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Research Article

SYSTEMIC DELIVERY OF DICLOFENAC SODIUM AFTER TOPICAL APPLICATION OF GELS INCORPORATED WITH DRUG-LOADED SOLID LIPID NANOPARTICLES (SLN)

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ABSTRACT

The aim of this study was to prepare and evaluate gels incorporating solid lipid nanoparticles (SLNs) of diclofenac sodium for systemic delivery of the active after topical application. SLNs were prepared using hot homogenization followed by sonication technique and these were incorporated into freshly prepared carbopol gel. Three different gel formulations (DSL1, DSL2 and DSL3) were prepared and characterized for particle size, charge, viscosity, morphology, and drug-lipid compatibility. The gels were evaluated for in vitro drug release, ex vivo permeation studies and in vivo absorption. The gels enriched with SLN sustained the drug release for 24 h both in vitro and in vivo. The results suggest enhancement in systemic delivery of diclofenac sodium with gels incorporating SLNs.

Key words: solid lipid nanoparticles, diclofenac sodium, systemic delivery, topical gels, anti-inflammatory activity.

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INTRODUCTION

Diclofenac Sodium (DS) is widely used for antirheumatic, analgesic, osteoarthritis, and antipyretic activities [1]. It is currently popular to treat the aforementioned first three ailments using a topical formulation. However, oral diclofenac is still popular despite the side-effects, especially for certain conditions and also for its antipyretic activity. The most common adverse effects of the drug after oral administration are gastritis, peptic ulceration, and depression of renal functions. Additionally, it also has short biological half-life which forces higher doses for oral administration, further increasing its GIT side-effects. Because of these disadvantages of oral diclofenac, topical diclofenac has been investigated very early on and now several successful formulations are available in the market [2]. However, for certain ailments where in diclofenac is useful topical route is not preferred. The drug should be systemically available. For this purpose, the drug was either given by intravenous route or oral route [3]. Oral route is disadvantageous as mentioned previously while intravenous route is less patient compliant. Thus, this study aims to investigate the systemic delivery of diclofenac after topical administration. Topical semi-solids for systemic delivery of drugs is also the state of art research in topical formulations [4,5]. Previous studies indicate that diclofenac sodium reaches systemic circulation after topical administration [6]. This suggests that topical semisolids for systemic delivery of diclofenac is a viable option. In this study, a novel gel incorporating SLNs taking the advantage of effective skin penetration using solid lipid nanoparticles was used to demonstrate better systemic delivery of diclofenac compared to conventional semi-solid formulations. SLN formulations previously demonstrated to aid in better skin penetration of the active after topical administration.

The main challenge in systemic drug delivery via topical route is to overcome the inherent barrier of the skin. The rate-limiting step in transdermal transport generally occurs at the stratum corneum, the outermost layer of the skin. Many approaches have been used to enhance the penetration of drugs though this layer of the skin. SLN approach is also one among them [7, 8]. The small particle size ensures close contact with the stratum corneum and increases the amount of encapsulated compounds penetrating into the skin [9, 10, 11]. Moreover, SLNs have distinct occlusive properties due to the formation of an intact film on the skin surface upon drying, which decreases transepidermal water loss and favours the drug penetrating though the stratum corneum [12, 13]. The nanometer sized particles can make close contact with superficial junctions of corneocyte clusters and furrows between corneocyte islands, which may favour accumulation for several hours allowing for sustained drug release [14, 15]. The advantages of the carrier include negligible skin irritation, controlled release, and protection of active substances [16]. Because they are composed of non-irritative and non-toxic lipids, SLNs seem to be well suited for use on inflamed and damaged skin. However, SLN suspension has very low viscosity; therefore, it is not convenient for use on the skin. An alternative i.e., incorporation of SLN into gels and further their administration topically has been suggested and investigated [8, 17, 18]. In this study a carbopol gel which is a hydrogel was used as a vehicle for SLN to achieve systemic delivery of diclofenac sodium after topical administration. Hydrogels are clinically acceptable systems that offer many advantages, such as suitable rheological properties, good tissue

compatibility and convenience in handing and ease of application [19]. Carbopol gels incorporating diclofenac sodium loaded SLN formulations were prepared and evaluated. Furthermore, to demonstrate the systemic penetration of the drug, an ex vivo permeation with rat skin and a pharmacodynamic study to evaluate its anti-inflammatory activity using a carrageenan-induced rat paw edema model for the gel formulations were investigated.

