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Formulation and Evaluation of Solid Lipid Nanoparticle (SLN) Based Topical Gel of Etoricoxib

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ABSTRACT

The objective of present investigation was to prepare & evaluate solid lipid nanoparticle (SLN) based topical gel of non- steroidal anti-inflammatory drug (NSAID) etoricoxib for the treatment of arthritis which would attenuate the gastrointestinal related toxicities associated with oral administration. SLN were formulated by melt emulsification and solidification at low temperature method using stearic acid & tween 80. All the formulation were subjected to particle size, particle size distribution, zeta potential, scanning electron microscopy, crystallinity study by DSC and in-vitro release studies. It has been observed that, the high lipid concentration containing formulation have higher entrapment as compare to other two formulation. The SLN- dispersion shows 70.766% entrapment & zeta potential of the formulation were -25.6 which indicates the stability of formulation. The *In Vitro* drug release rate of gel was evaluated using Modified franz diffusion cell containing dialysis membrane with phosphate buffer pH 7.4 as the receptor medium. The in-vitro release was carried out in comparison with a carbopol gel & hydroxypropylmethylcellulose (HPMC) gel. The permeability parameters steady-state flux (Jss) was significantly increased in SLN-F3C (carbopol) formulation as compared with SLN-F3HPMC (hydroxypropyl methylcellulose) formulation. It was concluded that the Etoricoxib loaded SLN based gel formulation containing carbopol was suitable for topical application and shows much better result of anti-inflammatory activity.

INTRODUCTION

Etoricoxib is a COX-2 selective inhibitor which selectively inhibits isoform 2 of the enzyme cyclooxygenase (COX-2) which reduces the generation of prostaglandins (PGs) from arachidonic acid (Takemoto *et al.*, 2008). It is a potent analgesic, antipyretic and anti-inflammatory agent has been approved for significantly reduces joint inflammation, pain intensity and the duration of morning stiffness and improved handgrip strength (Gonzalez *et al.*, 1994). An arthritic condition demands a controlled release drug delivery system for a prolong period so that can satisfy the goals of the treatment like reduction of the pain and inflammation, slowing the disease progression and prevention of adverse reaction. The requirement for designing of a topical drug delivery system of etoricoxib, which could not only increase the presence of the drug locally and for a prolonged period but also reduce the risk of systemic toxicity (Lee *et al.*, 2005). Colloidal particles ranging in size between 10 and 1000 nm are known as nanoparticles. They are manufactured from synthetic/natural polymers and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size (Westesen *et al.*, 2000; Mukherjee *et al.*, 2009).

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Solid lipid nanoparticles (SLN) introduced in 1991 represent an alternative carrier system to tradition colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid, dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals (Ekambaram *et al.,* 2012).

MATERIALS AND METHODS

Etoricoxib was received as a gift sample from Unison Pharmaceuticals, Baddi, INDIA, Carbopol 934, HPMC were kindly provided by Guapha Pharmaceuticals, M.P., INDIA, Stearic acid, Isopropyl Myristate, Tween 80 & Glycerol were purchased from Fizmerk Chemicals, U.P., INDIA, Dialysis membrane was purchased from Hi Media Laboratories Pvt. Ltd., Mumbai. All the reagents and solvents were of analytical reagent (AR) grade.

Preparation of Etoricoxib loaded SLN dispersion

SLNs loaded with Etoricoxib were prepared using melt emulsification and low-temperature Solidification method**.** Etoricoxib was dissolved in methanol and mixed with acetone solution containing stearic acid. The mixtures were sonicated for 15 minute, and then added drop wise to Tween 80 solution, stirred at 3000 rpm for 0.5 h at 70 °C temperature. The mixed solution was transferred to icy water bath and stirring for four hour at 3000 rpm. Different formulations of drug loaded SLN were prepared by varying concentrations of stearic acid as shown in the below [Table 1] and these SLN dispersions used for further study (Dongfei *et al.,* 2010; Jain *et al.,* 2009).

Table 1: Composition of different SLN dispersion.

