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NANOTECHNOLOGY-ENABLED TRANSDERMAL DELIVERY OF KETOPROFEN FOR RHEUMATOID ARTHRITIS

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ABSTRACT

The present study aimed to develop and evaluate nanoparticles loaded transdermal drug delivery system of Ketoprofen for Rheumatoid arthritis. Solid lipid nanoparticles of Ketoprofen were prepared by Highspeed homogenization technique, by using Face centred CCD with 2^3 factorial design with 6 axial points and 1 center point that gives 15 trials with low, Intermediate and high limits of GMS was used as lipid and Tween 80 and Span 60 were used as surfactants. Particle size and Entrapment Efficiency were evaluated statistically. Numerical optimization recommended the optimized formulation with Particle size of 129nm, entrapment efficiency (83%) and drug release (106.4%). The optimised formulation was subjected for TEM and the surface of the particles were smooth and there is no aggregation of particles. So, optimized formulation of nanoparticles was then used for formulation of transdermal patch using HPMC K100 M as polymer and PEG-400 as plasticizer. The patch was evaluated for Weight uniformity, Folding endurance, Thickness, Drug Content, *In- vitro* drug release and Ex-vivo studies. The release of drug from the SLNs formulation was found to be more than the release from the transdermal patch.

KEYWORDS: Nanoparticles: Ketoprofen, GMS, Tween80, Span 60, Transdermal Patch: HPMC K100 M, PEG- 400.

INTRODUCTION

Rheumatoid arthritis is a chronic disease that primarily affects the peripheral joints and often lead to tissue degradation. It usually present with pain, stiffness and swelling of small joints

of hands and feet. Rheumatoid arthritis (RA) is a common form of arthritis; it is a chronic and autoimmune disease with a worldwide prevalence of approximately 0.5% to 1% among adults and higher in America and Europe than in Asia. RA causes inflammation of the joints, as well as other organs in the body. It is identified by persistent synovitis, systemic inflammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide). It is a progressive illness that can lead to long-term joint damage, loss of function and disability initially starting with inflammation and redness of a joint, deformation of limbs, stiffness of limbs during morning session, recurrent backpain.

Arthritis as a potential barrier to physical activity among adults contributing to an increased risk of obesity, high cholesterol or vulnerability to heart disease and also at increased risk of depression.[1]

Ketoprofen belongs to the family of propionic acid derivatives, which hold analgesic, anti-inflammatory and antipyretic properties. The mechanism of its action inhibits prostaglandin synthesis by non- specific blocking cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-COX 1 is responsible for the synthesis of prostaglandins with physiological functions, and COX 2 creates pro-inflammatory prostaglandins at the site of inflammation. Ketoprofen is an outstanding candidate for transdermal delivery among the various NSAIDs and it belongs to BCS class 2 as it has an optimum solubility and partition coefficient compared to other NSAIDs.[2]

Nanoparticles (NPs) are solid colloidal particles ranging from 10 to 1000nm in size in which an active ingredient(s) are dissolved, entrapped, encapsulated, adsorbed or attached to a nanoparticle matrix. When compared to alternative drug delivery methods, nanoparticles provide a number of benefits due to their unique features, which include small particle size, huge surface area, and the capacity to modify their surface properties. Recent advances in nanotechnology have made it possible to deliver macromolecules like proteins, peptides, or DNA, as well as small molecular weight medications, to cells and tissues while shielding them from enzymatic degradation. Nanoparticles as drug delivery systems are biodegradable, non-toxic and capable of being stored for longer periods as they are more stable.[3,4]

Oral dosing frequency of ketoprofen is 3-4times/day. Oral administration of ketoprofen might induce side effects involving the gastrointestinal system, such as digestive bleeding, intestinal burning and ulcerations. In this present study an attempt has been made to develop

nanoparticles loaded Transdermal patch to deliver drug across the skin to the targeted site to avoid the gastrointestinal side effects, improve patient compliance, easy termination of effect by removal of patch and reduce dosing frequency.

MATERIALS AND METHOD

MATERIALS

Active Ingredient: Ketoprofen

Excipients: GMS, Tween 80, Span 60, Ethanol, HPMC K100 M, PEG 400.

METHODOGOLY

Pre-formulation studies

Determination of λ max

25mg of Ketoprofen was weighed and dissolved in 25 ml of ethanol. 1ml of this solution was withdrawn and volume was made upto to 10ml with phosphate buffer pH 7.4. Appropriate dilutions were made with phosphate buffer pH 7.4 to give concentration of 10µg/ml. The solution was scanned in UV range from 200-400nm, which could be utilized for analysis and spectrum was recorded.

Preparation of Calibration Curve of Ketoprofen in Phosphate Buffer pH 7.4[5]

25mg of Ketoprofen was weighed accurately and transferred in 25ml volumetric flask and dissolved in ethanol and the volume is made up to the mark with ethanol (1000ug/ml) is a primary stock solution. 10 ml from above stock solution was taken and diluted to 100ml with pH 7.4 buffer as concentration 100 µg/ml which is stock 2. from stock 2 serial dilutions were made for the concentration 2, 4, 6, 8, and10 µg/ml. The absorbance was measured at 260nm using UV visible spectrophotometer. The standard graph was repeated for 3 times (n=3). The mean data was plotted by taking the concentration on X-axis and absorbance on Y-axis.

