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FORMULATION AND EVALUATION OF DICLOFENAC SODIUM MICROEMULSION TRANSDERMAL SPRAY FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Background: The growth of a topical vehicle microemulsions has been more enhanced compared to the normal skin applications such as creams, gels among others. These micro-structured vehicles showed enhanced solubilization of drug and improved skin permeation as compared to conventional topical systems. **Objective:** This study was aimed to formulate and evaluate the topical diclofenac sodium microemulsion spray claimed to be having better bioavailability, greater drug solubility, enhanced skin permeation, and lesser side effects. **Method:** Diclofenac sodium microemulsion was prepared by constructing pseudo ternary phase diagram followed by water titration method. The oil phase IPM 10%(v/v) was selected on the basis of drug solubility whereas the surfactant:cosurfactant mixture (tween80 : polyethylene glycol 400) 50%(v/v) was on the basis of their oil solubilization and efficiency to form ME from pseudo-ternary phase diagrams and then 40%(v/v) aqueous phase and 4%(w/v) drug was added. **Results:** This optimized micro emulsion spray was evaluated by some preliminary tests and confirmatory tests. Results of tests indicated that the formulation was optimized as it was transparent on visual inspection having 6.8 pH, 113nm droplet size, and 36.70cP viscosity. Dye solubility testing confirmed that micro emulsion was W/O. FTIR and DSC studies showed that micro emulsion was compatible with excipients. Drug content and release was more than 90%. The kinetics studies revealed that diclofenac sodium micro emulsion followed Korsmeyer Peppas Model, Higuchi Model, and first order kinetics. **Conclusion:** This study made a good effort to develop a unique drug delivery system that had increased drug solubility and skin penetration with lesser side effects.

Keywords: Diclofenac sodium, Microemulsion, Transdermal, Topical spray

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INTRODUCTION

Rheumatoid arthritis (RA), a chronic inflammatory disease affecting the synovial tissue of joints, bone, cartilage, and, unlikely in extra-articular locations. The synovial-lined joints suffer irreparable damage as a result of its progressive nature. According to estimates, 0.8% of the general population has RA, which is more common in women than males and first appears in the fourth and fifth decades of life and 1 million people over 65 in the world would develop arthritis by 2030 **[1]**. Therefore, improved RA therapies that limit bone loss and inflammatory signaling are required. Currently, treatments for RA include glucocorticoids, anti-rheumatic disease-modifying medications (DMARDs), and non-steroidal anti-inflammatory medicines (NSAIDs) **[2]**. Diclofenac sodium is a prescribed NSAID having analgesic, anti-inflammatory and antipyretic properties. **[3]**. It reversibly inhibits COX enzymes which results in decrease level of prostaglandins mainly PGE2 that is primarily involved in nociception. Inhibition of PGE2 results in inhibition of inflammation, pain sensation **[4]**. Diclofenac sodium has 60% oral bioavailability and elimination half-life is 1 to 2 hours. The major limitation using oral diclofenac is not due to the lack of adequate bioavailability or a short biological half-life as generally assumed, but due to increased risks of side effects such as gastrointestinal bleeding and small bowel injury, acute kidney injury, and cardiotoxicity. **[5]**. Topical application of diclofenac sodium shows higher tissue concentration, low systemic absorption and fewer side effects **[6]**.

Microemulsions therefore refers to an environment that is highly homogeneous, macroscopically and thermodynamically stable and contains at least three substances: a polar subject (usually water), a non polar subject (usually oil), surfactant and co surfactant. These systems consist of spherical micro-

droplets with a size range of 10-300 nm, and can be formed using either bottom-up or top-down technology. There are various varieties of micro-emulsions, for instance water in oil (w/o), oil in water (o/w) and others. **[7]**.

Microemulsion system has higher solubilizing capacity towards both hydrophilic and lipophilic drug. It proves excellent delivery system for hydrophobic drugs like diclofenac sodium. The hydrophilic phase of microemulsion hydrates the skin while organic phase increases the drug permeability through skin. The nano sized particle range provides large surface for drug solubilization, low surface tension and deeper penetration through skin. The balance between hydrophilicity and lipophilicity leads to better skin penetration but lesser systemic absorption, leading to very less chance of systemic side effects **[8]**.