Materials and methods

Materials

Diclofenac Sodium(DS) was obtained from Alkha pharmaceuticals (Hyderabad, India), Dynasan 116 was purchased from Sigma Aldrich (Mumbai, India). Carbopol 934 was purchased from Genuine Chemical co. (Mumbai, India). Chloroform and methanol were purchased from Finar chemicals (Ahmedabad, India). Acetonitrile (HPLC grade) was procured from Merck specialities (New Delhi, India). Centrisart filters (molecular weight cutoff 20,000) were purchased from Sartorious Stedim Biotech (Bangalore, India). Propylene glycol and tween 80 were purchased from Qualikems fine Chemicals (Mumbai, India). Soyalecithin was purchased from Hi-media (Mumbai, India). Carrageenan was procured from SD fine chemicals. The other chemicals were of analytical grade.

Preparation of SLNs of Diclofenac Sodium

To prepare SLNs, DS, dynasan 116, and phosphatidylcholine of different compositions (Table 1) were dissolved in 10 ml mixture of chloroform and methanol (8:2). Organic solvents were completely removed using a rotoevaporator (Laborota 4000, Heidolph, Germany) to form a drug-embeded lipid layer. This layer was melted by heating at 65°C above the melting point of the lipid. Aqueous phase was prepared by dissolving polysorbate 80 (2 % w/v) in double distilled water (10 ml) and heated to same temperature of oil phase. Hot aqueous phase was added to the oil phase, and homogenization was carried out (at 8000 rpm and temperature 70°C) using a REMI homogenizer (Mumbai, India) for 3 min. Coarse hot oil in water emulsion so obtained was ultrasonicated (150V/T probe) using a ultrahomogenizer (Biologics inc., USA) for 15 min. Diclofenac Sodium solid lipid nanoparticles were obtained by allowing hot nanoemulsion to cool to room temperature. This results in the formation of DS SNLs used in the preparation of DSL1, DSL2 and DSL3 gels.

Table 1. Composition of the investigated DSSLN (wt. %)

Formulations	DS	Dynasan 116	Soyalecithin	Tween 80	Water
DSL1	0.25	3	1	2	93.75
DSL2	0.50	3	1	2	93.50
DSL3	0.75	3	1	2	93.25

Preparation and Characterization of DS SLN gel

To prepare carbopol gel, carbopol 934 (1 g) was dispersed in demineralised water (88 ml) by stirring at 800 rpm (Remi, Mumbai, India) for 60 minutes. Then, propylene glycol (10 ml) was added and the mixture was neutralised by drop wise addition of 10% NaOH. Mixing was continued until a transparent gel appeared, while the amount of the base was adjusted to achieve a gel with pH 6.5. To prepare, DS SLN gel, aqueous DS SLN dispersions and carbopol hydrogel were mixed in a high speed stirrer (Remi, Mumbai, India) at approximately

1000 rpm for 5 min. The gel to SLN ratio was such that a 50% SLN was present in the gel.

The SLN enriched hydrogels were characterized for their physicochemical properties such as colour, odour and pH. The mean size and polydispersity index of the size distribution and zeta potential of SLN were determined using photon correlation spectroscopy (PCS) using Zetasizer 3000 HAS (Malvern Instruments, Malvern, UK). Briefly, the SLN dispersions were diluted 1:1000 with the aqueous phase of the formulation to get a suitable kilo counts per second (kcps). Analysis was performed at 25°C with an angle of detection of 90°. Entrapment Efficiency (EE) was determined by measuring the concentration of free drug (unentrapped) in aqueous medium as reported previously [20]. The diluted aqueous medium containing the DS SLN gel was subjected to ultra-filtration to separate the free drug from encapsulated drug. Centrisart tubes, which consists of filter membrane (M.wt. cut off 20,000 Da) at the base of the sample recovery chamber was used. About 1ml of the diluted formulation was placed in the outer chamber and sample recovery chamber was placed on top of the sample and centrifuged at 4000 rpm for 15 min. The formulation was diluted to 1000 times using the same buffer used in the preparation of the gels. The SLN along with encapsulated drug remained in the outer chamber while the aqueous phase moved into the sample recovery chamber through filter membrane. The amount of DS in the aqueous phase was estimated using a HPLC method previously described. A Cyberlab-Chrom HPLC system (cyberlabs, USA) was used for the purpose. The column used was C_{18} ODS column and the size of silica used in this column is 5µm and the dimensions of the column is 4.6 × 250mm. Mobile phase consisted of acetonitrile/distilled water/acetic acid (40:60:2) while the peak detection was measured at 276 nm. An injection volume of 20 µl and a flow rate of 1.1 ml/min were used, and diclofenac sodium could be detected at a retention time of 8.2 min and a wavelength of 276 nm. The data was recorded using ws-100 Workstation software. The entrapment efficiency was calculated by the equation:

