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FORMULATION AND DEVELOPMENT OF SOLID LIPID NANOPARTICLES BASED NANOGEL FOR DERMAL DELIVERY OF TOLMETIN.

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Abstract: *Topical administration of the Tolmetin is an anti-inflammatory agent with analgesic and antipyretic properties. It is used to treat osteoarthritis, rheumatoid arthritis and control acute pain. The therapeutic effects of Tolmetin are achieved via inhibition of the synthesis of prostaglandins involved in fever, pain, swelling and inflammation. Although, topical application of Tolmetin offers the advantage of delivering a drug directly to the disease site in order to maximize local effects without concurrent systemic activity yet, no formulation of Tolmetin is available in the market for topical use. The most difficult aspect of the topical drug delivery system is the formidable barrier properties of the stratum corneum (SC), the outermost layer of the skin that prevents percutaneous absorption of drugs.*

Keywords: *Tolmetin, Zeta potential, X-ray Diffraction Studies.*

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INTRODUCTION:

Novel drug delivery carriers have great potential for dermal delivery. The lipidic and nonlipidic vesicular systems like liposome, transfersome, ethosome, and niosome are used to overcome the problem associated with topical conventional formulation. Drug delivery system using novel vesicular carrier, such as liposome or niosome, has distinct advantages over microspheres, nanoparticles, and other carriers in terms of better entrapment of drugs (payload characteristics), target site specificity, and handling premature drug release (burst effect). In 1985, niosomes were studied as an alternative to liposome because they offer some benefits over liposome such as being more stable, nontoxic, and economic due to low cost of nonionic surfactant as compared to phospholipids which are prone to oxidation. Incorporation of surfactants within niosomes may also enhance the efficacy of the drug, possibly by facilitating its uptake by the target cells. Niosomes are biodegradable, biocompatible, relatively nontoxic, and an alternative of liposome. They can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic, and amphiphilic drugs. For transdermal route of administration NSAIDs, hormone, antibacterial, and antifungal drugs are most preferably used.

For the successful delivery of any new developed pharmaceutical formulation it is expected to deliver the therapeutic active drug to the target site at minimum effective concentration with negligible discomfort, maximum patient compliance to the therapeutic use and minimum side effects. Among various routes of administration, the topical route is the most favored route for local delivery of therapeutic agent. Due to its advantage of easy of application, low cost of production and convenience, topical route has become more popular over last few years. Current trend of oral and parenteral route offer the challenges related to adverse effects of drug and dosage form along with patient compliance and issue related to stability. However, conventional topical drug delivery systems have limitations such as less retention time and low bioavailability. Hence existing topical drug delivery and innovations in this system aims to improve the efficacy of drug and to achieve an optimal concentration of a certain drug at its site of action for an appropriate duration.

MATERIALS AND METHODS:

Table 1: Materials used

S.r No	Name
1	Tolmetin
2	Polysorbate 20
3	Polysorbate 80
4	GELRITE (Gellan Gum)
5	Methanol
6	DMSO
7	Triethanolamine
8	Propylene Glycol
9	Ethanol
10	Sodium Hydroxide
11	Glycerin
12	Sodium Chloride
13	Potassium phosphate monobasic
14	Sodium phosphate dibasic

Preparation of stock & buffer solutions:

1. Hydrochloric acid buffer pH1.2: 50ml of 0.2M potassium chloride and 85ml of 0.2 M HCl were taken in a 200 ml volumetric flask and made up to the volume with water.
2. Phosphate buffer pH 6.8: Dissolve 60.5 g of disodium hydrogen phosphate and 46 g of potassium dihydrogen phosphate in water add 100 ml of 0.02 M disodium edetate and 20 mg of mercuric chloride and dilute with water to produce 1000ml.
3. Phosphate buffer pH 7.4: 50 ml of 0.2 M potassium dihydrogen phosphate and 39.1 ml of 0.2 M NaOH were taken in a 200 ml volumetric flask and made up to the volume with water.
4. Sodium hydroxide solution (0.2 M): Accurately weighed 8.0 gm of sodium hydroxide was dissolved in 1000 ml of distilled water.
5. Potassium dihydrogen phosphate (0.2 M): Accurately weighed 27.218 gm of potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water.
6. Potassium chloride (0.2 M): Accurately weighed 14.91 gm of potassium chloride was dissolved in 1000 ml of distilled water.

Solid state characterization of drug:

Fourier Transfer Infrared Spectroscopy:

Drug was mixed with Potassium Bromide in a ratio of 9:1 which was triturated and blended evenly. The mixture was further compressed into pellets on a motorized pellet press at pressure of 15 ton. The prepared pellets were then scanned over range of 4000 – 400 cm^{-1} to get the IR spectra.

Differential Scanning Calorimetry:

Drug was hermitically sealed in perforated aluminum pan using crimper and heated at constant rate of 10°C/min over the temperature ranges of 30-300°C at 20mL/min nitrogen purging on a Mettler Toledo DSC apparatus, Switzerland

Melting Point Determination:

Capillary Method was employed for Melting Point Determination. Drug was filled in a one end sealed capillary tube and was placed in a Liquid Paraffin bath in a Thiele's Tube. Upon visual inspection, temperature on which the solid starts turning into a liquid was noted down.

Solubility Analysis:

The preparation of any dosage form, it required to know the solubility of drug. The solid dosage form need particular solvent to dissolve, and produces pharmacological effect to body. Additionally, the bioavailability of drug present in solid dosage form depends upon solubility of drug. If drug is sparingly soluble in solvent then it produces minimum therapeutic response due to less availability of drug to receptors. Hence solubility of drug play important role in therapeutic effects of drug.