The majority of medicines chosen for topical administration are typically less than 500 Da. The combination of these qualities allows diclofenac, an organic acid with a pKa value of 4, a Log P of 4.26, and a molecular weight of 296 Da, to pass through the skin and synovial lining of joints **[9]**. Following topical application, diclofenac was found in synovial fluid and tissue at values of 119-3320 ng/mL and 131-740 ng/g, respectively. These results are nearly 20 times higher than those observed for other NSAIDs and plasma 6-52 ng/ml **[10]**.

Furthermore, diclofenac is found in significantly higher concentrations in inflamed tissues. Several topical diclofenac preparations like gels, spray gels, foam and patch, containing 1% to 4% drug are approved by FDA and available in market around the globe **[8]**. Despite of these advancements in formulation design in topical dosage form, there are problems like the delivery of accurate dose administration, skin damage issues, patient compliance **[11]**. On the other hand, efforts have been made in another approach related to the modification of the formulation including the development of microemulsions **[12]**.

Previous studies on topical diclofenac sodium formulation were gels, foams, solution microemulsion having percentages less than 4%. Studies on dispensing of diclofenac sodium microemulsion in non-aerosol spray bottle were also not available.

Based on above literature, we aimed to develop topical formulation having better drug release, improved skin permeation, non-irritant to skin, less systemic side effects and easy to use. So this study was conducted to develop 4% diclofenac sodium microemulsion transdermal spray formulation and to evaluate its release and permeation through skin via intro studies. The use of spray delivery ensured site-specific delivery of drug, ease of application, adherence to therapy and patient compliance **[13]**. This study will help future researchers to conduct clinical trials on this formulation so that it would be manufactured commercially and available for public use.

MATERIALS AND METHOD

Diclofenac sodium, Propylene glycol, Polyethene glycol PEG 400, Tween 80, Isopropyl myristate, Oleic Acid and Sunflower oil were purchased from Merc, Pakistan. Monobasic potassium phosphate and Sodium hydroxide were purchased from Sigma-Aldrich. All the ingredients used were of analytical grade. Distilled water was used throughout the process.

Preparation of ME Formulation

A pseudo ternary phase diagram was constructed as shown in **(Fig. 1)**, using the water titration F1, F2, F4 and F5 formulations were prepared by mixing Tween 80 (surfactant) and propylene (co-surfactant) in different beakers with a homogenizer at about 600 rpm for 1 Hour. The oil phase was added to the above mixer dropwise at 650rpm for 1 hour. Distilled water was added to the above mixer dropwise at 1200 rpm for 1 hour. F3 formulation was prepared by mixing oil and tween 80(surfactant) in a beaker and mixed under a homogenizer at 650rpm for 20 minutes. Water and Poly eylene glycol (cosurfactant) were mixed in a beaker under a homogenizer at 650 rpm for 20 minutes. The water cosurfactant mixture was added drop-wise to the oil surfactant mixture at 1200rpm. Concentration of different ingredients used are mentioned in **(Table 1).**

Table 1: Formulations from the triangle phase diagram: Compositions (V/V %).

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
Sunflower oil (ml)	5	6	-	-	5
Oleic acid (ml)	-	-	-	6	-
Isopropyl myristate (ml)	-	-	5	-	-
Propylene glycol (ml)	4.2	4	-	3	5
Polyethene glycol 400 (ml)	-	-	4	-	-
Tween 80 (ml)	25.8	25	20	26	20
Distilled water (ml)	15	15	20	15	20
Diclofenac sodium (g)	2	2	2	2	2

Preparation of Drug Loaded ME Formulation

2g Diclofenac Sodium was added to 10ml of the prepared microemulsion formulations and was mixed with a stirrer until all drugs dissolved. Drug-loaded 10ml mixture was poured back into the remaining 40ml emulsion and mixed at 200rpm with a homogenizer for 20 minutes. The drug-loaded microemulsion was formed.