$$EE\ (\%) = \frac{\text{Wt. of drug used in the formulation} - \text{Wt. of drug in aqueous phase}}{\text{Wt. of drug used in the formulation}} \times 100$$

To predict if there is any drug-lipid interaction, DS, dynasan 116, soya lecithin and DS SLN were subjected to FTIR analysis. The morphology of DS loaded SLNs in the gels was examined by scanning electron microscope (SEM).

In vitro drug release studies were performed in vertical Franz diffusion cell. Phosphate buffer pH 7.4 (24 ml) was placed in the receiver compartment. A 0.5 gm of SLN gel of diclofenac was placed in the donor compartment. A dialysis membrane was used to separate the donor and receiver compartments. The diffusion cells were maintained at (37±0.5ºC) with stirring at 600rpm through out the experiment. At fixed time intervals, 5 ml of the sample was withdrawn from receiver compartment though side tube and analyzed by UV-Visible spectrophotometer at 276nm. Data obtained from *in vitro* release studies were fitted to various kinetic equations to find out the mechanism of diclofenac release from SLN gel. The kinetic models used were zero order equation, Higuchi release and Korsemeyer-Peppas.

The rheology of prepared gels was determined using a rheometer Brookfield Programmable Rheometer

LVDV-III + CP 230 equipped with a cone and plate test geometry (plate diameter 20 mm, cone angle 4°). All measurements were carried out at a temperature of 20 ± 0.1°C. The rheological properties of the developed hydrogels containing SLN were studied by continuous shear investigations, which were performed in order to evaluate the shear rate [1/s] as a function of shear stress [Pa]. This study started applying 0 Pa up to a maximum shear stress of 50 Pa and the resulting shear rate was measured.

Animal Studies

Male Wister rats (150-200 gm) purchased from the Mahaveer enterprises (Hyderabad, India) were used in the animal studies. The animals were kept under standard laboratory conditions, at 25 ± 1^0C and 55 ± 5% relative humidity with a 12 h light/dark cycle. The animals were housed in polypropylene cages, with free access to a standard laboratory diet and water. All surgical and experimental procedures were reviewed and approved by the animal and ethics review committee, Vaagdevi College of Pharmacy, Warangal, Andhra Pradesh, India. Ex Vivo drug permeation studies as well as pharmacodynamic studies were conducted using rats.

Ex Vivo Permeation Studies

Skin from the abdominal region was excised after hair was removed with a depilatory, and examined for integrity using a lamp-inspecting method. The subcutaneous fat and connective tissue were carefully removed. The obtained skin was rinsed with physiological saline and further used to study drug permeation. A system employing vertical Franz diffusion cells with a diffusional area of 4.15 cm^2 was used for permeation studies. The excised rat skin was set in place with the stratum corneum facing the donor compartment and the dermis facing the receiver compartment. A 0.5 gm of the gel containing DS or DS SLN was applied to the skin surface in the donor compartment and the receptor compartment of the cell was filled with 24 ml of phosphate buffer (pH 7.4). During the experiments, the diffusion cell was maintained at 37 ± 0.5°C and stirred at 600rpm. After application of the test formulation on the donor side, 5 ml aliquots were collected from the receiver compartment at designated time intervals (1, 2, 4, 8, 12, and 24 h). Each time after the sample was removed from the receiver, an equivalent volume of buffer was supplied to the receiver compartment. The collected samples were analysed by UV-Vis spectrophotometer at 276nm. The amount of diclofenac released was determined from a standard curve generated using UV-Vis spectrophotometer at 276 nm.