Compatibility studies: Infrared (IR) spectroscopy is a commonly employed non-thermal method to study the compatibility of drugs with their Excipients. It generates a distinct spectral profile reflecting the physical and chemical features of the components. In this study, Ketoprofen and the Excipients were separately mixed with IR-grade potassium bromide in a 1:10 proportion, pressed into clear pellets using a hydraulic press at 10-ton pressure, and scanned within the spectral range of 4000–400 cm^{-1}.[6]

Determination of melting point[7]

Determination of melting point gives an idea about purity of the drug. Melting point of Ketoprofen was determined by capillary method. Fine powder of Ketoprofen was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermometer and the thermometer was kept in a tube containing liquid paraffin. The assembly was kept on heating and temperature was allowed to increase gradually. Temperature at which the powder melts was noticed.

Preparation of Solid lipid nanoparticles

High Speed Homogenization Method[8,18]

In the present study, the Highspeed homogenization method was used to prepare Ketoprofen loaded solid lipid nanoparticles. The method is as follows:

- The lipid phase containing lipid (GMS) and Span 60 were melted above its melting point (65^0C and 54^0C respectively)
- The Ketoprofen was dissolved in ethanol and added to the melted lipid phase.
- The aqueous phase was prepared by dissolving the Tween 80 in distilled water and heating it up to the same temperature of the lipid phase.
- Aqueous phase was kept in a tray containing hot water and lipid phase was dropped into the hot aqueous phase using 23 guage syringe under stirring at 5000rpm for 30 mins using homogenizer and ice cubes were added to the tray and continue homogenization for 1hr.
- Nanoparticles thus produced were evaluated for different parameters such as particle size, zeta potential, polydispersity index, entrapment efficiency, drug content and drug release.

Table 1: Formulation chart of Ketoprofen loaded solid lipid nanoparticles as Face Centred CCD design.

Formulation code	Ketoprofen (mg)	GMS (mg)	Tween 80 (mg)	Span 60 (mg)	Ethanol (ml)	Distilled Water (ml)
F1	100	100	200	200	10	100
F2	100	100	350	0	10	100
F3	100	100	50	0	10	100
F4	100	100	350	400	10	100
F5	100	100	50	400	10	100
F6	100	300	350	200	10	100
F7	100	300	200	200	10	100
F8	100	300	50	200	10	100
F9	100	300	200	0	10	100
F10	100	300	200	400	10	100
F11	100	500	50	0	10	100

F12	100	500	350	400	10	100
F13	100	500	50	400	10	100
F14	100	500	200	200	10	100
F15	100	500	350	0	10	100

Particle size analysis and poly dispersity index

The Particle size of nanoparticles plays a very important role in drug permeation through the skin. Polydispersity index describes the particle size distribution of nanoparticles. It helps to know the average uniformity of particles size of the sample. High poly dispersity index value describes the high degree of non-uniformity of a distribution of the particles in the nanoparticle formulation. By using the dynamic light scattering (DLS) technology, the average particle size. and the poly dispersity index were evaluated in Horiba Scientific (Nano-particle) SZ-100 and agitated using magnetic stirrer with the speed of 100 rpm. Aliquots of 5 ml sample were at an angle of 90˚at 25℃. Before the measurement, 1ml of the sample diluted to 10ml with double distilled water and sonicated for 15 minutes and vortexed, kept in polystyrene cuvettes for the evaluation of the particle size and poly dispersity index.[9]

Zeta-potential determination

Zeta Potential (ZP) is the electric charge on the particle surface. It helps to predict the storage stability of the colloidal dispersion. At higher zeta potential, less particle size aggregation occurs due to electrical repulsions. Zeta potential was measured using Horiba Scientific (Nano-particle) SZ-100. 1ml of formulated SLNs was diluted to 10ml with double distilled water and sonicated for 15 minutes. Then the sample was transferred into the cuvette which contains electrode and kept inside the instrument and zeta potential of sample was measured.[10]

Entrapment Efficacy

The Entrapment efficiency of prepared sample was determined by indirect method by measuring the concentration of the drug in the dispersion medium. The free drug Ketoprofen was determined by adding 1ml of Ketoprofen loaded SLNs to centrifuge tubes and then this dispersion was centrifuged at 15000rpm for 30 mins at 25 °C. The supernatant was diluted with phosphate buffer pH 7.4 and absorbance was measured spectrophotometrically at 260nm. The entrapment efficiency was calculated using the following equation.[11]

$$\text{Entrapment Efficacy (EE\%)} = \frac{(W_{Total} - W_{free}) \times 100}{W_{total}}$$

Drug content

1ml of SLNs was transferred to 10ml volumetric flask and volume was made up with ethanol. and sonicated for 5 minutes. From this solution 1ml was diluted with phosphate buffer pH 7.4 in a 10 ml volumetric to get the concentration in the standard graph range and the drug content was estimated by using UV Spectrophotometry at 260 nm.

