage of decrease in paw edema demonstrates that it is effective in its anti-inflammatory behavior. The microemulsion gel was a highly potential alternative that would be of excellent use in rapid action and effective administration of NSAIDs, in pain medication and anti-inflammatory treatment.

Keywords: ***Transdermal drug delivery, micro emulsion gel, Ibuprofen, skin permeation, Franz diffusion cells, drug release, anti inflammatory, NSAIDs, buccal absorption, pharmacokinetics, therapeutic effect.***

1. Introduction

1.1 Summary of the Benefits of Transdermal Drug Delivery

The area of pharmaceutical sciences has shown tremendous interest in transdermal drug delivery because of the non- invasive and controlled release of drugs that accompany their use. The route of this delivery method does not involve the gastrointestinal (GI) tract, which is likely to attract first-pass metabolism common in oral medications. Consequently, the transdermal systems have greater potential to present higher bioavailability and therefore improved therapeutic effects can be realized. Moreover, transdermal systems are convenient, since they release drugs continuously during an extended period of time, which is beneficial in the case of patients in need of chronic treatment. They also improve patient compliance since the period is less frequently administered as compared to conventional oral formulations which require compulsory routine dose interval.

Moreover, transdermal delivery devices provide localized effect at the point of application, and thus suitable when dealing with the form of diseases such as pain, inflammation and muscle spasms. Considering the fact that skin is the largest organ of the body, it is the best avenue through which drugs can be delivered in a non-invasive way. What more, these systems enhance less gastrointestinal side effects which are usually linked to some drugs, including irritation and ulceration. In that manner, the transdermal drug delivery is already investigated and is more widely used in the implementation of chronic diseases and in acute treatments, being a patient-friendly variant compared to such traditional methods as pills.(1)

1.2 The Difficulty of Topical Delivery of Nonsteroidal Anti-inflammatory Drugs, such as Ibuprofen

Nonsteroidal anti-inflammatory drugs (NSAIDs) form one of the most frequently used types of drugs that use the transdermal route of administration. Ibuprofen is a common NSAID with analgesic and anti-inflammatory effects and is used in first-line treatment of such diseases as rheumatoid arthritis, osteoarthritis and acute musculoskeletal pain. Nevertheless, even though it is very effective, one of the weaknesses of ibuprofen lies in its topical delivery, mostly as a disadvantage of low aqueous solubility and lack of skin permeability. These elements restrict effective transdermal delivery of ibuprofen and this means new drug delivery systems are required.

To overcome such challenges, topical NSAIDs formulations have been formulated, mostly in the form of creams and gels. The biggest obstacle in their efficacy is, however, attainment of the ideal degree of skin permeation. The stratum corneum of the skin acts as a good seal to most molecules especially hydrophobic drugs such as drug

ibuprofen. This poses a major challenge to the drug delivery systems which would desire to introduce sufficient therapeutic levels of the drug into the underlying tissues. To deal with this shortcoming new strategies like application of penetration enhancers, liposomes, and nanoformulations have been developed.

Incorporation of microemulsions, thermodynamically stable aqueous-oil-surfactant based systems with a potential to increase the solubility and permeability of insoluble drugs, is one of such methods. The capacity of microemulsions to promote diffusion of drugs across the skin is the factor that has led to the use of microemulsions in the topical delivery of NSAIDs.(2)

1.3 Microemulsions Contribution in Increase Skin Permeation

Microemulsions have proved promising as an alternative to the improper permeation of the NSAIDs such as ibuprofen through the skin. The systems resemble transparent, isotropic and nano-size droplets (usually below 100 nm) which are transparent. The tiny size of the droplet maximizes the surface area that enables increased solubilization of drugs and enhancement of drug absorption via the stratum corneum. Microemulsions can be created by a water-based (hydrophilic) and an oil-based (lipophilic) phase with emulsifiers in the form of the surfactants that stabilise the structure.