Solubility of drug was studied in Methanol, Ethanol, DMSO, 0.1N HCl, pH 1.2 HCl buffer, pH 6.8 phosphate buffer to study the behavior of the drugs.

Drug-excipients incompatibility studies:

Fourier Transfer Infrared Spectroscopy:

The Fourier Transform – Infrared (FT-IR) spectroscopy has numerous application in Pharmaceutical field. It is widely used in determination of identification of known and unknown compound. Apart from this it can also be used in evaluating the drug interaction. During formulation the active ingredient are used mixed with various excipients to give proper shape and appearance. Sometimes it happens after mixing the active ingredients with excipient, it produces incompatibility due to drug excipient interaction. The incompatibility of drug can alter the potency of formulation. It can also produce adverse effects to the body. Hence for pharmaceutical industries it is prime work to check the drug and excipient incompatibility.

Drug was mixed with all excipients in equal proportion forming a physical mixture were all compressed as a KBr pellet respectively for each sample at a ratio of 9:1. The prepared pellets were then scanned over range of 4000 – 400 cm^{-1} to get the IR spectra. Functional group determination was studied visually by interpreting the peaks observed and any changes in parent peaks were observed.

Differential Scanning Calorimetry:

Physical Mixture of drug and excipients was prepared for both drugs and sealed in a pre-washed ampoule. It was set aside in a Programmable Environmental Test Chamber, Remi Instruments Ltd. Mumbai for 28 days. Following that the sample was hermitically sealed in perforated aluminum pan and heated at constant rate of 10°C/min over the temperature ranges of 30-300°C at 20mL/min nitrogen purging on a Mettler Toledo DSC apparatus, Switzerland.

Analytical method development:

Determination of λ_{max} for Tolmetin:

10 mg drug was suspended in 100 ml methanol to prepare a stock solution and 10ppm sample was taken out and studied for its UV Spectra photometrically on a UV- 2450 UV-Vis Spectrophotometer, Shimadzu, Kyoto, Japan.

Preparation of Stock Solution:

Accurately weighed 10 mg of Tolmetin was transferred to a 100 ml volumetric flask, dissolved in 10 ml Methanol by shaking manually for 10 min. The

volume was adjusted with the same up to the mark to give the final strength, i.e.100 µg/ml.

Preparation of Calibration Curve of APZ

Different aliquots of Tolmetin in the range 0.2-1 ml were transferred into series of 10 ml volumetric flasks, and the volume was made up to the mark with distilled water to get concentrations 2, 4, 6, 8 and 10 µg/ml, respectively. The solutions were scanned on a spectrophotometer in the UV range 200–400 nm. The absorbance was recorded at 354 nm.

Formulation of tolmetin solid lipid nanoparticles:

SLN were prepared by film hydration technique. The mixture of vesicle-forming ingredients namely lecithin and cholesterol was dissolved in a volatile organic solvent (dichloromethane and methanol) in a round-bottom flask. The rotary evaporator was rotated at 60°C for 45 min. Then the organic solvent was removed with gentle agitation and the organic solvent evaporated at 60°C, leaving a thin film of lipid on the wall of the rotary flash evaporator. The aqueous phase containing Meloxicam drug was added slowly with intermittent shaking of the flask at room temperature and sonicated for 30 min. The obtained nanolipid solution was cooled by placing in the freezer.

Table 2: Formulation design for Tolmetin SLN

Ingredients (%)	F1	F2	F3	F4	F5
Tolmetin	5	5	5	5	5
Lecithin	5	2.5	7.5	4	6
Cholesterol	5	7.5	2.5	6	4
Dichlormethane: Methanol (1:1)	25	25	25	25	25
Water	60	60	60	60	60

Formulation of Nanogel was prepared on the basis of drug entrapment efficiency of prepared SLNs. The batch of SLN that gave maximum entrapment was selected for preparation of Nanogel

Formulation of tolmetin nanogel:

After conducting trial batches, the excipients and their concentration ranges were selected and thus formulation chart was designed by using Design Expert 12.0 software.

Design Expert 12.0 software was used to create formulation design for the purpose of optimization of SLN for Tolmetin. Design of experiments is a method by which purposeful changes to input factors of process in order to observe the effects on the output can be made. DOE's can and have been performed in virtually every industry on the planet—agriculture, chemical, pharmaceutical, electronics, automotive, hard goods manufacturing, etc. Service industries have also benefited by obtaining data from their process and analyzing it appropriately. Traditionally, experimentation has been done in a haphazard one-factor-at-a time (OFAT) manner. This method is inefficient and very often yields misleading results. On the other hand, factorial designs are a very basic type of DOE, require only a minimal number of runs, yet they allow you to identify interactions in the process. This information leads to breakthroughs in process understanding, thus improving quality, reducing costs and increasing profits.

Table 3: Independent Factors for Formulation Design

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	GELRITE	%	Numeric	7.93	22.07	-1 ↔ 10.00	+1 ↔ 20.00	15.00	4.08
B	20:80	%	Numeric	7.93	22.07	-1 ↔ 10.00	+1 ↔ 20.00	15.00	4.08

Responses were selected as follows

Table 4: Responses for Formulation Design

Response	Name	Units
R1	Entrapment Efficiency	%
R2	In-Vitro drug release	%

A total of 13 runs were obtained out of which 5 were replicates. Hence a total of 9 definite experiments were obtained to be conducted practically

Table 5: Formulation Table for Tolmetin Nanogel composed by using Central Composite Design

Formulation Code	Tolmetin (%)	GELRITE (%)	Tween 20:80 (%)	Diluent to make 100%
F1	5	10	10	Q.S
F2	5	20	10	Q.S
F3	5	10	20	Q.S
F4	5	20	20	Q.S
F5	5	7.92893	15	Q.S
F6	5	22.0711	15	Q.S
F7	5	15	7.92893	Q.S
F8	5	15	22.0711	Q.S
F9	5	15	15	Q.S

The Tolmetin nanogel was synthesized with the aid of Gelrite as a polymer. Accurately weighed 5 mg of Tolmetin SLNs and variable concentration of GELRITE was dissolved in 1% v/v methanol followed by the drop wise addition of Tween 20:80 (1:1) at the rate of 2 ml/min with constant stirring for 3 h by using magnetic stirrer at 1000 rpm. pH was adjusted by gel Triethanalamine(0.05%). The mixture was allowed to achieve room temperature which resulted in gel formation.