In-vitro drug release studies

The in-vitro drug release of Ketoprofen from SLNs formulations were determined using dialysis membrane bag diffusion technique (Hi Media Laboratories Pvt. Ltd.). Which is regenerated with seamless cellulose tubing; membrane is partially permeable and has molecular weight cut off between 12000-14000Da. Pore size is 2.4 nm ideal for filtration and diffusion work, which is soaked overnight in pH 7.4 phosphate buffer. Soaking the membrane in water or buffer overnight allows it to become fully hydrated, achieving its optimal porosity and flexibility. This is essential for proper diffusion of solutes across the membrane, this helps avoid changes in the membrane dimensions during the experiment, which could alter its permeability. Ketoprofen loaded SLNs suspension equivalent to 5mg was taken in dialysis bag and the bag was placed in a beaker containing 200 ml of phosphate buffer pH 7.4 which acted as receptor compartment. The temperature of receptor medium was maintained at 37±0.5˚C withdrawn periodically and after each withdrawal same volume of medium was replaced. The collected samples were analysed using UV spectrophotometer at 260 nm (n=3).[12] and the data was plotted for zero order, first order, Higuchi and Korsmeyer peppas model.[13]

Table 2: Numerical Optimization.

Ketoprofen (mg)	GMS (mg)	Tween 80 (mg)	Span 60 (mg)	Ethanol (ml)	Water (ml)
100	189.90	350	399.99	10	100

The goal of optimization is to find a good set of conditions that will meet all the goals. Numerical optimization will search the design space, using the models created during analysis to find factor settings that meet defined goals. Numerical Optimization will optimize any combination of one or more goals. The goals may apply to either factors or responses. The possible goals are: maximize, minimize, target, within range, none (for responses only) and set to an exact value (factors only). A minimum and a maximum level must be provided for each parameter included in the optimization.

Table 3: Constraints.

Name	Goal	Lower limit	Intermediate limit	Upper limit
A.GMS	Is in range	100	300	500
B. Tween 80	Is in range	50	200	350
C. Span 60	Is in range	0	200	400
Particle Size	Minimize	114	168	228
Entrapment Efficiency	Maximize	55.5	73	92

Surface and Shape analysis by using Transmission Electron Microscopy

The Surface characteristics of prepared nanoparticles was determined via Transmission Electron Microscope after the selection of optimized formulation using DOE. To visualize the nanoparticle suspension, a drop of nanoparticle suspension was mounted on clear glass stub, air dried and Gold coated and subjected to TEM (Icon Labs, Mumbai).

TEM: Transmission Electron Microscope

Make- FEI

Model-Tecnai 12

Country-Netherland

Magnification: Ranges from 20x to 3.5lac x, Resolution :0.5nm, High voltage-120Kv

Source-Tungsten Filament

Software Tecnai Imaging and Analysis.

PREPARATION OF NANOPARTICLE LOADED TRANSDERMAL PATCH:

By Solvent casting method[14]

Ketoprofen nanoparticles loaded Transdermal patch was prepared by solvent casting method using the SLNs (optimised), HPMC K100 M was used as polymer and Polyethylene glycol-400 was used as plasticizer. Required quantity of HPMC K100 M was weighed and dissolved in 10ml of distilled water and stirred with magnetic stirrer until complete swelling. Polyethylene glycol-400 (10% w/w of polymer concentration) was added into polymer solution. The prepared nanoparticle suspension was selected in such a way that 2.25 sq.cm of casting area would have 2.5mg of drug by slowly added into the polymeric mixture and stirred for 1hr. Stirring was continued for complete mixing, later the mixture was poured into round shaped petri plate with area (diameter) of 63.64 square cm. The polymer solution containing drug was carefully spread without any air bubble entrapment by keeping it overnight. The formulation was kept in hot air oven for drying at 40°C. Each patch was cut

by the measurement of 1.5×1.5cm^2 which contains dose equivalent to2.5 mg. The patch was folded into aluminium foil and placed in a desiccator until further study.

Table 4: Formulation chart of nanoparticles loaded Transdermal patch.

SLNs Equivalent to Ketoprofen	HPMC K100 M	Polyethylene glycol- 400 (10% of Polymer)	Distilled water(ml)
60mg	600mg	60mg	10

Evaluation of patch[15,16]

Physical appearance

The patch was physically inspected for colour, clarity, uniformity, flexibility and smoothness.

Determination of thickness of patch: Vernier callipers was used to determine the thickness of randomly selected patches. The patch was measured at different points and the average of three readings was taken.

Folding endurance: Folding endurance of patch was measured manually by folding the patch at one place a number of times till it breaks. This gives a value of folding endurance.

Weight variation: weight variation was studied by individually weighing 3 randomly selected patches. The mean value was calculated.

Drug content: A prepared patch was added to 100ml pH 7.4 Phosphate buffer and stirred vigorously for 2 hours using a magnetic stirrer. Filter, take 1ml in a 10ml volumetric flask and make up the volume with pH 7.4 phosphate buffer and Ketoprofen was estimated spectrophotometrically at wavelength of 260 nm.

***Ex-vivo* permeation studies**

Franz diffusion cell with an effective diffusion area of 2.25 cm^2 was used for the experiment. Porcine ear skin, which was obtained from commercial slaughter house, was cleaned by removing the hair without damaging the epidermis. Subcutaneous fat was removed by dipping the tissue in warm water. The isolated skin with intact epidermis tissue was placed between the donor and receptor compartment of Franz diffusion cell with the stratum corneum facing the donor compartment. SLN, SLN-Patch, Ketoprofen-Patch (Ruplast-20, mfg by -Rusan Pharma Limited and Mkt by-Rusan Healthcare Private Limited) containing ketoprofen equivalent to 2.25 mg was placed on the membrane and release profiles were taken. The receptor chamber was filled with 135ml of diffusion medium (pH 7.4 phosphate

buffer). The receptor medium was maintained at 37±0.5°c and stirred magnetically at 50rpm. Samples were withdrawn at predetermined time intervals and were analysed by UV spectrophotometer. The fresh buffer was immediately replenished into the receptor compartment after each sampling. Using the data obtained from Ex-vivo study skin parameters like flux (J, µg/cm^2/h), cumulative permeation of Ketoprofen across the skin per unit area(µg/cm2), permeability coefficient (Kp, cm/h) was determined. The flux (µg/cm2 .h) of Ketoprofen was calculated from the slope of the plot of the cumulative amount of Ketoprofen permeated per cm^2 of porcine skin at steady state against the time using linear regression analysis. The steady state permeability coefficient (kp) of the drug through porcine, was calculated by using the following equation kp = J/C, where 'J' is the drug flux and 'C' is the initial concentration of Ketoprofen in donor cell.[17]