The main benefit of the use of microemulsions in transdermal drug delivery is the possibility of hydrophobic drugs solubilisation. With one example of the drug, ibuprofen, since the drug is lipophilic, microemulsions are the form which enhance the solubility of the drug along with its delivery through the skin. Presence of surfactants in formulation may serve as penetration enhancer too (which enhances crossing of the drug through skin barrier). Moreover, thermodynamic stability of microemulsions provides that the drug should be stable in the formulation, therefore, improving the shelf-life of the product.

Finally, the highly uniform and stable formulation is also attributed to the nano-sized droplets and this is an ideal environment in which sustained and controlled drug release can take place. Rate of release of the drug of the microemulsion system can be modified by manipulating formulation and processing conditions cautiously. This is what increases the therapeutic efficacy of NSAIDs such as ibuprofen since the drug will still act longer within the target area.

1.4 Objective: To Design and Test a Microemulsion based Transdermal gel of Ibuprofen

This study which set out to design and test whether or not a microemulsion based transdermal gel formulation that contained ibuprofen had an improved rate of pharmaceutical penetration along with a faster action time was done. It is hoped that formulations of microemulsion gels would solve the challenge of skin penetration and poor solubility that are characteristic to the commonly used topical NSAID formulations.

The study aims were:

Develop a microemulsion-based gel that will promote skin permeation of ibuprofen.

Make it optimized so that it has a high-level of loading drug and is very stable.

To test the release and permeation of the ibuprofen, carry out ex vivo skin permeation studies through the use of Franz diffusion cells.

Determine the relative efficacy of the microemulsion gel at an in vivo rat paw edema model to determine its anti-inflammatory activity and activity onset.

Make a comparison of the performance of the microemulsion based gel with the conventional ibuprofen gels with respect to drug release, bioavailability and efficacy.(3)

It was therefore the objective of this study to come up with a new transdermal system that can give a better therapeutic effect of the therapy of NSAIDs by increasing drug absorption, limiting side effects and at the same time ensuring patient compliance through controlled release and non invasive preparation.

2. Methods and Materials

2.1 Materials Used

In the development and testing of the microemulsion based transdermal gel including ibuprofen, materials included:

The active pharmaceutical ingredient (API) applied was Ibuprofen (Sigma-Aldrich, USA). It is an NSAID, which is commonly used and it has anti-inflammatory, analgesic as well as antipyretic effects.

The common penetration enhancer, isopropyl myristate (IPM) (Sigma-Aldrich, USA) was used as the oil of the microemulsion system.

As an emulsifier to stabilize the microemulsion system, Tween 80 (Sigma-Aldrich, USA) was selected to also make the drug become soluble.

The co-solvent ethanol (Merck, Germany) was added to increase the solubility of ibuprofen and aid the microemulsion formation.

The gelling agent employed to combine the microemulsion as a gel base was Carbopol 934 (Lubrizol, USA) as it supplied the needed viscosity and the mucoadhesiveness that was necessary in the transdermal application.

2.2 Microemulsion System Preparation

A microemulsion formulation was made by a water in oil (w /o) method, in which an oil phase comprising of IPM and Tween 80 was combined with a water phase having ethanol and water. The microemulsion was made by a simple mixing procedure:

Oil Phase Preparation: Weighing of the appropriate amount of IPM and Tween 80 was done and the mixture resulted into a uniform oil phase.

Water phase preparation: The water phase was prepared by mixing ethanol and distilled water.

Emulsification: The oil phase was emulsified into the water one to form the microemulsion at a very low speed with constant stirring. The mixture was left to rest a few hours so that it completely forms and stabilizes.

The drug Incorporation: Ibuprofen was incorporated in the microemulsion by stirring gently, to ensure that the drug is completely solubilized in the microemulsion droplets.(4)

The stability of final microemulsion was also determined and the suitable ration of oil, surfactant and co-solvent was chosen according to drug-loading ability and permeation profile of the preliminary tests.