Formulation code	Amount of drug (mg)	Amount of Stearic Acid (mg)	Amount of Tween 80 (%)
Blank SLN	----	1000	2.5
SLN-F1	100	1000	2.5
SLN-F2	100	1250	2.5
SLN-F3	100	1500	2.5
SLN-F4	100	1000	2.0
SLN-F5	100	1250	2.0
SLN-F6	100	1500	2.0

Characterization of Etoricoxib Loaded SLN Dispersion

The SLNs characterization parameter like Particle size and size distribution, zeta potential, drug entrapment efficiency (EE), scanning electron microscopy (SEM), FTIR, differential scanning calorimeter analysis (DSC) are described below:

Particle size, Particle size Distribution & Zeta potential

The mean particle size and polydispersity index of SLN for size distribution was measured using Malvern Mastersizer 2000MU (Malvern instrument UK). The obtained data were evaluated using the volume distribution ($d_{10\%}$, $d_{50\%}$, $d_{90\%}$). The PI was measured by the span which can be calculated from the following equation.

$$SPAN = \frac{D90\% - D10\%}{D50\%}$$

Where $d_{90\%}$ is the particle diameter at 90% cumulative size, $d_{10\%}$ is the particle diameter at 10% cumulative size, and $d_{50\%}$ is the particle diameter at 50% cumulative size (Teeranachaideekul *et al.,* 2007; Sanad *et al.,* 2010; Patel *et al.,* 2012). Zeta potential of SLNs was measured by using Zetasizer 2000 (Malvern Instruments, UK) at 25 °C.

Drug entrapment efficiency

The entrapment efficiency (EE), which corresponds to the percentage of Etoricoxib encapsulated within and adsorbed on to the nanoparticles, was determined by measuring the concentration of free Etoricoxib in the dispersion medium A volume of 2.0 ml of each drug-loaded sample was centrifuged at 5300 rpm for 70 min to separate the lipid and aqueous phase. The supernatant was then diluted with methanol and analyzed by UV-VIS spectrophotometer at 233 nm using a Model- 1371, Electronics India. The entrapment efficacy of nanoparticle was calculated as follows:

$$EE = \left(\frac{Wa - Ws}{Wa}\right) \times 100$$

Where EE is entrapment efficiency, Wa stands for the mass of Etoricoxib added to the formulation and Ws is the analyzed weight of drug in supernatant (Doktorovova *et al.,* 2010).

Scanning Electron Microscopy

The morphological characteristic of SLN was determined by scanning electron microscope (JEOL-JSM-6360 JAPAN). One drop of sample was placed on a slide and excess water was left to dry at room temperature. then the slide was attached to the specimen holder using a double coated adhesive tape and gold coated under vacuum using a sputter coater (Model JFC-1100, Jeol, JAPAN)for 10 minute and investigated at 20kV (Nasr *et al.,* 2008).

Infrared spectroscopy (FTIR)

Physicochemical characterization was performed using Fourier transform infrared (FTIR) spectroscopy. For this purpose, sample were analysed as KBr pellets by using a FTIR spectrometer (Shimadzu Corporation, Japan).

Differential Scanning Calorimeter Analysis (DSC)

The sample were analysed by using differential scanning calorimeter (Model- Perkin Elmer DSC) as a constant scanning

speed of 10^0 c min^{-1} from 20-220 °C. The 5-7mg sample was heated in aluminum pans using dry nitrogen as the effluent gas. (Bhaskar *et al.*, 2009).

Formulation of Etoricoxib Loaded SLN Based Gel

SLN gel was prepared in following manner, required quantity of carbopol 934 and hydroxypropylmethyl cellulose (HPMC) were weighed and dispersed in small quantity of distilled water to prepare aqueous dispersion, and the dispersion was allowed to hydrate for 4 to 5 hour. Glycerol (10% w/w) was added subsequently to the aqueous dispersion equivalent to 1% of Etoricoxib was incorporated in it. Triethanolamine was added to the above dispersion using an overhead stirrer at speed of 1200 rpm (Singhla Scientific Industries). Stirring was continued till the carbopol get dispersed. The gel was allowed to stand overnight to remove entrapped air (Lala *et al.*, 2014; Bhalekar *et al.*, 2009; Joshi *et al.*, 2008; Sanad *et al.*, 2010).

Table 2: Composition of SLN Gel formulation.

S. No.	Composition In % W/W	FORMULATION CODE SLN-Gel Carbopol (C)	FORMULATION CODE SLN-Gel Hydroxypropyl methyl Cellulose (HPMC)
1	Carbopol934/HPMC	1	1
2	SLN eq to 1% of Etoricoxib	1	1
3	Glycerin	10	10
4	Triethanolamine	q.s.	q.s.
5	Distilled water	q.s.	q.s.