Stability study[18]

Stability study of Keto-SLNs and Keto-SLN -P were carried out according to the ICH Q1C (International Conference on Harmonization). Keto-SLN was stored at refrigerated temperatures (4^0C) for one month. The formulation was evaluated for physicochemical changes and by measuring particle size, PDI, ZP, and EE after 1 day, 15 days and 30 days of storage. The Keto-SLN-P was stored at room temperature (25 ± 2^0C) and the patch was covered in aluminium foil and stored in a desiccator containing saturated sodium chloride (NaCl) at a temperature of (25 ± 2^0C) for 1month and collected at regular intervals of 1 day, 15 days, and 30 days and evaluated for drug content and %cumulative drug release up to 8 hours.

RESULTS AND DISCUSSION

Pre-formulation Studies

Determination of λ max

Standard solution of Ketoprofen was scanned in UV spectrometer with the wavelength range of 200- 400nm. The absorption maxima was found to be 260nm.

Compatibility studies

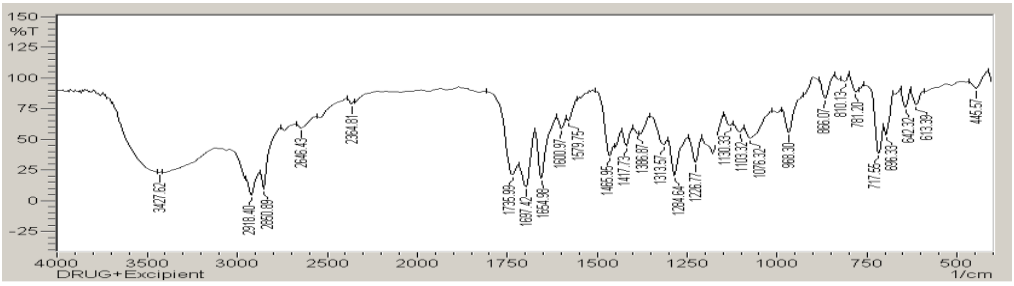


Fig. 1: FTIR Spectra of Ketoprofen.

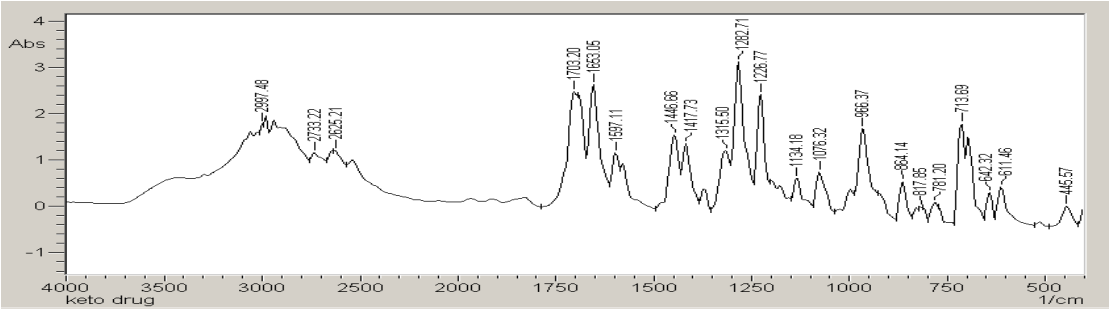


Fig. 2: FTIR Spectra of Ketoprofen + all Excipients.

It was observed that there is no chemical interaction between the drug and the excipients used in the formulations. There were no changes in the main peaks of FTIR spectra of Ketoprofen when drug was mixed with excipients which indicates that the drug was compatible with the formulation components.

Table 5: Evaluated parameters for formulation of Ketoprofen loaded solid lipid nanoparticles as per Face centred CCD design.

Formulation code	Particle size(nm)	PDI	Drug content (%)	Zeta Potential	Entrapment efficacy (%)
F1	123	0.42	97	-23	72
F2	120	0.3	99	-23	74
F3	156	0.2	99	-16	55.5
F4	114	0.2	100	-24	73
F5	134	0.5	99	-23	69
F6	160	0.2	98	-10.4	78
F7	164	0.3	100	-18.2	77
F8	189	0.4	99	-20.8	74.5
F9	179	0.5	99	-30	76
F10	168	0.2	97	-18	75
F11	228	0.4	100	-28	82
F12	192	0.3	98	-25	88.2658
F13	219	0.2	99	-28	83