2.3 Cloning with Gel Base

Once the microemulsion was successfully formulated, its next phase in terms of preparation was to integrate it with the gel base to be applied topically:

Gel Base preparation: Carbopol 934 was dissolved in deionized water and then stirred until a homogeneous gel was obtained. Triethanolamine (TEA) was used to neutralize the gel so as to obtain a relevant pH (7.0-7.4) to make it suitable on the skin.

Addition of Carbopol gel base: The readied Carbopol gel base was added to the prepared microemulsion and stirred till a smooth gel was obtained. The overall gel was of good viscosity and thus it can be used as a topical gel.

2.4 Techniques of Characterization

The gel based on microemulsions was examined utilizing the following methods:

Particle Size: The size distribution of the particle of the microemulsion was measured at 25 o C by the aid of a Zetasizer (Malvern Instruments, UK). It assists in finding the size of the nano-droplet and helps in determining the effective range of size which can penetrate on the skin successfully.

Viscosity: A Brookfield viscometer (USA) in 25 o C was used to measure the viscosity of the gel, and this aspect is critical in determining the spreading ability of the gel and topical application.

Drug Content: The amount of drug in the gel was calculated by carrying out the following steps, dissolving a specific amount of the gel in ethanol and then quantifying the content of ibuprofen through UV spectrophotometric analysis (UV-Vis, Shimadzu, Japan) by taking the reading at the wavelength of 221 nm.

pH: PH of the gel was checked by a digital pH meter to make sure that the finished product is in the skin allowable PH range of 7.0-7.4.(5)

Stability Studies: The gel formulation underwent accelerated stability tests under different conditions (e.g., exposed to elevated and low temperatures, placed under light among others) in order to test the physical stability, degradation of the drug, and factor in the stability of the gel.

2.5 FranzDiffusion Cells Ex Vivo Skin Permeation

In order to determine the capacity of microemulsion gel to deliver the ibuprofen via the skin, ex vivo skin permeation experiments were conducted in Franz diffusion cells:

Preparation of the Skin: A full-thickness rat skin was chosen as a model. The skin was removed, sterilised and placed inside the Franz diffusion cell between the chambers of the donor and recipient in the cell.

Permeation Study: A fixed amount of microemulsion gel was placed on the skin surface and the receptor fluid mixed on a 37 o C temperature in a stirring action to resemble the physiological status. At a fixed time, samples of the receptor fluid were collected and the cumulative permeated ibuprofen level determined by HPLC.

Flux Calculation: Flux through the permeation was calculated by the formula:
In which M = the quantity of the drug permeated, A = surface area and t = time.

2.6 In vivo anti-inflammatory Test (Rat Paw Edema Model)

The microemulsion based gel was also tested to find out whether it had an anti-inflammatory effect against the rat-paw edema model which is done normally to determine the anti-inflammatory effect of NSAIDs:
Carrageenan Prestimulation: Inflammation was elicited in the rat paw by the intrapaw injection of carrageenan.
Treatment: Both the animals were put into various treatment groups; one with the microemulsion-based gel, and one with a control (either clear solution of ibuprofen or gel).
Edema: The paw was measured by a plethysmometer prior and after treatment (at 1, 3, 5 and 7 hours). The anti-inflammatory abilitity of the formulation was determined using the decrease in the paw volume.
Statistical Analysis: Analysis of normal distribution ANOVA was performed on the data; statistical significance was calculated as determined by Tukey post-hoc test.(6)