Isolation of Nanogel:
Centrifugation of Nanogel dispersion was done for the sepration of nanoparticles by using Optima "MAX-XP" ultracentrifuge at 45,000 rpm for 35 minutes. Deposited particulate was redispersed in minimum quantity of water with appropriate concentration of mannitol.

Characterization of tolmetin slns and nanogel:
a. Mean Particle size:
The MPS were determined by PCS with a Malvern Zetasizer (Nano ZS 90, Malvern ltd., UK). The measurement using PCS is based on the light scattering phenomena in which the statistical intensity fluctuations of the scattered light from the particles in the measuring cell are measured. Prior to the measurements, all samples were diluted with double distilled water to produce a suitable scattering intensity. The z-average and PDI values were obtained at an angle of 90° using disposable polystyrene cells having 10 mm diameter cells at 25°C, which were equilibrating for 120 seconds.

b. Zeta potential:
The zeta potential (ZP), reflecting the electric charge on the particle surface and indicating the physical stability of colloidal systems, was measured by determining the electrophoretic mobility using the Malvern Zetasizer (Nano ZS 90, Malvern ltd., UK). The measurements were performed with diluting in double-distilled water. It was measured using Dip cell with applying field strength 20 V/cm and the average of the zeta potential was given from 30 runs.

c. Production yield:
The production yield of nanogel formulation were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of nanogel.
Production Yield = Practical/ Theoretical Yield * 100

d. Entrapment Efficiency and Drug loading:
Percent Entrapment efficiency (EE) is defined as the percentage of drug incorporated into the polymeric nanogel relative to the total drug added. It specifies how much percent of drug is included in the particles and how much percent of free drug are still present in the dispersion medium. For this both, Tolmetin SLNs and NG were centrifuge at 45,000 rpm for 35 min ; 1.0 mL of the supernatant collected after centrifugation was diluted with 3.0 mL of DMSO and methanol and then make up volume up to 10 ml in 10ml volumetric flask and measured spectrophotometrically at 354 nm using UV-Visible spectrophotometer (UV 1700,Shimadzu, Japan). The entrapment efficiency and standard deviation was calculated.

e. Surface morphology:
The morphology of nanogel were examined by scanning electron® microscopy (JSM 6390, Japan). Samples of nanogel were dusted onto double-sided

tape on an aluminum stub and coated with gold using a cold sputter coater to a thickness of 400°A, and then imaged using a 20 kv electron beam.

f. X-ray Diffraction Studies

X-ray diffraction patterns optimized Tolmetin NG formulation was obtained using X-ray diffractometer (BruckerAxs, D8 Advance; Germany) in which Cu-Kα line used as a source of radiation by operating at the voltage 40 kV and the current applied was 30 mA. All samples were measured in the 2θ angle range between 10° and 60° with a scanning rate of 3°/min and a step size of 0.02°.

g. Differential Scanning Calorimetry

Thermal analysis was performed using a differential scanning calorimetry (DSC) (Mettler-Toledo, Zurich, Switzerland) for optimized formulation. The samples, weighing 2 mg, were analyzed in sealed and pin-holed standard 40 µl aluminum pan, with a heating rate of 10°C/min from 30°C to 300°C and during the measurement the sample cell were continuously purged with nitrogen at a flow rate of 40 ml/min.

h. Swelling Studies:

The degree of swelling was calculated by finding out weight of swollen nanogels. The swelling behavior of the nanogels was studied at two different pH 6.8. The swelling ratio was calculated using the following formula after determining the dry as well as wet weight of the lyophilized, nanogel after sufficient exposure to the corresponding pH solution.

Swelling ratio= Final- Initial Weight * 100

i. In vitro Drug Release

In vitro diffusion study of Nanogels was carried out by Franz diffusion cell having 2.0 cm diameter and 25 ml capacity. Dialysis membrane (Himedia) having molecular weight cut off range 12000 – 14000 kDa was used as Diffusion membrane. Pieces of dialysis membrane were soaked in Phosphate buffer solution (PBS) pH 6.8 with 1% nanogel for 24 h prior to experiment. Diffusion cell was filled with PBS pH 6.8 and dialysis membrane was mounted on cell. The temperature was maintained at 37oC. After a pre-incubation time of 20 minutes, the lyophilized powder equivalent to 50mg of Tolmetin was dispersed in 3ml of PBS and was placed in the donor chamber. Samples were periodically withdrawn from the receptor compartment for 11hours and replaced with the same amount of fresh PBS, and assayed by a UV spectrophotometer at 354 nm. In this type of nanogel drug release through stimuli responsive If alteration in pH then drug release start.

RESULT AND DISCUSSION:

Solid State Characterization Of Drug:

Fourier Transfer Infrared Spectroscopy:

Fourier transformed infrared spectra of Tolmetin was taken by using the KBr disk method. The scanning range was 450 to 4000 cm^{-1} and the resolution was 1cm-1. The obtained IR spectra of drug sample. Observed peaks of the drug which are similar to the standard IR spectra of drug reported in the literature.