F14	203	0.2	96	-13.6	84
F15	199	0.3	100	-24	92.0289

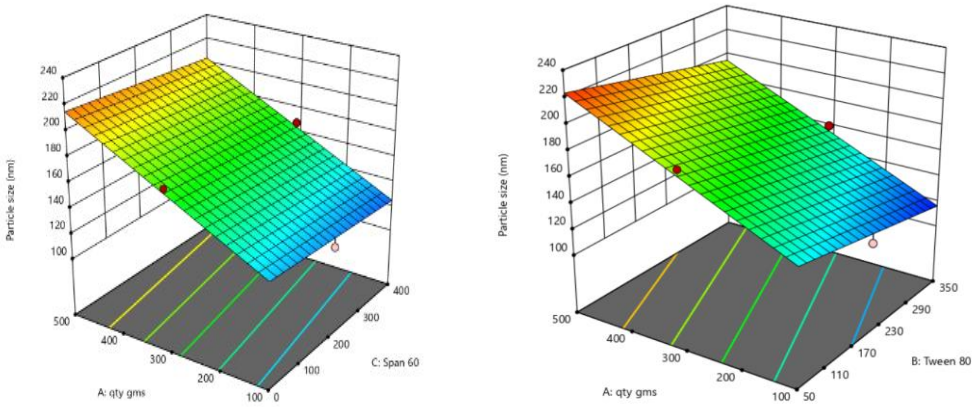


Fig. 3: 3-D graph of Particle Size.

Final Equation in Terms of Coded Factors

Particle size= 169.87+39.40 *A-14.1*B-5.5*C

Where,

A=GMS, B=Tween 80 and c=Span 60

The particle size range for transdermal delivery is 50 to 500 nm.[19]

The particle size of obtained nanoparticles was ranged from 114 to 228nm.

According to the coded factor equation of particle size, GMS positively affects particle size; as its concentration increases, particle size also increases. Increasing Tween 80 and Span 60 concentration decreases particle size.

The amount of lipid has a great effect on particle size, since with small increase in amount of lipid, the particle size increases drastically due its molecular weight and structure.

Lipids with higher melting point shows higher particle size. Here the melting point of GMS is (68^0C),[20] High melting point results in increase in viscosity and leads to an inefficient homogenization which cause an inefficient reduction of particle size.[21] When the concentration of lipid exceeds with fixed amount of surfactants, there is insufficient surfactant available to coat the surface of all the lipid droplets, resulting in particle aggregation and increase in particle size.[18]

Surfactant reduce particle size. on increase in concentration of surfactant particle size reduces because it lowers the interfacial tension between the aqueous and lipid phase and stabilize newly formed surfaces during processes like homogenization and also prevent aggregation of particles.[22]

Zeta potential

The zeta potential of obtained nanoparticles was ranged from -10.4mv to -30mv.

According to the DLVO theory, a system is regarded as stable if the electrostatic repulsion dominates the attractive van der Waals forces. Particles must overcome an energy barrier due to electrostatic repulsion to come together and form agglomerates. If their velocity or kinetic energy is sufficiently high, they will collide. Increased temperatures and light raise the system's kinetic energy, while a lower zeta potential promotes aggregation of solid lipid nanoparticles (SLNs).

A zeta potential value in the range of -30 mV to +30 mV is generally considered as the standard value in which particles shows the sufficient repulsive force to attain better physical colloidal stability.[23]

Entrapment Efficiency

The results showed that the entrapment efficiency of the Ketoprofen loaded solid lipid nanoparticles ranged from 55.5% to 92.02%.

The Predicted R^2 of 0.7110 is in reasonable agreement with the Adjusted R^2 of 0.8343; i.e. the difference is less than 0.2.

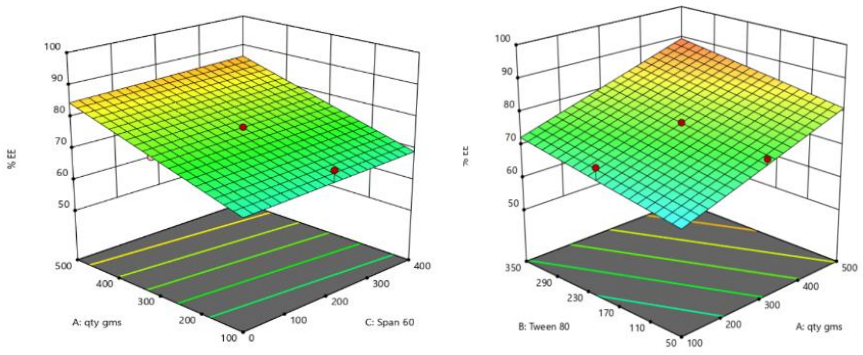


Fig. 4: 3-D graph of Entrapment efficiency.

Final Equation in Terms of Coded Factors

$$\%EE=76.89 + 8.58*A + 4.13*B + 0.8737* C$$

According to equation as GMS increases EE increases, Tween80 and Span60 also shows positive effect on EE but compare to Tween 80, Span 60 shows less effect.

The entrapment efficiency increased with lipid content. The possible reason is lipid content can afford more space to encapsulate drug. Moreover, the entrapment efficiency was affected by the concentration of surfactant in outer phase. Entrapment efficiency increase with increase in lipids.[24]

The EE was found to increase with increasing concentration of surfactant. HLB value of surfactant effect entrapment efficiency ,if it has higher HLB value entrapment will be more and vice versa ,in this study Tween 80 has higher HLB value than Span 60.Surfactant with HLB value >15 gives more EE.[25]

Drug Content of SLNs

Drug content of SLNs from F1 to F15 was found to be 97 to 100%. Formulation with Tween 80 gives more drug content due to its high HLB 15 value.