Pharmacodynamic Studies

Carrageenan induced paw edema method was used to study the *in vivo* performance of the prepared drug delivery system. Anti-inflammatory activity was determined by measuring change in the volume of inflamed paw, produced by injection of carrageenan (0.1 ml of 1% w/v) using plethysmometer (INCO, India). Male wister rats selected for the study were weighed and marks were made on the right hind paw just behind tibia-tarsal junction on each animal. To ensure constant paw volume, every time the paw was dipped in the plethysmograph (mercury displacement method) up to the fixed mark. Rats were divided into four groups including one controlled group with each group comprising of 3 animals. The control group received normal saline orally. The other three groups received oral diclofenac, diclofenac carbopol gel and DSL3. Diclofenac gel was prepared as the DSLs were prepared, excepting the drug was added as a dispersion in the gel. DSL3 was used in the antiinflammatory studies because of higher drug release and higher drug permeation when compared to other two formulations (Figure 3 and Figure 4). Oral diclofenac was given in the form of suspension made in sodium CMC. The drug in all the three formulations was equal and was 5 mg. The paw volume was noted at 0, 1, 2, 4, 6, 8, 12 and 24 h.

The formulation was applied transdermally to the abdomen of albino rats of respective groups, excluding the animals of controlled group. After 30 min of transdermal application or oral administration of formulations, 0.1 ml of 1% w/v carrageenan (in 0.9% normal saline) was injected in the sub planter region of the right hind paw of rats. The initial reading just after injection and subsequent paw volumes was measured up to 24 h. The percent inhibition of edema induced by carrageenan was calculated for each group using the following equation [22]:

% *inhibition of edema* = 100(1- (a-x/b-y))

Where a = mean paw volume of treated animals after carrageenan injection

x = mean paw volume of treated animals before carrageenan injection

b = mean paw volume of control animals after carrageenan injection

y =mean paw volume of control animals before carrageenan injection

Results and Discussion

For the current study, three batches of SLNs were successfully prepared and the composition of the formulations prepared is shown in Table 1. And these SLN formulations were successfully incorporated into carbopol gel; it was prepared using a optimal stabilizer combination of water, carbopol and propylene glycol as hydrating agent. The DSSLN dispersions were white in colour, odourless and fluid in nature. Gels loaded with DSSLN dispersions were colourless, odourless with smooth appearance. The SEM image of DSSLN dispersion was presented in Figure 1. The figure shows that the particles were spherical in shape. The Entrapment Efficiency values were determined for three formulations and observed as 60%±0.545, 54%±0.62 and 50%±0.75 for DSL1, DSL2 andDSL3, respectively. The reports revealed by the FTIR study confers that there is no interaction between the lipids and drug (data not shown). Particle size, polydispersity index (PDI) and Zeta potential values of the formulation DSL3 in carbopol gel was found to be 158.1±9.2 nm, 0.273±0.032 and -35.9±2.66 respectively (mean±S.D (n=3)). DSL3 formulation was the final formulation selected for the investigation of anti-inflammatory activity of the formulation.

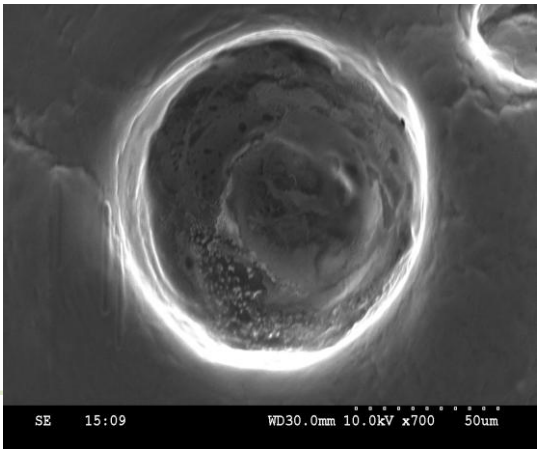

Fig. 1. SEM photograph of diclofenac loaded solid lipid nanoparticles

The rheological status of a semisolid drug carrier system is a very important physical parameter. Rheology measurements provide essential information about different aspects concerning semisolid preparations. Rheological properties therefore affect all stages of manufacture like mixing, pumping, filling etc. Moreover, rheological measurements are valuable tools in quality control of ingredients and final products. Concerning application and performance on skin they provide essential information. Furthermore, drug release from semisolid vehicles is influenced by the rheological behaviour. The rheological behaviour of hydrogels loaded with SLN was evaluated after 1 week of storage at

room temperature. The flow curves of the gels are shown in Figure 2.