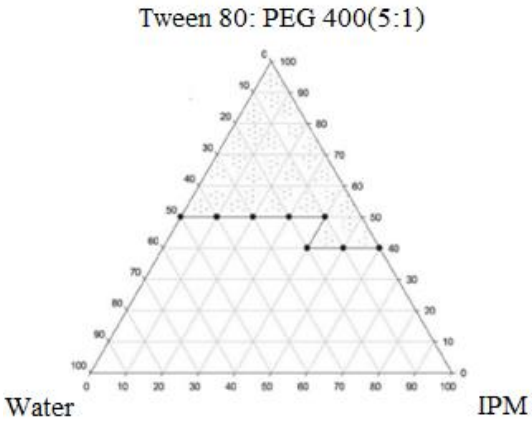

Figure 1: Pseudo ternary phase diagram for Tween 80 and PEG 400 and isopropyl myristate.

Pre-formulation Studies

Bulk Characterization

Crystallinity

Crystallinity of the diclofenac sodium was checked by making a mixture of chloroform and the drug, placing one drop of this mixture on glass slide and a cover slip was placed on it. It was checked under microscope using 100x resolution.

Flowability

Inverted funnel method was used to calculate angle of repose. Heap of powdered drug was formed on paper and circle is drawn around it and its height and radius were measured to determine angle of repose. To find out compressibility index and Hausner ratio, powdered drug was filled in measuring cylinder and tapped by standard tapping procedure.

Particle Size Analysis by Sieve Method

Stack of sieves was set according to Tyler's method of sieve analysis i.e, sieves (8, 10, 14, 18, 20, 25, 30) stacked in order from smallest to largest. 5 gram of powdered drug was carefully weighed and added on sieves. Sieves were shaken by standard shaking procedure shaken and the amount of powder retained was weighed at every sieve. The percentage of the retained mass was calculated.

Hygroscopicity

Hygroscopicity of drug sample was measured by taking 0.5 g of sample on China dish and heated. The difference in weight upon drying was noted and LOD was calculated.

Melting Point

Melting point of drug sample was measured by placing the sample on the chamber of the hot plate of Fisher-Johns's melting point apparatus. Change in temperature was noted and the melting point of the drug was determined.

Solubility Analysis

Solubility of drug sample was measured by Gravimetric method. 8pH buffer was prepared by dissolving 1.361g monobasic potassium phosphate and 0.368g sodium hydroxide in 50ml and 46.1ml of distilled water respectively. The two solutions were mixed and final volume was made up to 200ml. Empty test tube was weighed. The drug diclofenac sodium was dissolved in 10ml of pH 8 phosphate buffer until it started precipitating. This solution was filtered and the filtrate was heated until it evaporated. After heating test tube was again weighed. Difference between the two weights were calculated and then the solubility of drug in this buffer was determined.

Standard Calibration Curve

Stock solution and a working solution was prepared then dilutions of strength 4µg/mL, 8µg/mL, 12µg/mL, 16µg/mL, 20µg/mL were prepared. These solutions were analyzed on a spectrophotometer (Cecil) at the wavelength of 278nm. The values were noted and a graph was made on excel by comparing these values.

Partition Coefficient

Partition coefficient of drug sample was measured by separating funnel method. 10ml of pH 8 buffer and 10ml of octanol were taken in the separating funnel followed by addition of 100mg of diclofenac sodium. The mixture was shaken for 30 minutes and funnel was made to stand for 15 minutes, so the layers separated out. Both layers were extracted and filtered in a separate beaker. Buffer extract was diluted with distilled water and octanol extract was diluted with methanol then it was analyzed on a spectrophotometer

Preliminary Tests

pH Analysis

pH analysis was carried out by Calibrated pH meter was used for measuring pH of all microemulsion formulations one by one and readings were recorded at room temperature.

Dye Solubility Test

All microemulsions were mixed with a water soluble dye (amaranth) separately and observed under the microscope.

Stress Testing

Microemulsions were evaluated for stress testing by phase separation technique and heating cooling cycle analysis. For phase separation analysis, microemulsion formulations were taken in Eppendorf tube separately and were placed in a centrifuge under

1000rpm for 15 minutes. Eppendorf tube was placed for 24hours to settle the microemulsion and were checked for any precipitations.

Microemulsion formulations subjected to heating cooling cycle analysis. Formulations were taken in separate beakers and placed in a Fridge at 4 ± 1ºC for 48 hours and then placed in an oven at hot air oven at 45 ± 1ºC for 48 hours. This procedure was repeated 6 times and physical appearance, transparency and absence or presence of phase separation were noted.