EVALUATION OF ETORICOXIB LOADED SLN GEL

Physical appearance & Homogeneity

Physical appearance and homogenecity of gel was observed visually.

Spreadibility study of SLN gel

The spreadibility of the gel formulations was determined using an apparatus modified in the laboratory. The apparatus was made with two glass plate and glass plate having a pan mounted on pulley.Excess amount of gel was placed between glass slide (10 x 10 cm^2). A weight of 100g was placed on the upper glass plate for 5 min to compress the formulation . The100g weight tied was added on the pan. The time in seconds required to separate the slides was taken as the measure of spreadability . The spreadibility was calculated by using the following formula.

$$S = M \times \frac{L}{t}$$

Where S is spreadibility, M is weight tied on upper slide. L is the length of glass slide, t is time taken (Biswal *et al.*, 2014).

***In-vitro* drug release studies of SLN Based gel**

The *In Vitro* release studies were performed using modified franz diffusion cell to evaluate the amount of Etoricoxib released from each formulation. Franz glass structure is represented in given Fig.1. These cells consist of donor compartment, acceptor compartment, Dialysis membrane 70, magnetic stirring, thermostatic water bath and sampling device.

Fig. 1: Modified Franz Diffusion Cell.

Dialysis membrane 70 (Hi-Media, Mumbai, India) having pore size 2.4 nm, molecular weight cut-off between 12,000-14,000 was used and mounted on the Franz diffusion cells. The surface area of the release membrane was 3.14 cm^2. The receptor medium was approximately 45 ml and composed of phosphate buffer saline (PBS), pH 7.4, and stirred by magnetic bar at 700 rpm to avoid different concentrations within the acceptor medium and to minimize stagnant layers. SLN Based gels (equivalent to 1 mg of drug) were placed in the donor compartment. During the experiments, the solution in receptor side was maintained at 37 °C ± 0.5 °C.

After certain time interval, 3-mL of the sample medium were withdrawn from receiver compartment through side tube and same volumes of freshly prepared receptor medium were added. The samples were analyzed by UV-VISIBLE spectrophotometer at 233nm. For each formulation, the release studies were performed in triplicate (Mazumder *et al.*, 2009; Sachan *et al.*, 2009).

Permeation Data Analysis

The permeation profiles were constructed by plotting the cumulative amount of etoricoxib permeated per unit dialysis membrane area (µg/cm2) versus time. The steady state flux (Jss, µg/cm2/hr) (Edwards *et al.*, 1994) of etoricoxib was calculated from the slope of the plot using linear regression analysis.

Release Kinetics

Data obtained from *In Vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from the SLN the dissolved amount of drug (M) is a function of the time (t), or M=f(t). In order to analyze the drug release mechanism, the ata is fitted in zero order, first order, Higuchi model.

RESULT & DISCUSSION

Particle size, Particle size distribution & Zeta potential

The d_{90} for SLN F1, F2, F3, F4, F5, F6 and Blank SLN determined using Malvern Mastersizer showed size 1527, 2241, 334, 7232, 1286, 4264 and 16729 nanometer respectively. The particle sizes of formulations were increases as the concentration of tween 80 decreases as shown in table 3.

The zeta potential of the SLN dispersion is given in the table 3. Zeta potential of blank SLN was -27.2 while for SLN-F3 & SLN-F6 dispersion it was -25.6 & -21.5. The presence of drug causes a diminution of surface charge of all the investigated samples because probably a share of drug is situated on the lipid nanoparticles surface.

Drug entrapment efficiency

From the results given in table 3, it has been observed that, the high lipid concentration containing formulation SLN-F3 have higher entrapment as compare to other formulations. The SLN-F3 dispersion has 70.766% entrapment, while SLN-F1 & SLN-F2 have 61.583% & 67.366% respectively. Same as seen in SLN-F6 as compare to SLN-F4 & SLN-F5.

Table 3: Particle size distribution, zeta potential & entrapment efficiency of different formulations of SLN.