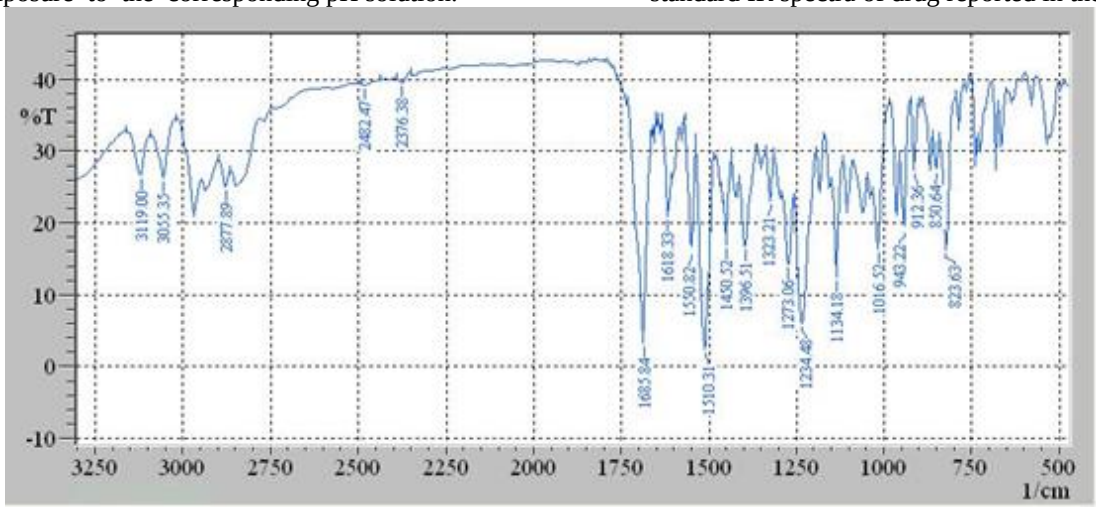

Figure 1: FTIR spectra of Tolmetin

Table 6: Principal peak and chemical group present in IR spectra of Tolmetin

Observed peaks	Reported peaks	Interpretation of chemical groups
3510.56	3500-3450	C=O stretch carbonyl
3014.84	3100-3000	=C-H stretching alkene
2943.47	3000-2850	C-H stretching alkane
1602.90	1650-1580	C=O, carbonyl group
1585.54	1685-1550	C=C stretch aromatics
1429.30	1450-1400	C-H bend alkenes
1381.08	1320-1000	C-O stretch alcohols, esters, carboxylic acid

Differential Scanning Calorimetry:

To verify the existence in the physical interaction between drug and excipients, sample was analyzed by differential scanning calorimetry (DSC). The DSC results presented demonstrated an endothermic peak for Tolmetin at 250 ^{0}C corresponding to the melting point. The physical mixture Thermogram was nearly identical to that of pure Tolmetin and showed an endothermic peak at 270^{0}C.

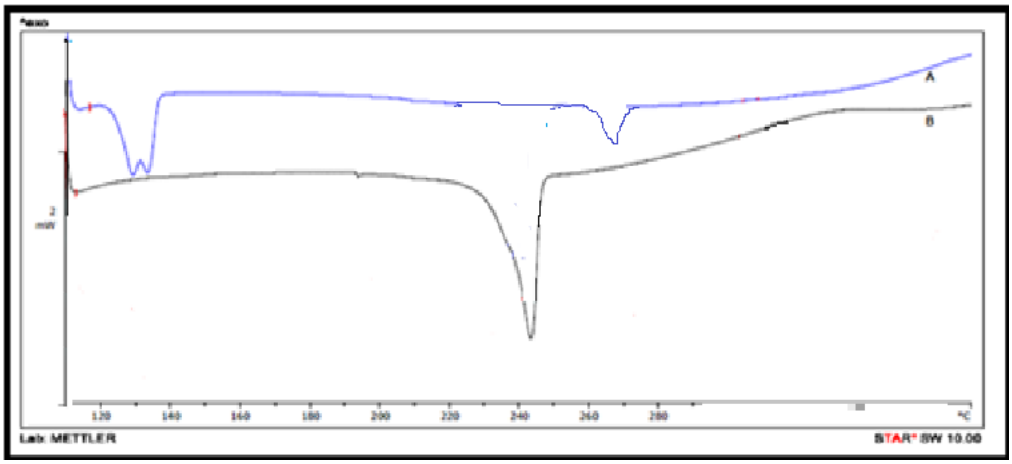

Figure 2: Overlay of DSC Thermogram of Tolmetin, Physical mixture

Melting Point Determination:

Melting point of Tolmetin was found by glass capillary method to be 245- 256 ^{0}C. The observed melting point of Tolmetin was confirmed with the standard melting point of Tolmetin.

Solubility Analysis:

The solubility of Tolmetin was assessed in different solvent system viz., Methanol and DMSO mixture and Phosphate buffer saline pH 6.8 at 37 ± 0.5°C.

Table 7: Solubility of TOLMETIN in different solvent system

S/N	Solvent	Observed solubility mg/ml
1	Methanol	16±0.000
2	DMSO	15±0.180
3	Methanol :DMSO (98:2)	16±0.90
4	Methanol	29±0.90
5	Phosphate buffer 6.8	9.88±0.05