Rheological Study

The viscosity of microemulsions was measured using the calibrated viscometer (Brookfield viscometer). The required Spindle of viscometer was cleaned. Beaker was placed under viscometer. At 30s interval the spindle was rotated about 150rpm by using its digital buttons. Viscosity was noted from the display screen.

Droplet Size Analysis

Droplet size of microemulsion formulation was determined by scanning electron microscope (SEM). The electron beam utilized by SEM was generated by an electron gun at the top of the microscope. The microscope was kept in a vacuum and the electron beam travelled through it in a vertical path. The beam was focused downward toward the sample as it passed via electromagnetic fields and lenses. Electrons and X-rays were ejected from the sample after the beam struck it. These X-rays, backscattered electrons, and secondary electrons were collected by detectors, and they were then transformed into a signal and sent to a screen like to a television. The result was the finished picture.

Percentage Yield of Formulation

Percentage yield of formulation was calculated by using actual and theoretical yield of formulations. Total volume of formulation that would be produced after combing ingredients, was calculated and labeled as theoretical yield. After the formulation was prepared, it was transferred into measuring cylinder and volume was noted and labeled as practical yield. Percentage yield was calculated afterwards.

Zeta Potential Analysis

Zeta potential of sample was determined by Laser Doppler Micro-electrophoresis technique was adopted while using Zetasizer Nano ZS (Malvern Panalytical) system. Sample was diluted with distilled water and then, it was placed in clear disposable zeta cells. Analysis time was kept for 50 seconds. Measurements were carried out as three replicates and the data was calculated as mean ± SD. The procedure was carried out with all formulations.

Stability Studies

Accelerated stability test was carried out by exposing the drug to a temperature 40°C, far higher than ambient temperature (25°C) to observe the degradation occurred upon applying stress

Similarly mechanical stress was applied using centrifugation. Samples of the microemulsion preparation were centrifuged at 3800 rpm for 5 hrs. This treatment is equivalent to the gravitational effect for 1 year. Organoleptic observations were done on the physical condition of the preparation before and after centrifugation. This experiment was performed 3 times

Refractive Index

The refractive index of microemulsion formulations were determined by calibrated refractometer (Brix Refractometer). A small amount of microemulsion formulation (usually 2-5 drops) was placed on the prism and secured the cover plate. The prism end of the refractometer was towards a light source and focused the eyepiece until the scale was clearly visible. The scale value at the point where the dark and light portions were met was noted. The procedure was repeated with remaining formulations.

Differential Scanning Calorimetry Test

Differential Scanning Calorimetry (DSC) analysis of optimized microemulsion formulation was evaluated using DSC-60 calorimeter (SHIMADZU). DSC scanning was performed by heating the material (1.5mg of pure diclofenac sodium, 0.15 ml of F3 Micro-emulsion, and 1.5mg of excipients) in an aluminum pan one by one from ambient temperature to 400 ◦C at 10 ◦C/min under liquid nitrogen. Thermograms of pure diclofenac sodium, excipient, and F3 Micro-emulsion were obtained and compared.

Fourier Transform Infrared Radiation Analysis (FTIR)

FTIR of diclofenac sodium microemulsion was performed by ATR method. The ATR technique was used to perform FTIR on a microemulsion of diclofenac sodium. The pure diclofenac sodium and drug loaded microemulsion formulation sample was utilized to measure the changes in an internally reflected IR beam as it came into contact with the ATR attachment. An optically dense crystal with a high refractive index was exposed to an IR beam at a specific angle. This internal reflection produced an evanescent wave that penetrated the crystal's surface and into the sample that was kept in touch with it. The evanescent wave was dampened in parts of the IR spectrum where the sample absorbed energy. After returning to the crystal, the attenuated beam left the other end and was pointed towards the detector in the IR spectrometer.