Formulation code	Mean volume distribution			Span	Zeta potential of SLN Dispersion (mV)	Percentage Entrapment efficiency*
	$d_{10\%}$	$d_{50\%}$	$d_{90\%}$			
SLN-F1	0.127	0.175	1.527	7.983	-22.9	61.583±0.897
SLN-F2	0.126	0.171	2.241	0.673	-24.1	67.366±1.934
SLN-F3	0.126	0.171	0.334	0.633	-25.6	70.766±1.450
SLN-F4	0.248	0.328	7.232	21.292	-20.2	59.542±0.824
SLN-F5	0.124	0.202	1.286	5.752	-20.8	65.322±1.947
SLN-F6	0.126	0.324	4.264	12.771	-21.5	68.732±1.440
B-SLN (Blank)	0.132	0.202	16.729	82.105	-27.2	……..

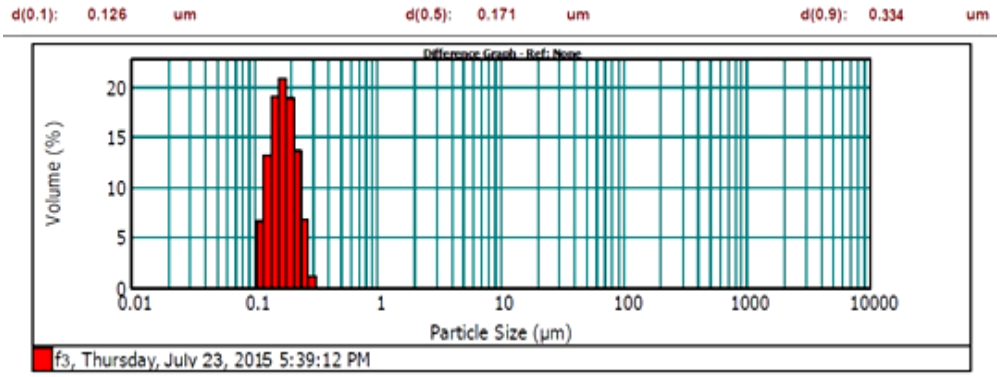


Fig. 2: Particle size distribution graph of SLN-F3.

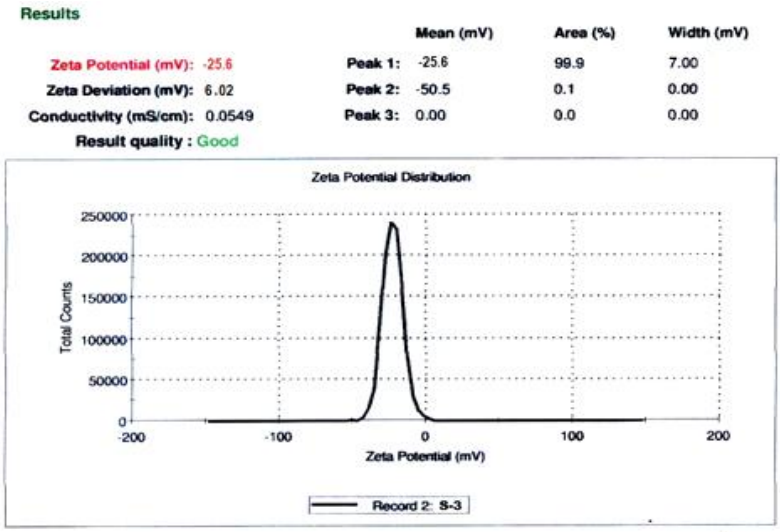


Fig. 3: Zeta potential of SLN-F3 Dispersion.

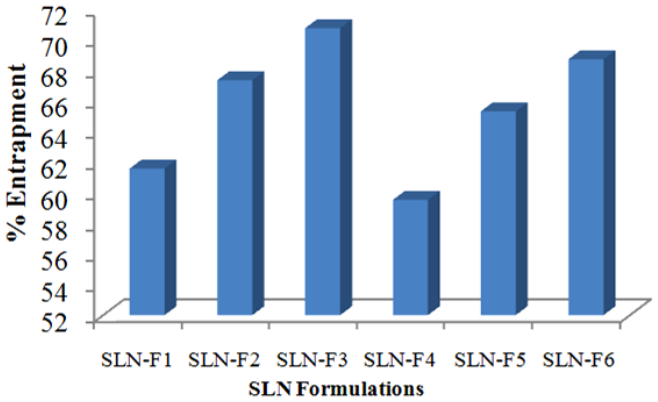


Fig. 4: Percentage of drug Entrapment plot.