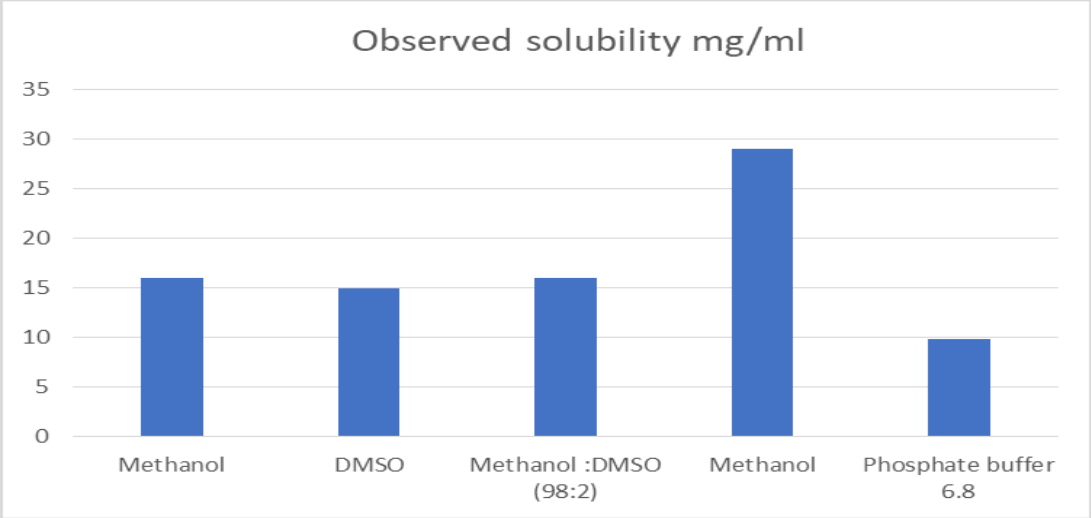

Figure 3: Solubility of Tolmetin in different solvent systems

Drug-Excipients Incompatibility Studies:

Fourier Transfer Infrared Spectroscopy:

Identification of any possible incompatibilities between the drug and excipients is major task to be achieved through preformulation and compatibility studies. Compatibility studies deal with understanding of any physicochemical interactions of drug and excipients. Development of a robust and effective formulation necessitates careful selection of the excipients that maintain the quality, safety, efficacy and stability of the drug product.. It also reflects the molecular-level changes in oscillation of molecular dipoles

FTIR study of Tolmetin, its physical mixture in ratios of 1:9 and 1:1 shows no significant drug-drug interactions.

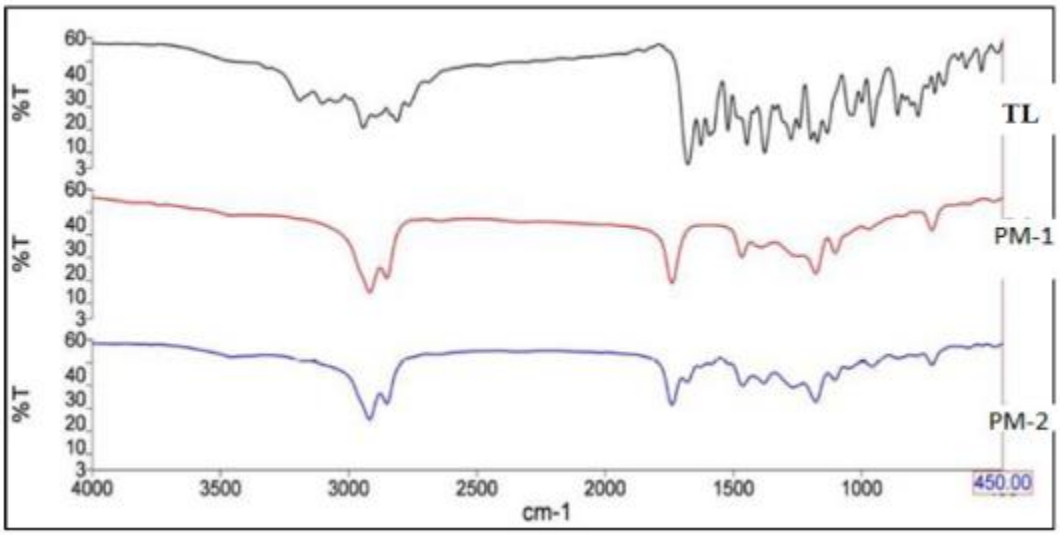

Figure 4: FTIR Spectra of Tolmetin and their Physical Mixture

Analytical Method Development:

DETERMINATION OF λ_{MAX} FOR TOLMETIN:

The solution of Tolmetin in methanol was found to exhibit maximum absorption at 354 nm after scanning on the UV-Vis spectrophotometer which was reported as λmax in the literature. Thus the procured drug sample of Tolmetin complies with the reference spectra.

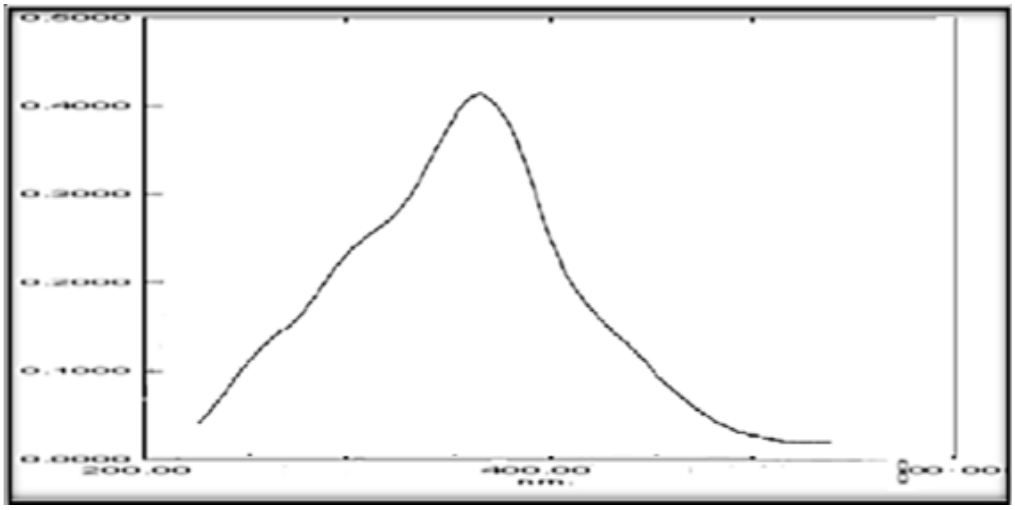

Figure 5: UV spectrum of Tolmetin in Methanol

Preparation of Calibration Curve of Tolmetin:

Graph of absorbance vs. concentration was plotted and found to be linear over the range of 2 to 12µg/mL indicating its compliance with Beer's and Lambert's law.