***In-vitro* Drug release study (F1-F15)**

Table 6: In-vitro Drug release profile of F1 to F5 formulations.

Time (hrs)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	43.51±0.49	59.98±0.09	67.89±0.02	31.55±0.09	38.42±0.02
2	66.90±0.12	73.53±0.27	88.84±0.17	40.76±0.09	52.56±o.10
3	71.69±0.13	81.26±0.23	93.34±0.10	55.42±0.04	59.74±0.16
4	79.03±0.12	88.31±0.14	108.31±0.12	60.14±0.04	64.81±0.03
5	81.56±0.24	89.49±0.12	90.53±0.03	63.94±0.04	69.09±0.08
6	91.54±0.83	94.12±0.21	90.39±0.05	92.06±0.01	96.11±0.10

Table 7: In-vitro Drug release profile of F6 to F10 formulations.

Time (hrs)	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	46.66±0.08	38.86±0.05	51.48±0.11	57.51±0.15	52.34±0.19
2	56.21±0.03	47.58±0.06	73.89±0.10	66.65±0.13	56.71±0.06
3	67.18±0.02	195.25±0.07	86.08±0.07	70.77±0.21	61.24±0.22
4	72.56±0.10	74.17±0.05	90.56±0.09	77.49±0.12	72.57±0.13
5	77.76±0.11	88.12±0.10	65.13±0.13	82.55±0.09	78.74±0.22
6	92.25±0.25	98.50±0.04	63.86±0.6	94.11±0.12	90.24±0.27

Table 8: In-vitro Drug release profile of F11 to F15 formulations.

Time (hrs)	F11	F12	F13	F14	F15
0	0	0	0	0	0
1	44.36±0.19	54.63±0.38	55.60±0.40	55.33±0.20	56.92±0.11
2	57.55±0.29	64.22±0.26	61.81±0.23	62.54±0.24	65.96±0.11
3	67.15±0.09	73.52±0.41	66.72±0.33	69.52±0.24	76.22±0.18
4	70.37±0.09	79.58±0.41	75.01±0.20	80±0.12	83.63±0.13
5	78.11±0.11	85.53±0.42	83.60±0.33	90.98±0.10	88.30±0.14
6	91.22±0.10	92.31±0.48	90.77±0.35	65.20±0.18	95.89±10

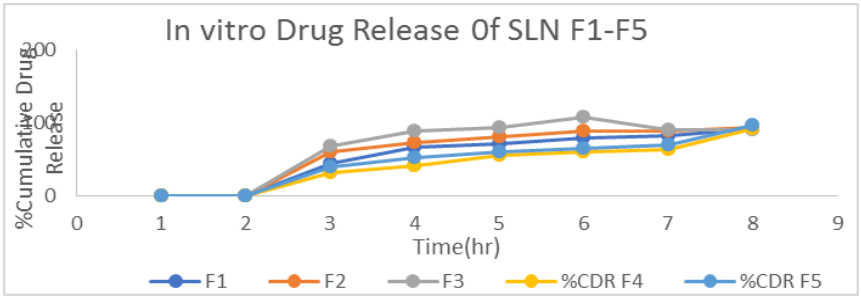


Fig. 5: In vitro drug release of SLN F1-F5.

Here lipid 100mg is constant and surfactants were varied from lowest to highest

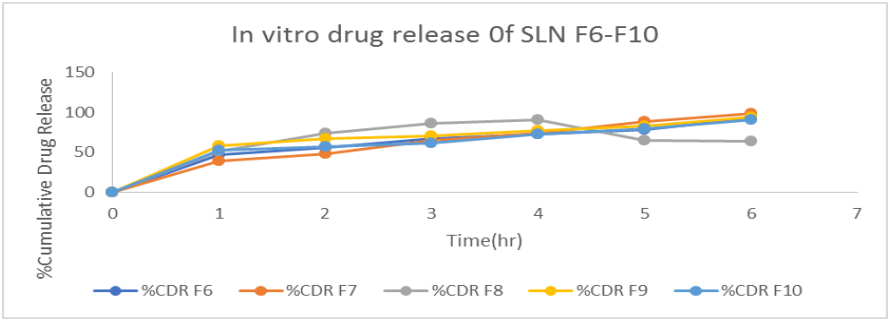


Fig. 6: In vitro drug Release of SLN F6-F10.

Here lipid 300mg is constant and surfactants were varied from lowest to highest.

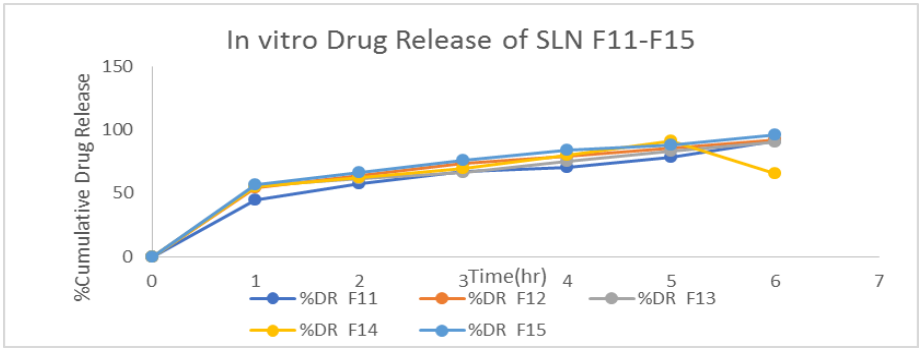


Fig. 7: In vitro Drug Release 0f SLN F11-F15.