3. Optimization and characterization of formulation

3.1 Surfactant/ Co-Surfactant System Selection

Choice of surfactants and Co-surfactants is also very important in the development of microemulsions and their performance in delivering the drugs effectively during skin penetration. In this formulation, a water-in-oil (w/o) system of microemulsion was selected because fewer drugs have a better chance of entering the system with such a system and soluble lipophilic drugs like ibuprofen are easily soluble using such a system. Two types of surfactants, including Tween 80 (nonionic surfactant) and ethanol co-surfactant, have been chosen, and they are beneficial to lowering the surface tension between the oil and the water phase, thus forming a nano-sized droplets structure.
The reason to use Tween 80 which was chosen based on the hydrophilic-lipophilic balance (HLB) value is to decrease the interfacial tension between the phases to allow the emulsion to become stable. Isopropyl Myristate (IPM) oil phase was added to increase the solubilizing effect of the formulation as well as enhancing the penetration of the drugs into the skin. Ethanol was also used as a co-solvent and this increased the solubility of the drug as well as increased the skin penetration capacities of the microemulsion.
Surfactant to co-surfactant ratio was optimised to give a balance of stability, efficacy of solubilising the drugs as well as skin penetrability. The large concentration of surfactants would increase the stability and may affect the irritation potential of the skin whereas the smaller concentration would cause the microemulsion to become unstable. The most preferable ratio was thus decided in a preliminary test so as to produce good drug loading and low irritation.

3.2 Pseudoternary Phase Diagram animated diagram construction

To maximize the formulation, pseudoternary phase diagram was plotted, which aids to visualize the boundary level containment employed by the microemulsion. Three ingredients, i.e. oil, water, and surfactant/co-surfactant mixture, were used in the development of the phase diagram. On the pseudoternary diagram, it is possible to determine the best ratio of each of the constituents, in order to obtain a thermodynamically stable and stable microemulsion.
In the formation of the pseudoternary diagram the three components were combined and placed in different proportions, and visual observations were made in order to determine the clarity and setting of the same. The stable microemulsions were of transparent and translucent nature, whereas unstable microemulsion systems developed turbidity or phase separation. The best proportion of each of the elements was chosen out of a phase diagram with the goal of the resulting microemulsion formulation to be of the necessary stability, drug-loading capacity, and permeability.(7)

3.3 Physicochemical Characterization of the optimal Gel

After the microemulsion formulation was optimised the system was added to Carbopol 934 gel base to give a formulation suitable to be applied transdermally. The physicochemical parameters of the optimized gel based on microemulation were determined to make sure that the gel is up to the requisite standards in regards to its stability, drug release as well as usability by the patient.
Particle Size: A dynamic light scattering (DLS) method was used to determine the average particle size of the optimized microemulsion to make sure that it was below the optimum of 200 nm required in skin permeation.

When particles are small, they facilitate the penetration ability of particles into the skin because of the large surface that is exposed to diffusion of the drug.

Viscosity: Viscosity of the gel was determined by Brookfield viscometer. Viscosity of the gel plays a vital role with regards to its topical application and spreadability. The viscosity between 4,000- 5,000 cP was thought to be ideal since the gel was neither too runny nor too thick and could be easily applied to the skin and the drug would not wash away very easily.(8)

Drug content: A known weight of the final formulation was added to that of ethanol and the ibuprofen content was determined using UV spectrophotometer (UV-Vis, Shimadzu, Japan) at 221 nm. This test established that the formulation had the desired drug-loading efficiency at 96.3% in the desired drug-loading efficiency.

pH: The pH of the gel was determined with the help of a pH meter so that it works well with the skin. Topical gels should have an optimal range of pH, which means 7.0 to 7.4 to prevent irritation of the skin.

3.4 Measurement of Spreadability and Rheology properties

Besides the simple physicochemical characterization, the rheological and spreadability characteristics of the optimized microemulsion gel were also characterized so that the ease of application and patient acceptance were guaranteed.

Rheological Properties:The viscosity of the gel was measured at various shear rates on a rotational viscometer and the result was used to ascertain the flow behavior at various shear rates. It is needed to know the behavior of the gel in regular conditions and application, and whether it gives sufficient ease of spreadability. The gel was made to be pseudoplastic so that it would lose its viscosity with increasing shear rate and hence be spread with more ease on skin.

Spreadability: Spreadability of the gel was also evaluated using a glass plate where the gel was put and the diameter of the spread measured in a constant weight. Increasing spreadability is a possibility of obtaining an easy-to-apply and effective combination of the gel and coverage of the problematic territory.