In-vitro Release

Release studies of all five formulations were performed using the Franz diffusion cell and dialysis filter membrane. Phosphate buffer solution was filled in lower portion and 1mL of the micro emulsion

formulation was inserted in the upper portion of the Franz diffusion cell and was separated by filter membrane. The study of in-vitro drug release was obtained at 37 ◦C ± 0.5 ◦C. The magnetic stirrer was set on 60rpm. 0.5 ml sample was taken from the central compartment at regular time intervals like 0.5h, 1h, 2h, 3h, 4h, 6h and 0.5 ml of buffer solution of pH 6.8 was added each time. Samples were checked using UV–Visible spectrophotometer (Cecil) and drug concentrations were calculated with the help of each calibration curve of all 5 formulations at wavelength 278 for Diclofenac Sodium. The results attained were plotted as CDR % versus time. Data of drug release for each micro emulsion formulation were assessed using various mathematical models to explain the release kinetics from different formulas.

Drug Content

Drug content of micro emulsion formulations was analyzed using UV–Visible spectrophotometer (Cecil). 1ml micro emulsion formulations were added in 9ml pH 6.8 phosphate buffer separately and was mixed using magnetic stirrer at 200rpm for 30 minutes. The mixture was soaked at room temperature for 24 h and then again mixed with magnetic stirrer at 200rpm for 30min. The mixture was centrifuged at 4000 rpm for 15min and supernatant was collected. 1 ml supernatant was diluted in 9ml buffer and named as 1st dilution. 1ml 1st dilution was further diluted in 9ml buffer and named as 2nd dilution which was run on UV–Visible spectrophotometer (Cecil).

RESULTS AND DISCUSSION

Pre-formulation Tests

Pre-formulation tests like crystallinity, flowability, particle size distribution, hygroscopicity, melting point, solubility, partition coefficient was carried out with pure diclofenac sodium. Results showed that Diclofenac sodium used in study was white, tetragonal, crystalline powder with particle size in range of 840–1680 µm, showed excellent flow and 279-289℃ melting point. It was slightly hygroscopic in nature which showed that during packaging and transportation it should be protected from humidity. Diclofenac sodium showed poor solubility in water and sparingly soluble in phosphate buffer solution of pH 8. Diclofenac sodium was more soluble in organic solvent than water which showed that drug was lipophilic in nature and help in predicting bioavailability of drug. Details are given in given in **(Table 2)**.

Post-formulation studies

pH Analysis

As shown in **(Table. 3)** all selected formulations (F1-F5) had a pH range of 5.8-6.8 which was close to the water and could not irritate the skin So, all were safe and nonirritant for transdermal use**.**

Droplet Size and Zeta Potential Analysis

Droplet size and zeta potential values for F1, F2, F3, F4, and F5 are shown in **(Table 3)** High-resolution images of all selected formulations showed particle sizes less than 500 nanometers. This decrease in globule size could be explained by a considerable decrease in interfacial tension brought on by the presence of co-surfactant and the highest proportion of S/COS mix, Increased contact surface area between the ME system and the skin by reducing the particle size could make it easier to transport drugs over the skin. Zeta potential values was ranged from-18.0 to -33mv for all selected formulations. The negative zeta potential values were due to the presence of nonionic surfactant tween 80 that imparted stability to systems. Values indicating that all formulations had sufficient charge and mobility to inhibit particle aggregation. F3 formulation showed the highest zeta potential and smallest particle size among all formulations.

Dye Solubility Test

Under microscope, all selected formulations (F1, F2, F3, F4-F5) continuous phase was appeared red indicating that they were oil in water type micro-emulsions that contained oil globules dispersed in a continuous aqueous phase.

Stress Testing

Upon high-speed centrifugation and under different heating cooling cycles phase separation was appeared for F1, F2, F4, and F5 formulations. Only the F3 formulation remained homogenous after 1hr that indicating its stability.

Refractive Index

Refractive index values of F1, F2, F3, F4, and F5 are shown in **(Table 3)**. Values ranged from 1.077-1.29, near the refractive index of water (1.33) indicating the clarity and isotropy of the formulations.

Rheology

Viscosity values for F1, F2, F3, F4, and F5 are shown in **(Table 3)**. All values were under 100cp indicating the Newtonian fluid behaviors

Table 2: The pre formulation study of diclofenac sodium.