Scanning Electron Microscopy

SEM was used to obtain more information about particle size and shape of SLN dispersion. Further no sign of drug precipitation was observed inferring the stable nature of formed dispersion. The size of particle observed in micrograph is in agreement with data obtained by Malvern Mastersizer (Teeranachaideekul *et al.*, 2007).

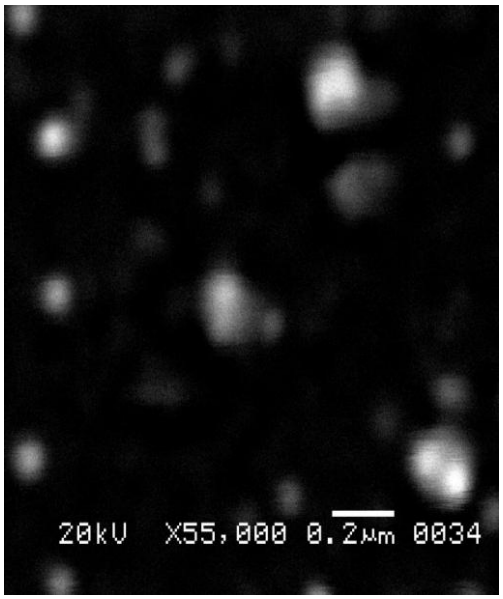


Fig. 5: SEM of SLN-F3 Dispersion at 55000X.

FTIR Analysis

The IR spectra of pure drug etoricoxib, SA+ Drug, Drug loaded SLN, are shown in Figure 3.18, 3.19, 3.20, 3.21 and 3.22 respectively. This result indicates that there is no chemical interaction between the SA and etoricoxib.

However, in the IR spectrum of etoricoxib loaded SLN (Fig. 6) peaks corresponding to etoricoxib disappear or buried in the peak of stearic acid indicating drug entrapment in lipid matrix as shown in (Fig. 8). The Etoricoxib due to high melting point have precipitated as core and the stearic acid may have formed the coating around the drug core as suggested from the above data. (Nasr *et al.*, 2008).

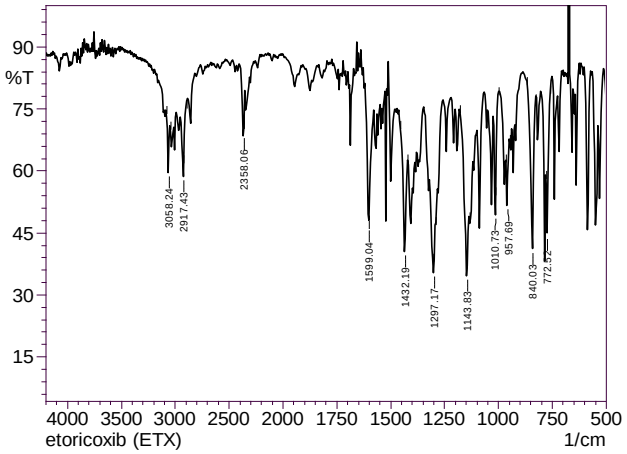


Fig. 6: IR spectrum of Etoricoxib.