Table 8: Standard calibration curve of Tolmetin in Methanol

Sr. No.	Concentration (µg/ml)	Absorbance
1.	2	0.136
2.	4	0.316
3.	6	0.481
4.	8	0.631
5.	10	0.795
6.	12	0.939

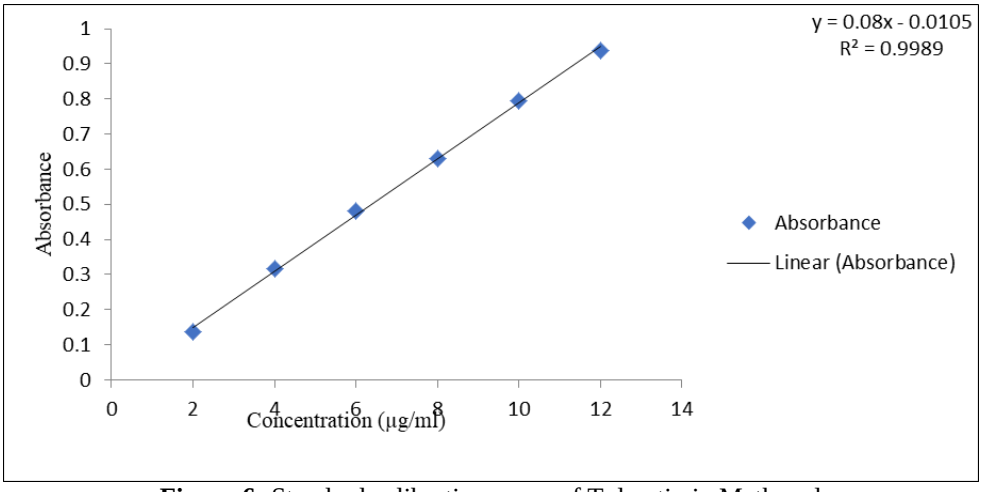

Figure 6: Standard calibration curve of Tolmetin in Methanol

Characterization of tolmetin slns and nanogel:

Selection of suitable Tolmetin SLN formula for further preparation of Nanogel:

Formula F1 was selected as the most optimized formula for preparation of Nanogel. This decision was based upon the Entrapment Efficiency results (99.98 %) for F1 SLNs.

a. Mean Particle size

The particle size and PDI the drug free NG was found to be 201nm and 0.3 respectively. After then drug loading partical size of TOLMETIN loaded NG was increase 226 nm there was no significant change in PDI. Partical size of NG a crucial factor because it determines the rate and extent of drug release as well as drug absorption.

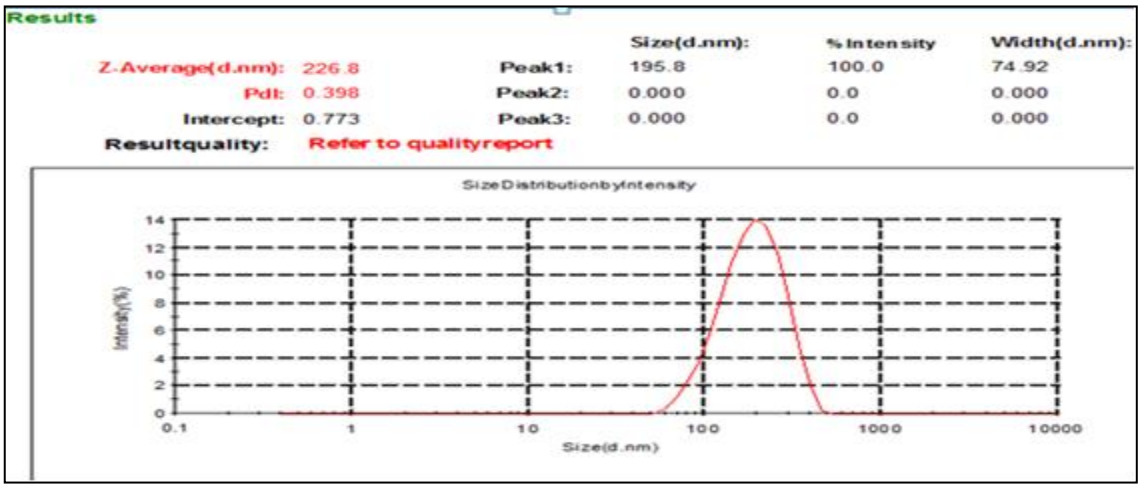

Figure 7: Particle size analysis of Optimized Formulation of Tolmetin NG

b. Zeta potential:

The obtained zeta potential of Tolmetin -loaded NG was found to be 5.52. The Zeta potential represents the electrical charge to the NG surface. The greater the ZP value, more likely the suspension is to be stable because the charged particles repel one another and thus overcome the natural tendency to aggregate. It is currently admitted that higher ZP values, either positively or negatively charged, indicates that the dispersion having long term stability.