Aqueous Solubility	Melting Point	Log P	Particle size µm	Hausner's Ratio	Angle of Repose	Compressibility index
Poor	282°C	4.9	840- 1680	1.06	28.8	5%

Percentage Yield

The percentage yield of the F3 formulation was the highest i.e. 99%., among other formulations. Other formulations yield was less than of F3 as shown in **(Table. 3)** indicating loss of ingredients due to many factors that affected percentage yield like, the reactants were not completely convert to the product, unwanted products got to produce in side-reactions, impurities stopped the reaction, improper handling of ingredients or spillage.

DSC

Pure diclofenac sodium characteristic melting point peak was showed at 280.05 ˚C as shown in **(Fig. 2).** Characteristic Diclofenac Sodium peak was appeared in the thermogram of the F3-Micro emulsion indicating that the drug was completely dissolved in the microemulsion. The differential scanning Calorimetry technique confirmed that there was no incompatibility between the excipients and drug in microemulsion formulation as shown in figure 5. Other microemulsion formulations did not show distinctive diclofenac sodium peaks indicating that the drug was not perfectly solubilized in the microemulsion formulation.

FTIR

Pure drug diclofenac sodium shows a peak of NH of

Table 3: The post formulation studies of all microemulsion formulations.

Tests	**F1**	**F2**	**F3**	**F4**	**F5**
Physical appearance	Clear	Clear	Clear	Clear	Clear
Refractive index	1.09 ± 0.12	1.20 ± 0.11	1.077 ± 0.47	1.23 ± 0.32	1.99± 0.42
Phase separation	Yes	Yes	No	Yes	Yes
Stress Testing	Changed	Changed	No change	Changed	Changed
Particle size analysis (nm)	121	125	113	329	455
Zeta potential analysis (mV)	-20.0	-25.6	-33.3	-28.1	-18.9
pH measurement	5.8	6.1	6.8	6.4	6.2
Rheological analysis (cp)	35.88 ± 0.45	51.90 ± 0.32	36.70 ± 0.21	42.70 ± 0.21	86.70 ± 0.21
Dye solubility test	o/w	o/w	o/w	o/w	o/w
% Yield of formulation	95	96	99	95	91
Drug content %	63.6	74.4	93.2	69.4	83.3