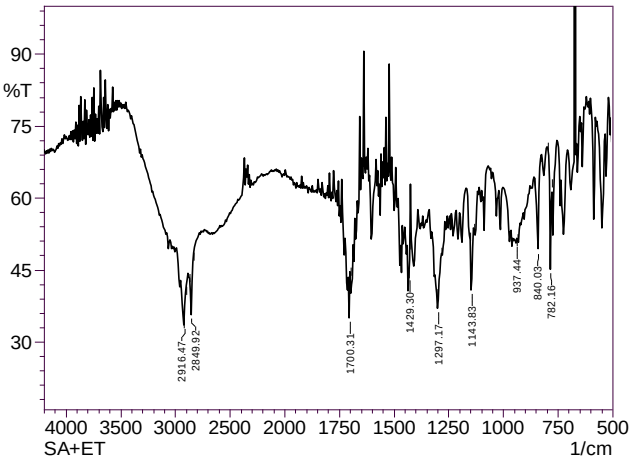


Fig. 7: IR spectrum of Stearic acid + Drug

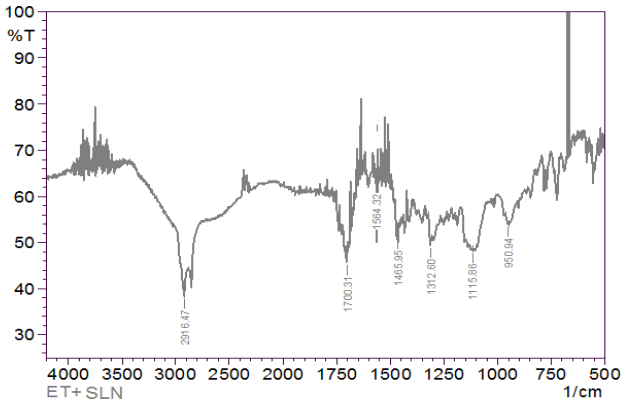


Fig. 8: IR spectrum of Drug loaded SLN.

Differential Scanning Calorimeter Analysis (DSC)

DSC is considered as a tool to investigate the melting behavior of crystalline materials like solid lipid nanoparticles. Blended matrix of lipid shows a melting point depression as compared to solid lipid. e.g. melting point of stearic acid was 67.81 °C but mixture of stearic acid and etoricoxib showed a melting point depression 66.78 °C (Table 4). Formulation SLN-F3 was chosen as a representative of etoricoxib SLN as it possessed

the highest entrapment efficiency. DSC thermogram of etoricoxib showed endothermic peak at 136.12 °C as evident in (Fig. 9), which is the reported melting point of the drug. Drug loaded SLN showed a large endothermic peak at 59.78 °C (Fig. 10) and disappearance of the drug peak suggesting a molecular dispersion (lees amount of drug solubilize in lipid) of etoricoxib into the loaded SLN and that etoricoxib exists in amorphous state (Liquid state) rather than in crystalline state. (Nasr *et al.*, 2008; Agrawal *et al.*, 2010; Jia *et al.*, 2010; Hou *et al.*, 2003).

Table 4: DSC parameters of excipient and SLN dispersion.

Sample	Onset (°C)	Melting point (°C)
Etoricoxib	133.20	136.12
Stearic acid	54.65	67.81
SA+ Etori	57.24	66.78
DSLN	50.00	59.78

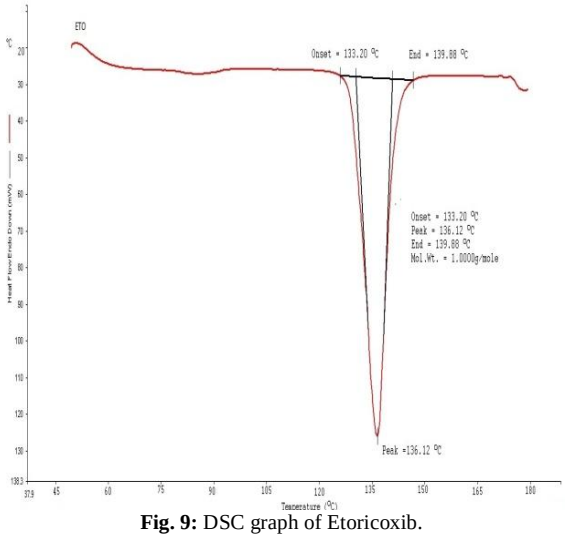


Fig. 9: DSC graph of Etoricoxib.

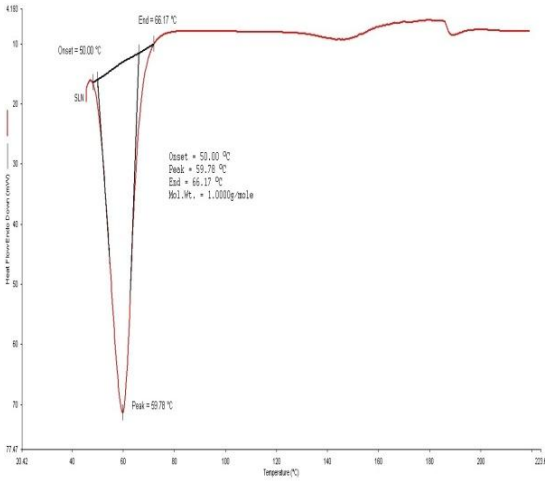


Fig. 10: DSC graph of Drug loaded SLN.