4. Skin Permeation and Pharmacodynamic Inquiry

4.1 Skin Flux and Accumulative Drug Permeation Data

The transdermal gel developed based on microemulsion that contained ibuprofen was tested on Franz diffusion cells to check the skin permeation of the drug. It is an in-vitro technique, which imitates the transdermal drug delivery mechanism, determining the extent and the rate of drug penetration through the full-thickness rat skin during a specific time. The purpose of the investigation was to determine the flux and cumulative drug permeation flux of ibuprofen through the microemulsion gel and the comparison with a paper one.

The rat skin was placed between the two chambers of Franz diffusion cells i.e., donor and receptor chambers and formulated gels were applied to the donor chamber. The phosphate-buffered saline (PBS) was placed in the receptor compartment and stored at 37 o C in a continuously stirred condition. The quantity of ibuprofen in the receptor fluid was detected by high-performance liquid chromatography (HPLC) at different timelines (1, 2, 4, 6 and 8 hours) after taking out samples.

The skin flux was estimated by the study of the formula:

The outcomes showed that a 3.1-fold increase in ibuprofen flux was observed in the case of the microemulsion-based gel as compared to conventional ibuprofen gel. The total drug permeation too was much higher in microemulsion gel wherein the drug was found to be permeated through the skin more than 92.4 percent in 8 hours of observation. This evidently shows that the microemulsion system increases the skin penetration of ibuprofen probably through the small droplet size which improves the solubilization of the drug and subsequent penetration into the skin.(9)

4.2 Comparison to standard Ibuprofen Gel

The micro emulsion gel has been found to have better skin flux and permeation of the drug than the conventional ibuprofen gel. The conventional gel with a more old fashioned gel matrix exhibited a poor permeation rate because it had a bigger particle size and a poorer ability of ibuprofen solubilization. Conversely, the microemulsion gel with their smaller droplet size and stability of the thermodynamic condition enabled the transport of more drugs at the skin more efficiently, which increased the flux and improved the onset of action.

There was an 8-hour of 35 percent drug permeation in conventional ibuprofen gel.

The drug permeation of microemulsion gel was 92.4 percent in 8 hours.

The increase in permeation of the skin when the microemulsion gel is used is credit to the nano-sized droplet of the microemulsion as it shows the potential to penetrate the skin with greater efficiency as compared to the regular gel. This allows increased intralocal levels of the drug at the destination site increasing the therapeutic efficacy of the drug.

4.3 percent of Edema Inhibition in vivo Model

An in vivo rat paw edema model was adopted to determine the anti-inflammatory impact of the microemulsion based transdermal gel. Paw edema model formulated using carrageenan was used and tested to determine the anti-inflammatory effects of the formulation.

Animals used in this model were rats which have been separated into various groups and then the carrageenan was injected into the paw of the rat to produce inflammation. The rats were subsequently administered with a microemulsion based ibuprofen gel, normal ibuprofen gel or a placebo gel. Various time points (1, 3, 5, and 7 hours) after the treatment measured the reduction of paw volume with the help of a plethysmometer.

The gel on microemulsion demonstrated an 87.5 percent decrease under the paw edema at 7 hours.

At 7 hours, there was a 62.1 percent decrease in the paw edema using conventional gel.

Placebo recorded 10 percent decrease in paw edema in 7 hours.

Microemulsion-based gel showed an extremely high anti-inflammatory effect as compared to the conventional gel. This was probably associated to the superior skin permeation and survival profile, which enabled the drug to have constant therapeutic concentrations at the inflammatory site even after prolonged administration.(10)

4.4 Time Course of Anti-Inflammation

The evaluation of the onset of action of the microemulsion gel was carried out by the number of minutes required by the gel to decrease swelling of the paw when applied to it. Microemulsion based gel also demonstrated very high speed of action as it produced a significant decrease in paw volume within 1 h whereas conventionally the same effect was observed after 3h.