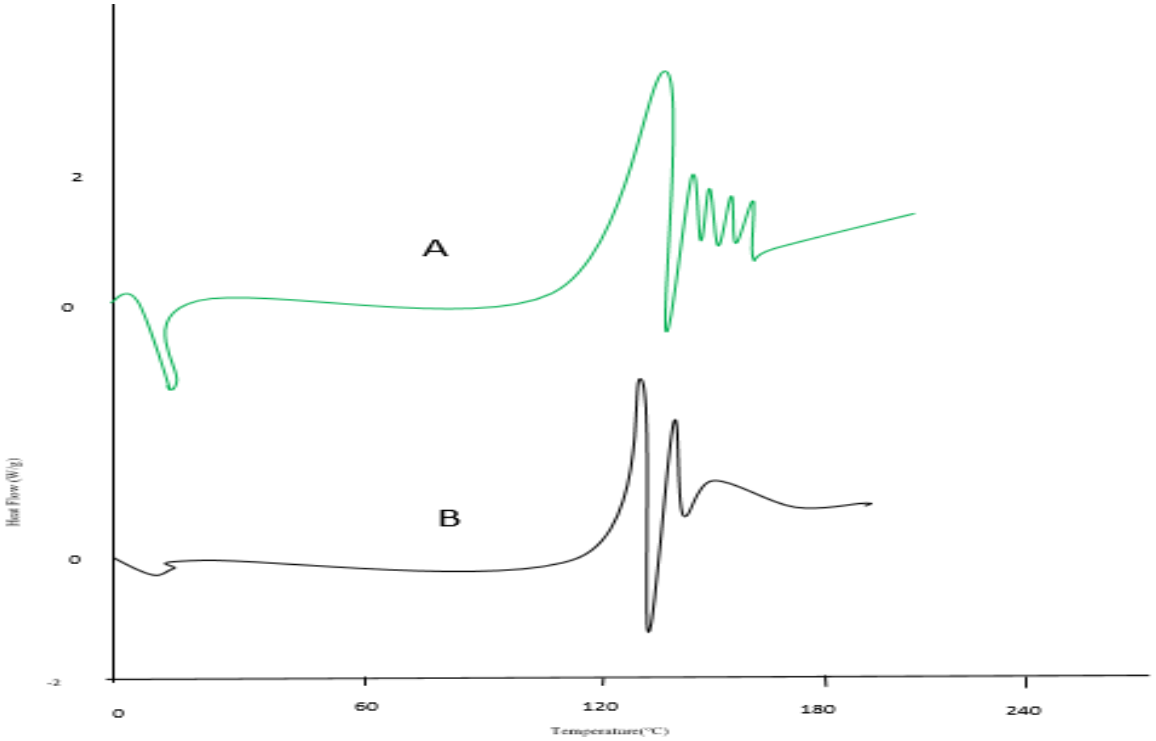

Figure 2: Thermogram of A. Microemulsion loaded diclofenac sodium, B. Pure diclofenac sodium.

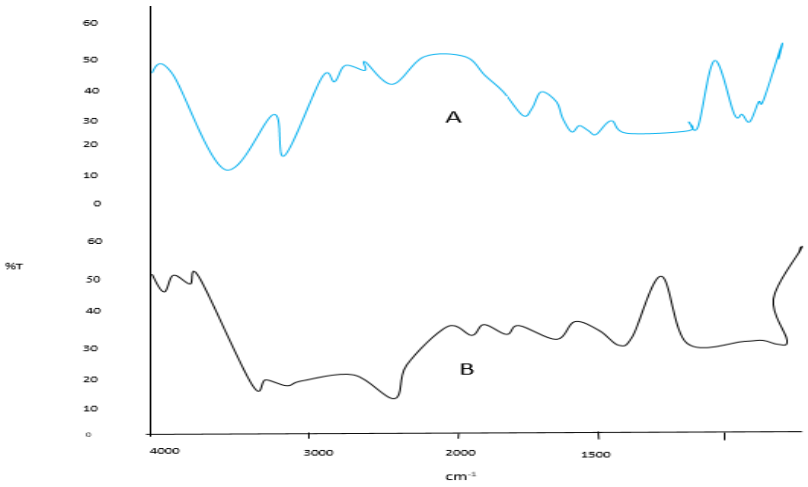

Figure 3: FTIR graph of A. pure diclofenac sodium, B Microemulsion formulation.

secondary amines at 3421 cm^{-1}, CN stretching which was present as two strong peaks at 1315- 1110cm^{-1}, C—O of carboxyl ion and C—C of the aromatic rings at 1569cm^{-1} and 1500cm^{-1} respectively, and to C-CL peak present at 738cm^{-1} as shown in **(Fig. 3)**. The drug-loaded Micro-emulsion formulation F3 showed an exact wide peak at 3421 cm^{-1} of NH as it was presents in Diclofenac Sodium. As per Diclofenac sodium in the formulation sample, CN and C—O didn't show any shift from 1315 and 1569 cm^{-1} respectively, C—C was present at 1500 cm^{-1}, which showed that there is no difference in the chemical structure of diclofenac sodium in the drug-loaded micro-emulsion sample, while C-CL peak showed a very little shift at 730 cm^{-1} as shown in figure 3. Diclofenac Sodium typical peaks were present in the formulation sample and did not show any significant change in peaks or any addition in the peaks that was indicating no chemical incompatibility and degradation between the excipients and the drug Diclofenac sodium were detected. But other formulations showed differences and shifts of peaks, showing that there was a difference in the chemical structure of diclofenac sodium when the drug was loaded in a micro-emulsion sample. Diclofenac Sodium characteristic peaks were not present in other formulations samples and showed some additional peaks like C-O-C and C-OH and some significant changes in peaks that indicated chemical incompatibility and degradation between excipients and the drug Diclofenac sodium.

Drug Content

As shown in table, drug content of formulation F1, F2, F3 F4, and F5 ranged from 63% -93%, was analyzed by absorbance measured through spectrophotometer. F3 formulation showed greater drug content that was more than 90% which indicated drug was properly solubilized in the micro emulsion and compatible with other ingredients. Ratio of surfactants and co-surfactants mixture with water also rendered it an optimized micro emulsion. Moreover, drug release was influenced due to use of 10 percent of IPM also in F3. Other formulations did not show drug release more than 80% due to incompatibility of ingredients with drug.