Preparation & Evaluation of Etoricoxib Loaded SLN based Gel

Based on the particle size, entrapment efficiency, SLN-F3 formulation having optimum physicochemical properties was selected for gel. SLN dispersion was incorporated into the gel**.** The physical appearance of drug loaded SLN gel was found to be off-white in color, smooth in texture and translucent. All the formulation was found to be homogenous**.** All the formulated gel was evaluated for spreading diameter at 1 min, as a measure of stiffness. The result showed that spreadibility coefficient of Carbopol SLN gel was somewhat equal to Hydroxypropylmethyl cellulose (HPMC) SLN gel.

Table 5: Spreadibility of SLN-F3C gel & SLN-F3 HPMC gel.

S. No.	Spreadibility* (g.cm/sec)	Formulation Code
1	206.947 ± 14.520	SLN-F3 C
2	209.841 ± 10.003	SLN-F3 HPMC

*Mean ± S.D.

In Vitro Release Study of SLN Gel

In Vitro studies were performed to compare the release rate of the drug from the SLN gel formulation using carbopol and SLN gel using hydroxypropylmethylcellulose (HPMC), which was code named as SLN-F3C & SLN-F3HPMC. The cumulative percentage release of etoricoxib from SLN based Gel were investigated for a period of 24 hours. Each sample was analyzed in triplicate.

Table 6: Drug release profile of SLN-F3C and SLN-F3HPMC.

S.No.	Time (hr)	% Release of drug from SLN gel *	
		SLN-F3HPMC	SLN-F3C
1	0.25	14.469±11.025	6.900±0.289
2	0.50	17.322±2.018	9.987±3.044
3	1.00	19.379±0.880	14.239±3.096
4	2.00	21.088±1.683	28.242±3.915
5	3.00	26.769±2.981	37.771±2.711
6	4.00	30.718.±3.034	41.356.±1.166
7	5.0	35.000±1.691	44.835±0.893
8	6.0	40.972±3.295	48.234±0.768
9	8.00	41.101±30.532	56.829±4.064
10	12.0	53.459±3.547	65.868±1.626
11	24.0	74.956±5.294	82.791±3.696

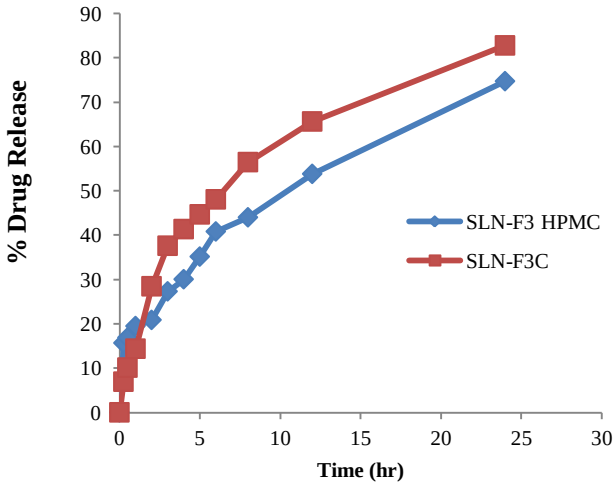


Fig. 11: Comparative drug release profile of SLN-F3C and SLN-F3HPMC.

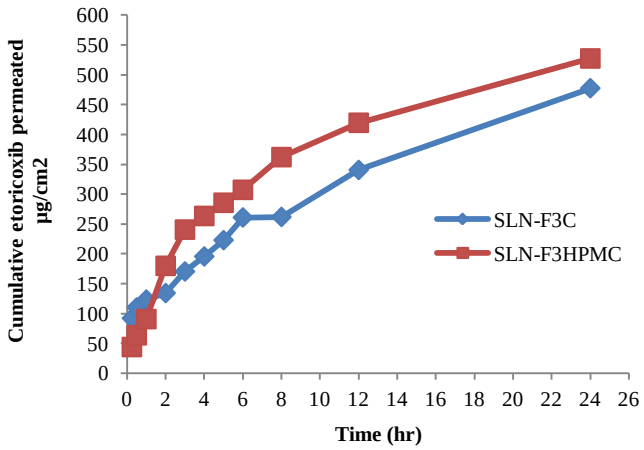


Fig. 12: Comparative drug permeation profile of SLN-F3C &SLN-F3HPMC.