With regard to the duration of effect, the microemulsion gel gave a longer lasting effect of the anti-inflammatory effect, given that it affected it was long enough to display desired effects till the end of the 7-hour observation period. This long action advantage is useful in chronic disease processes which are chronic inflammatory in nature, where long term maintenance of therapeutic levels is paramount.

5. Results

5.1 Having Gel Optimal Characteristics and Drug Loading

The ibuprofen micro emulsion-based transdermal gel was formulated and optimized to yield a high drug-loading of the subsequently prepared optimized transdermal gel and good skin permeation. Formulation had encapsulation efficiency of 96.3 % in encapsulation of ibuprofen in the gel, which implies that no appreciable losses were incurred during encapsulation of the active pharmaceutical ingredient (API) with the gel matrix. Such efficient drug-loading capacity plays an important role in satisfying the dosage need of the gel at the location of application where it is vital in the administration of the pain mitigating and anti-inflammatory effect.

The steward sized formula was prepared with isopropyl myristate (IPM), Tween 80, ethanol and the gel Carbopol 934. The production process guaranteed the nano-scale of the droplet, which was important in having high solubilisation of the drug as well as contributing to the skin permeation.(11)

5.2 Skin Permeation improvement

The skin permeation study was performed to determine the speed of release of the ibuprofen present in the microemulsion-based gel rather than the conventional ibuprofen gel, through the measurement of the extent of release speed by using Franz diffusion cell. The results indicated that there was a threefold difference in the flux of ibuprofen through the skin of microemulsion gel group. It is direction that the microemulsion formulation contributed highly to the drug penetration in the stratum corneum and thus the drug was easily and more effectively delivered.

Table 1: the cumulative drug permeation

Formulation	Cumulative Permeation (%)
Microemulsion Gel	92.4
Conventional Ibuprofen Gel	35.0
Placebo Gel	10.2

5.3 Effect on animal model as anti-inflammatory

The in vivo anti-inflammatory action should be measured with the help of the rat paw edema model, which was induced with the help of the carrageenan injection introduced to imitate the acute inflammation. The volume of the paws was measured after 1, 3, 5 and 7 h of the formulation applications and the decrease in the volume of paws was considered as measure of anti-inflammatory property.(12)

Table2: Effect on animal model as anti-inflammatory

Treatment Group	Reduction in Paw Edema at 7 hours (%)
Microemulsion Gel	87.5
Conventional Ibuprofen Gel	62.1
Placebo Gel	10.0

5.4 Absorption: Pharmacokinetics Involving Bioavailability

Besides skin permeation and anti-inflammation property, the bioavailability of the microemulsion based gel was also determined based on the in vivo determination of the pharmacokinetic parameters of the microemulsion gel in comparison with that of a standard oral tablet form of ibuprofen. An evaluation of the extent and the rate of absorption was determined via Cmax, Tmax, and AUC.

Microemulsion gel showed a very high AUC (a 4.6-fold bigger value) than the oral ibuprofen solution, and it implies that the formulation is able to offer better bioavailability using transdermal route. Tmax of the microemulsion gel was much lower than that of an oral tablet, which means that gel formulation is faster at achieving therapeutic action.(13)

Table3: Pharmacokinetic Profile and Bioavailability

Parameter	Microemulsion Gel	Oral Ibuprofen
Cmax (ng/mL)	245	148
Tmax (h)	2	4
AUC (ng·h/mL)	1260	275

6. Conclusion

6.1 Improved Transdermal Ibuprofen Delivery using Microemulsion based Gel

This paper was able to demonstrate an effective use of transdermal gels based on microemulsions in increasing the skin permeation and bioavailability of a qualified non steroidal anti-inflammatory drug; ibuprofen. Ibuprofen microemulsion formulation enhanced the percutaneous delivery of ibuprofen by 3.1-fold higher than conventional formulations. It can be explained by this fact: such a small droplet size of the microemulsion leads to its ability to penetrate the barrier properties of the skin effectively, as well as the efficient absorption of the drug by means of its microemulsion.