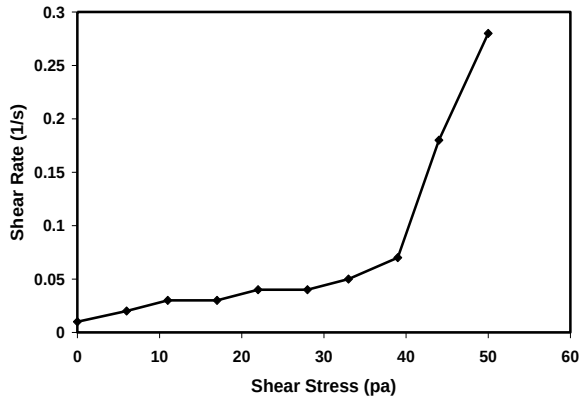

Fig. 2. Shear rates of SLN containing hydrogels as a function of shear stress, measured after 7 days of storage at room temperature.

The cumulative amount release of DS from DSL1, DSL2, DSL3 gels were investigated for a period of 24 h. Figure 3 shows the *in vitro* release profile of DSSLN gels. DSL1, DSL2, DSL3 (DSSLN-gel) could prolong the drug release by the fact that the drug molecules are entrapped in the solid lipid matrix. The amount of drug release at the end of 24 h in DSL1, DSL2 and DSL3 (DSSLN) gel formulations was found to 0.88, 1.52 and 2.21 mg, respectively. A different release kinetic was observed for the SLN dispersions and SLN gel formulations. Fick's law of diffusion seems not to be applicable in each case**.** All the SLNs enriched gel formulations showed controlled drug release and also an increase in release rate was observed after 24 h. The log percent cumulative drug released was plotted as a function of log time and the slope of the curves was determined as the values of diffusional release exponent (η). The values of diffusional release exponent (η) from the straight lines were noted to be 0.79, 0.78 and 0.69 in SLN gel formulations of DSL1, DSL2 and DSL3 respectively, which showed that the release of drug from formulations followed a non-Fickian pattern [23]. From the cumulative amount drug released versus time plot, the slope values were determined as release rate constants. The release rate constants were 0.038, 0.0618 and 0.089 mg/cm^2/h for DSL1, DSL2 and DSL3 gel, formulations respectively. Thus, the formulations with higher drug content shows higher release rate constants. The slower release of drug from SLN enriched carbopol gel maintained the drug concentration for longer period of time.

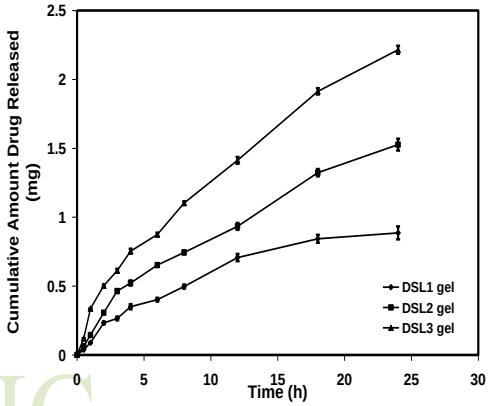

Fig. 3.

Fig. 3. *In vitro* release of DS from gels enriched with SLN dispersions, Mean S.D (n = 3)

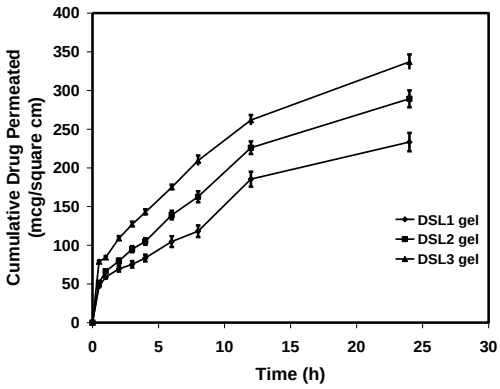

Fig. 4.

Fig. 4. *In vitro* permeation of DS from gels enriched with SLN dispersions, Mean S.D (n = 3)

The cumulative amount permeated of DS from DSL1, DSL2, DSL3 gels were investigated for a period of 24 h.