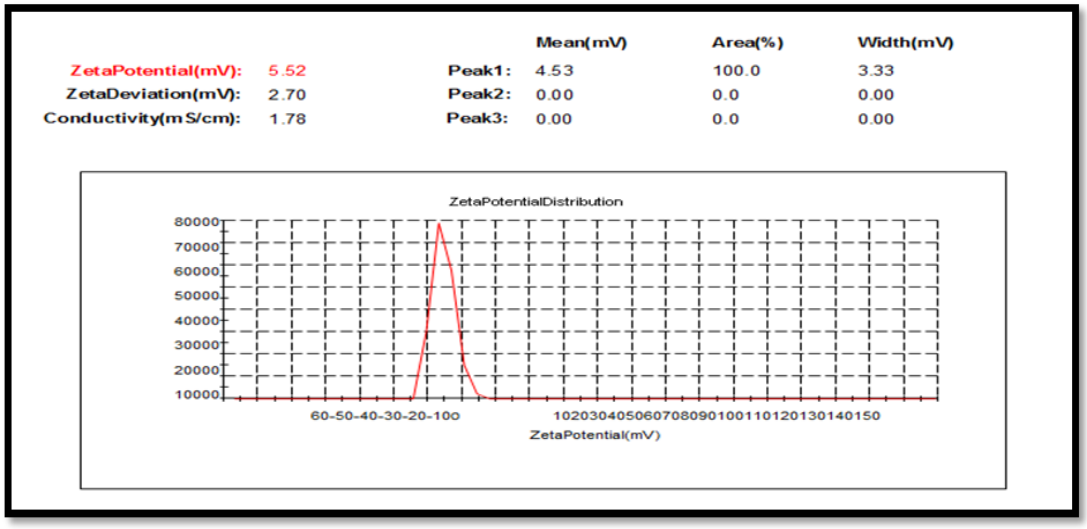

Figure 8: Zeta potential distribution of Optimized Formulation of Tolmetin NG

Production yield, Entrapment Efficiency and Drug loading

Table 9: Results

Formulation Code	Production yield (%)	Entrapment Efficiency (%)	Drug loading (%)
F1	77.2	98.7	7.3
F2	69.8	99.8	6.5
F3	74.6	89.0	7.7
F4	79.0	95.4	5.8
F5	72.1	99.9	7.4
F6	74.2	100.8	8.2
F7	78.0	94.3	9.5
F8	73.2	89.1	8.3
F9	70.0	91.1	7.1

c. X-ray Diffraction Studies:

XRD for optimized Tolmetin NG shows amorphous property thus also confirming resemblance with SEM images and proving to be smooth on surface

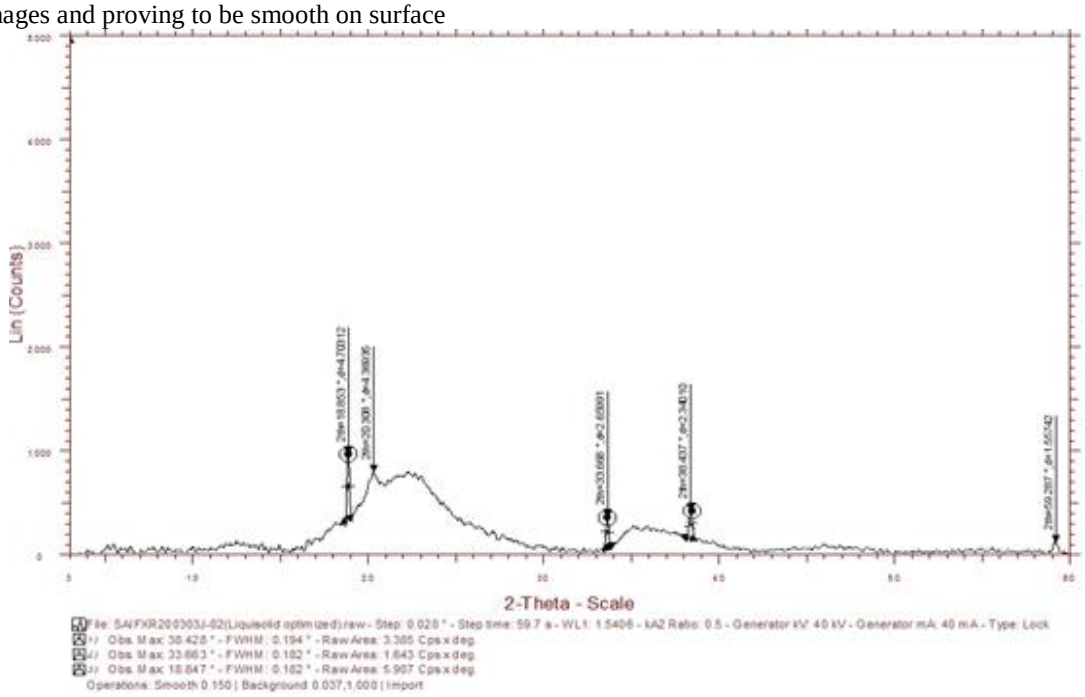

Figure 9: XRD of Tolmetin -loaded Optimized Formulation of NG

d. Differential Scanning Calorimetry:

DSC was a basic method to investigate the crystallization or amorphous state of drug in the compounds and NG by determining the variation of temperature and energy at phase transition. DSC curve of Tolmetin NG. The disappearance of the endothermic peak of Tolmetin in the Tolmetin–NG powder suggests that the drug is completely encapsulated in the polymer crosslinking matrix and converted to amorphous state from crystalline state.