Here lipid 500mg is constant and surfactants were varied from lowest to highest.

Increase in concentration of surfactant increase the %DR with higher HLB value of surfactant and in some cases %DR decreases due to higher melting point of lipid).

By increasing the concentration of lipid result in corresponding decrease in the drug release. In another words, as the lipid concentration in SLN preparation was increased, the thickness of the lipid coating increased thereby increasing the length of diffusion resulting in decrease in drug release.[26]

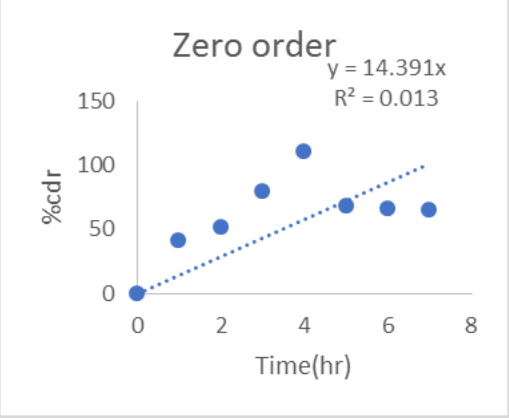
Optimized Formulation

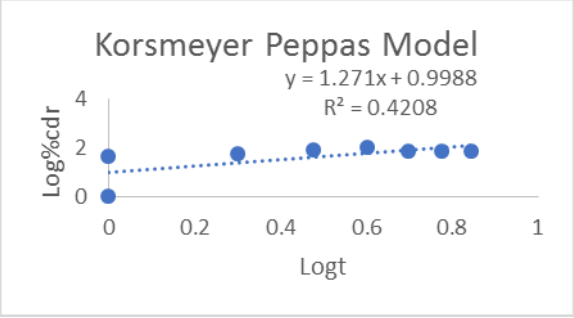
Table 9: Evaluation of optimized formulation.

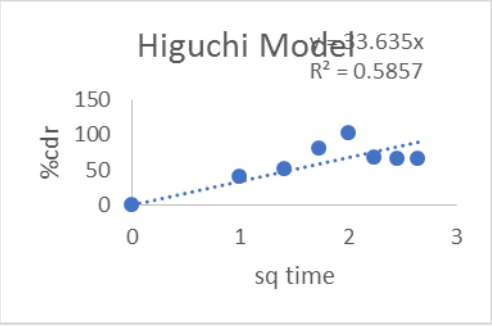
Optimised	Particle size nm	PDI	Zeta Potential mv	%EE	In-vitro drug Release at 4th hour (%)
1	129	0.33mv	-25.2	83.19±0.35	106.4±0.4

Table 10: kinetics of optimized formulation.

Formulation code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer Peppas n-value	Mechanism Of Drug Release
F Optimised	0.8062	0.8202	0.9235	1.271	Non Fickian diffusion







The values for the release rate constant (K_0 and K_1), the correlation coefficients (R^2) were calculated using different equations. The correlation coefficients (R^2) were used as an indication of the best fit models, for each of the model considered. Based on correlation coefficient (R^2), the best fitted model was determined and formulation Fopt followed First order model. The result was shown in table no.5.5. For the best formulation Fopt, the model that fits the data was first order model (R2=0.8202) n value for Korsmeyer-Peppas equation was found to be 1.27 and mechanism of drug release follows non-Fickian diffusion.

Table 11: Comparison of DOE predictions of optimum formulation evaluation versus actual results.

	%Entrapment Efficiency	Particle Size (nm)
DOE Prediction	77.14	128.4
Actual Results	83.19	129

Transmission Electron Microscopy of Optimised Formulation

The morphology of the samples was investigated using TEM. In figure.11, We observed spherical particles with a smooth surface with a very low grade of aggregation or clustering and size ranging from 86 to 120nm Size was analysed using **image J software** and the particle size was found to116nm that was almost near to the size detected **by Haribo Particle size analyser 129nm.**

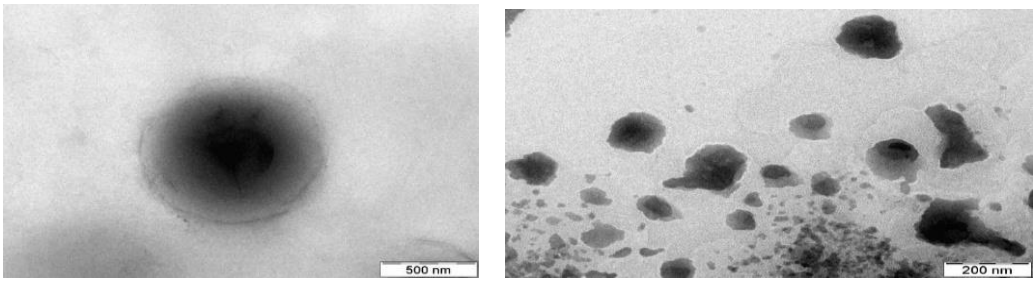


Fig. 8: TEM image of SLNs.

Table 12: Evaluation of Ketoprofen-SLN-P.