In Vitro Release

The percentage of cumulative permeation release of diclofenac sodium was ranged from 57% - 94.7% after 6 hours as shown in **(Table 2)**. The highest percentage release was 94.7% of F3 formulation at 6 hours. F1, F2, F4, and F5 formulations showed release that was less than 85% in the range of 57%-80%. The experimental findings were fitted to several order kinetic equations to determine the order kinetics of drug penetration from all of these formulations. According to kinetic modeling as shown in **(Table. 5)**. F1, F2, F3, and F5 formulation followed the 1st order model, Higuchi model, and in addition Korsmeyer Peppas model. The first order indicated that drug release depended on concentration and followed the dissolution mechanism. The Higuchi model showed that the release of the drug depended on the square root of time, independent of concentration, and followed the diffusion mechanism However Korsmeyer Peppas confirmed both 1st order and Higuchi model and gave non-Fickian release by n value which was 0.5-0.9. Hence, drug release started from diffusion and is followed by the mechanism of dissolution. Moreover, the F4 formulation only followed the Higuchi and in addition, Korsmeyer Peppas model and its n value showed Fickian release. Only the F3 formulation was optimized as dissolution diffusion control microemulsion, as shown in **(Fig.4)**. Because as a comparison to other formulations its values were more close to standard model values.

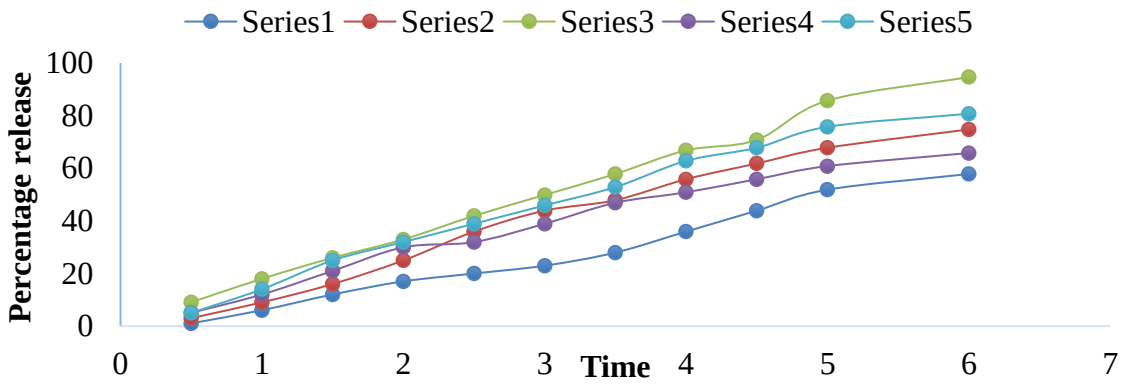

Figure 4: In vitro release study of formulations.

Table 5: R^2 value for kinetic models of in vitro drug release for formulations.

Formulations	Zero order	1st order	Higuchi	Hixon	Korsmeyer-Peppas	Diffusional exponent n
F1	0.8512	0.9644	0.9458	0.9404	0.9788	0.646
F2	0.6281	0.9480	0.95130	0.8933	0.9479	0.528
F3	0.5990	0.9833	0.9851	0.9587	0.9836	0.507
F4	0.4064	0.8340	0.9557	0.7382	0.9573	0.457
F5	0.5143	0.9509	0.9665	0.8913	0.9635	0.485

CONCLUSION

The transdermal formulation incorporating 4% diclofenac sodium has been successfully developed by constructing a pseudo ternary phase diagram using 4% w/v diclofenac sodium as active ingredient, 10% (v/v) IPM as organic phase, 50% (v/v) Smix (5:1, surfactant: cosurfactant). Tween 80 and polyethylene glycol 400 was used as surfactant and co surfactant respectively. In this study promising results were shown by the optimized topical diclofenac sodium microemulsion spray formulation. Particle size was around 100nm, pH was close to skin, FTIR and DSC showed suitable peaks and drug release was more than 95% release that claimed its stability, non-irritant nature, compatibility and better drug release and skin permeation respectively.

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