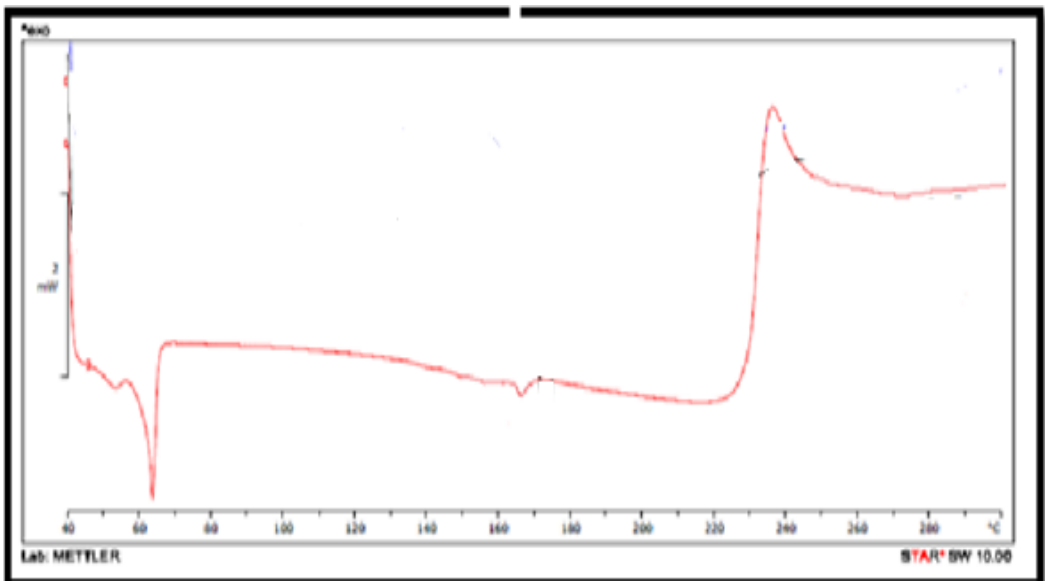

Figure 10: DSC thermogram of Optimized formulation of Tolmetin –NG

e. Swelling Studies:

The swelling ratio was found to be 0.5 at pH 5.4 and 0.2 at pH 7 for optimized formulation

f. In vitro Drug Release

Table 10: - In-Vitro drug release studies for Tolmetin NG formulations

Formulation Code	Drug release at 30 minutes (%)
F1	93.2
F2	96.4
F3	94.5
F4	97.8
F5	98.1
F6	99.5
F7	100.8
F8	94.3
F9	92.9

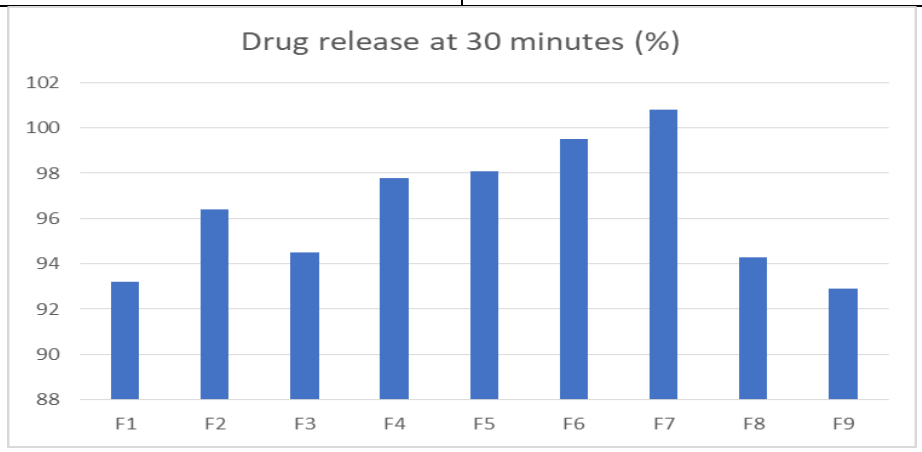

Figure 11: - In-Vitro drug release studies for Tolmetin NG formulations

Formulation F7 showed maximum drug release at 100.8 % in 30 minutes. Hence, F7 was considered as

optimized formulation.

g. Accelerated stability study

Table 11: Stability studies

Stability parameter	Test period			
	0 Days	**30 Days**	**60 Days**	**90 Days**
MPS (nm)	226.2 ± 0.027	227.2 ± 1.80	229.9 ± 0.03	230.1 ±0.013
PDI	0.3 ± 0.19	0.3 ± 0.53	0.3 ± 0.57	0.3 ± 0.96
% EE	96.66 ± 1.18	94.02 ± 0.02	90.98 ± 1.05	87.01 ± 1.35

SUMMARY AND CONCLUSION:

Although, Tolmetin possesses some favorable properties for topical administration like low molecular weight, low daily therapeutic dose yet, the inherent poor aqueous solubility and high melting point make it unsuitable for topical application. It does not exhibit enough lipophilicity for permeation across the skin. A number of topical/transdermal drug delivery systems, which vary in their compositions and structures have been developed to improve the skin permeation of Tolmetin. However, the poor drug loading capacity, poor drug controlled and sustained release capacities have limited their use as topical/transdermal carriers. The level of interest in lipid-based carrier systems have increased substantially for topical administration of drugs because of the use of fats and oils of natural origin and pharmaceutically accepted surfactant as excipients.

Suitable excipients were selected for formulation of Solid Lipid Nanoparticles based Nanogel through preliminary trials to achieve desired Entrapment Efficiency, Ex-Vivo Permeation Studies and In-Vitro drug release. Drug excipient compatibility study using DSC and FTIR was performed Using GELRITE as polymer in varying concentrations for Solid Lipid Nanoparticles based Nanogel formulation followed by Formulation of Nanogel of Tolmetin. The prepared Nanogel was evaluated for Mean Particle size, Zeta potential, Production yield, Entrapment Efficiency and Drug loading, Surface morphology, XRD, DSC, Swelling Studies, and In-Vitro Drug release. At last, conducted the ageing studies of the optimized formulation.

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CONFLICTS OF INTEREST:

Authors have no conflicts of interest to declare.

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