Formulation	Thickness (mm±sd n=3)	Folding endurance	Weight Variation (mg ± sd n=3)	Drug Content (%)
P opt	0.16±0.04	More than 200 times	34.5±0.02	99.66

Thickness

The thickness of the patch was found to be 0.16 ±0.04mm as shown in the table above

Folding Endurance

The folding endurance of the patch was found to be more than 200 foldings shown in table 12 indicating that the patch did not break easily and maintained its integrity with general skin folding when applied and it had the ability to withstand rapture.

Weight uniformity

The patch was subjected to mass variation by individually weighing dried square patch Of side 1.5 cm. The weight variation was found to be 34.5±0.02mg shown in table 12.

Drug Content

The drug content was found to be 99.66% shown in table 17. The thickness and weight of the patch depends on the concentration of polymer used in the formulation. An excessive increase in the concentration of the polymer could lead to an increase in weight and thickness of the patch.

The % drug release will largely depend on the concentration and type of polymer used hence; the concentration of polymer used must be carefully considered when formulating the patch.[27]

Ex-vivo permeation study

Table 13: The steady state flux and permeability coefficient.

Formulation	Fss(µg/cm2 /h)	Kp(cm/h)
SLNs suspension	13.48	5.39
SLNs loaded patch	14.33	5.73
MKT patch	13.33	5.33

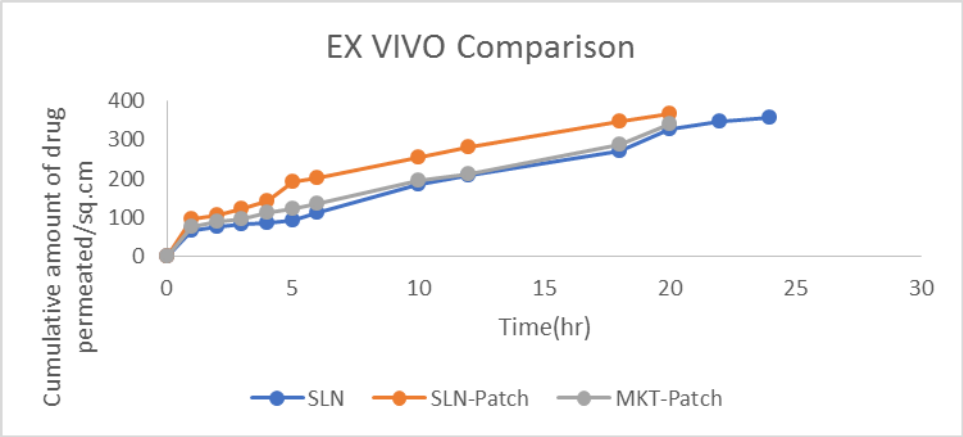


Fig. 9: Graph showing Ex vivo comparison study of SLNs, SLN Patch and Mkt Patch through porcine tissue.

Ex-vivo permeation studies were performed using Franz diffusion cell coupled with Pig ear skin as a permeation membrane. Phosphate buffer pH7.4 was used as a permeation medium. Pure drug-based transdermal patches showed less permeation through the skin than SLN patch (Figure 5.18) The steady state flux of SLNs, SLN-Patch and Keto-Patch was found to be 13.48,14.33 and 13.33µg/cm2 /h respectively and permeability coefficient SLNs, SLN-Patch and Keto-Patch was found be5.39, 5.73 and 5.33 respectively as shown in(Table 13). It has been reported that HPMC was used as a polymer to prepare the transdermal patch. As HPMC is highly hydrophilic, therefore lipophilic SLN is not soluble, and structure of nanoparticles remain intact. PEG400 was used as a plasticizer, as It helps to soften the polymer matrix by diffusing. It reduces the inter actions between the polymer molecules like hydrogen bonding and also forms a bond with polymer molecules that helps in the patch formation. The effect of particle size on permeation was also analysed. The results showed that permeation increases with decrease particle size, i.e. the smaller the particle size, the higher the surface of particles, and more intimate their contact with corneocytes, thus a greater the penetration of the drug through stratum corneum. When the effect of surfactant on permeation was analysed, it was observed that there was an increase in permeation of drug through the skin with an increase in surfactant to lipid ratio. Likely, the surfactant helps to loosen the lipid bilayers of the stratum corneum, thus enhancing drug penetration.[28]

Table 14: Stability study of optimized SLNs formulation at Refrigerated condition.

Optimized Keto-SLN formulation	Size (nm)	PDI	ZP (mV)	%EE
Initial	129	0.3	-25.2	83.19
15 days	129	0.3	-25.2	83.19
30 days	131	0.33	-24	82.6

Table 15: Stability study for optimized Keto-SLN-P at room temperature.

Optimized Patch	Drug content (%)	Weight Variation (mg±sd)	%Cumulative drug release
Initial	99.66	34±0.02	98.19 ± 0.43
15 days	99.52	34±0.01	98 ± 0.23
30 days	99	33.6±0.04	97.61± 0.53

The values for entrapment efficiency (EE), particle size (PS), polydispersity index (PDI), and zeta potential (ZP) showed minimal variation, indicating high stability even under Refrigirated conditions. No significant changes were observed at room temperature for SLN Patch. Drug content, weight variation and %Cumulative drug release was not significantly

changed, it remained within acceptable limits. These findings suggest that the formulation exhibited no susceptibility to stability-related issues during storage.

CONCLUSION

Transdermal patch of Ketoprofen nanoparticles were developed to overcome the side effects of oral dose of Ketoprofen like effects such as digestive bleeding, intestinal burning and ulcerations.

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