PERMEATION DATA ANALYSIS

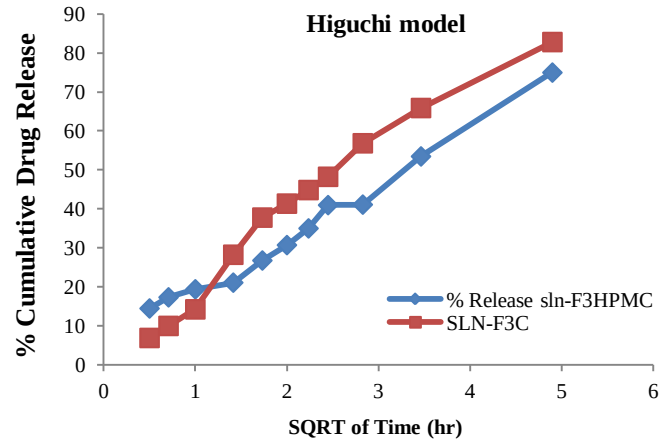
Permeability parameters steady-state flux (J_{ss}) was significantly increased in SLN-F3C formulation as compared with SLN-F3HPMC formulation. This is because SLN-F3C contains carbopol and HPMC is gummy in nature as compare to carbopol. The permeability parameters of both formulations are given in Table 7

Table 7: permeation data of SLN-F3C and SLN-F3HPMC.

Formulation code	Jss± S.D. (µg/cm2/hr)
SLN-F3HPMC	19.892±1.934
SLN-F3C	21.968±0.862

RELEASE ORDER KINETICS STUDY

Data obtained from *In Vitro* release studies were fitted to various kinetic equations to find out the mechanism of drug release from the gel formulation. The kinetic models used were zero order equation, first order equation, Higuchi model. From the release kinetics table it can be observed that the release of etoricoxib from the SLN- SLN-F3C exhibit Anomalous (non-Fickian) diffusion, and closely follows Korsmeyer-Peppas Model and also highly correlated with Higuchi Model. Whereas the release of Etoricoxib from the SLN-F3 HPMC exhibit Higuchi Model and closely follows Korsmeyer-Peppas Model.



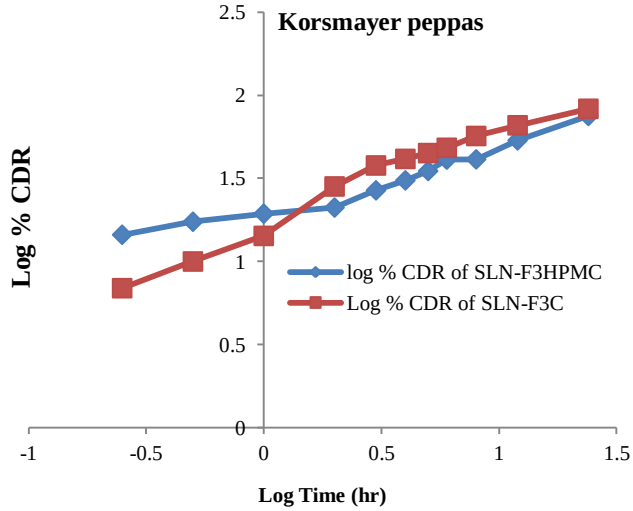


Fig. 13 & 14: Comparative Higuchi & Korsmeyer-pepas plot SLN-F3C and SLN- F3HPMC.

CONCLUSION

The Solid lipid nanoparticles were successfully developed for topical delivery of etoricoxib. SLN dispersions were prepared by melt emulsification and solidification at low temperature method. Physicochemical characterization including particle size, particle size distribution, Zeta potential, scanning electron microscopy, crystallinity study by DSC and *in-vitro* release profile were carried out. It was seen that increasing the stearic acid concentration led to higher entrapment and by increasing the concentration of tween 80 lead to smaller the particle size. *In-vitro* drug release pattern of SLN gel showed fast and control release. Immediate releases as well as sustained release both are of interest for topical application. Immediate release can be useful to improve the penetration of drug & maintain the concentration work as loading dose, while sustained release supplied the drug over a prolonged period of time.

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