Figure 4 shows the *in vitro* permeation profile of DSSLN gels of DSL1, DSL2, DSL3 (DSSLN-gel). Cumulative amount of drug permeated in 24 h were 233.33, 289.23 and 336.93 µg/cm^2 for DSL1, DSL2 and DSL3 (DSSLN-gel) formulations respectively. The release kinetics was established by determining the diffusional release exponent from the plot of log of cumulative drug permeated versus log time. This plot yielded a straight line from which diffusional release exponent (η) were calculated and found to be 0.41, 0.46 and 0.40 in SLN gel formulations of DSL1, DSL2 and DSL3, respectively. The results indicate that permeation of drug from these formulations followed a Fickian pattern [23]. A lag time (15min–1h) was observed in DSL1 and DSL2 SLN gel formulations. This could be because in these formulations the drug has to cross two diffusion barriers, one the gel and the other is skin. No lag time was observed with DSL3 gel formulation. This could be because of higher amount of drug available. The SLN enriched gel formulations possessed a sustained drug release over a period of 24 h period. From the cumulative drug permeated versus time plot, the slope values were determined and these are considered as the skin permeation rates. The permeation rate constants were found to be 8.83, 11.14 and 12.43 µg/cm^2/h. The slower release of drug from SLN carbopol gels maintained the drug concentration for longer period of time. The results of this study indicate that significant diclofenac travels across the skin and there could be likely systemic delivery of diclofenac from these formulations after topical administration. To corroborate the fact, a study to investigate systemic delivery in live animals was conducted. The formulation DSL3 which demonstrated good in vitro release as well as in vitro permeation was selected for this study.

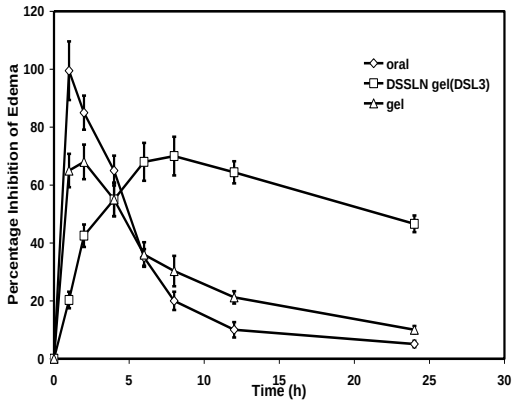

Fig. 5.

Fig. 5. Anti-inflammatory activity of diclofenac sodium SLN enriched hydrogels after transdermal application in comparison to oral administration and diclofenac sodium gel in carrageenan induced rat paw oedema (n = 3)

The *in vivo* performance of selected DSL3 (DSSLN) enriched hydrogel was evaluated in a carrageenan-induced rat paw edema model (Figure 5). Formulations DSL3 under study not only decreased the inflammation to the larger magnitude, but also sustained this magnitude. In DSL3 formulation the maximum inhibition was observed at 8th h with higher value (70%), and even after 24 h, 46% inhibition was observed. However, in case oral administration, inhibition was displayed at 1 h with magnitude of 99.5% and just after 4 h it scored below 65% and in case DS gel administration, inhibition was displayed at 2 h with magnitude of 68% and just after 6 h it scored below 36 % (Figure 5). There are is a sharp rise in the activity with oral administration. This can be explained because significant drug concentrations might have reached the systemic circulation after oral administration and the activity also subsided quickly. This is because of the short half-life of the drug. Also the inhibition when compared to topical formulations was very high. The dose administration in all the cases is the same. This indicates that the drug reaches the target tissue quickly from the systemic circulation. On the other

hand, the gel formulations although demonstrated a profound antiinflammatory activity, it was considerably lower than oral administration. This suggests that drug reaches the systemic circulation after topical administration. Interestingly, the effect with DSL3 is sustained. The possible reason could be the drug concentration in the blood, which was maintained for longer duration in case of formulation DSL3 in comparison to the drug administered orally and gel form. Thus, in comparison to orally administered DS and DS gel, the formulations DSL3 which was applied transdermally gave good results. The maximum inhibition for DSL3 was observed at 8 h and the inhibition was maintained up to 12 h and also even after 24 h inhibition was observed. The anti-inflammatory activity of the formulation (DSL3) was maintained for longer period of time due to slow release of the drug. This was attributed to gel structure and the surface active properties of the gel.

Conclusion

Diclofenac sodium SLN were prepared by hot homogenization method and successfully incorporated into carbopol gel for topical delivery. The drug permeated from the rat skin. Gels enriched with SLN possessed a sustained drug release over period of 24 h. Topical administration of DSSLN gel demonstrated sustained systemic delivery of the drug. It shows good anti-inflammatory activity upto 24 h, in comparison to oral and conventional gel administration of diclofenac sodium.

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