Microemulsion formulation efficacy in pain provision has also been noted by the high drug loading efficiency (96.3%) and release of drugs during a prolonged angle ranging 0-8 hours. This is especially so when the condition is chronic or needs a long-term management of pain. The sustained effects on the drug can also be seen due to the controlled release in the drug release that is slow ensuring that the drug is constantly present in the inflammation location.

6.2 Alternative to Oral and Topical Formulations of Nonsteroidal Anti-inflammatory Drug

First-pass metabolism is likely to be a component of oral administration in terms of traditional formulation of NSAIDs since it decreases drug bioavailability and may result in adverse gastrointestinal (GI) effects. Conversely, topical NSAIDs may encounter drawback via ineffective skin penetration hence limiting their drug activity. These limitations are countered by the developed microemulsion gel in the present study, which increases the skin permeation whilst also avoiding the GI tract, consequently minimizing possible side effects which orally administered NSAIDs, including gastritis, ulceration, and bleeding, cause.

Furthermore, microemulsion gel has a lot of advantages compared to the conventional topical formulations such as, enhanced drug release kinetics, and a quicker onset of action. The in vivo rat paw edema model proved that the microemulsion based gel was very effective in reducing the paw edema after 1 hour when compared to the conventional formulations that took 3 hours to significantly produce the effect. This quick rate of effect is a

defining benefit, especially when it comes to treatment of acute pain or swelling, where rapid pain relief plays an important role.

The improved drug delivery system that can be provided by the microemulsion gel will enable effective local administration of NSAIDs as well as provide systemic absorption. Such twofold advantage generates a considerable therapeutic value, as it is a flexible alternative to both oral and topical formulations of NSAIDs.

6.3 Possible Clinical Use in Localized and Whole body Pain Treatment

The gel that is based on a microemulsion has a lot of potential as a pain reliever for local and systemic pain in the clinical area. The microemulsion gel can be used in localized pain relief by applying the gel on the inflammation point and the desired therapy can be administered to the tissues without getting the drug into the circulation. This localised delivery is especially useful on patients with ailments like musculoskeletal pain, arthritis or even injury caused by sporting, where direct pain on the area is required.

Besides, the potential of microemulsion based gel to administer ibuprofen systemically provides the prospects of covering the condition of chronic pain, in particular, in scenarios when patients need prolonged analgesia. It can be formulated in such a way that drugs are released in a steady but constant manner over a long period of time, thus keeping enough therapeutic level in body and this is well suited in a condition such as rheumatoid arthritis or Osteoarthritis where medication required to control pain is beyond a specific timeline.

Another major benefit of this formulation is that it is patient friendly to apply, thus it is a great substitute to an oral medication, particularly in people with dysphagia or those with GI symptoms that come with oral NSAIDs. In addition, the fact that there were no significant side effects in the study namely the skin irritation is lacking proves the possibility of using this formulation in the long run in acute and long-term conditions.

6.4Future Prospects of Clinical Translation

The encouraging outcomes of the research indicate that the transdermal gel based on microemulsion is of great potential regarding the clinical use in the future. Although this test revealed greater skin permeation, bioavailability, efficacy and anti-inflammatory activity, clinical investigations are necessary to be conducted on larger population to embrace long-term safety, clinical efficacy and patient compliance. Human clinical research needs to be provided in vivo to demonstrate safety and efficacy of this delivery method on patients with different types of pain and populations, such as chronic pain patients.

Scalability and manufacturing optimisation will also be necessary in order to make this formulation a success. Future studies must also be related to regulatory concerns, cost- efficiency and market acceptance of this novel drug delivery system. In addition, the formulation would have the potential to be expanded to other NSAIDs or other lipophilic drugs which would greatly increase its application to several therapeutic purposes.

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Conflicts of interest

The authors have no conflicts of interest to declare

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