Research article

Nanocarrier based transdermal formulation of NSAID: Optimization of drug loading and analysis of permeation characteristics

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Abstract
Arthritis is a major cause of disability and morbidity, particularly in older individuals. The symptoms and signs of arthritis and related conditions include pain, stiffness, swelling, muscle weakness, and limitation of movement of the joints.
The objective of the present work was to provide a dosage form for localized action of drugs used in treatment of arthritis to the affected tissues for prolonged period and to avoid side effects in non-target organs. To achieve this, drug loaded liposomes and transferosomes were prepared for Nonsteroidal anti inflammatory drugs and further incorporated in transdermal gel formulation. The formulations were prepared by Experimental design using screened factors and their levels and by optimized process parameters.
The transdermal drug permeation was found to be highest for transferosomal gel, whereas drug was found to be slightly retained in skin during permeation from liposomal gel formulation. The reason may be fusion of Phospholipids during diffusion through skin. Both the Transferosomal gel formulation and Liposomal gel formulation showed sustained release of drug for more than 6 hrs.
Based on the pharmacokinetic studies, both the liposomal gel and transferosomal gel were found to have better bioavailability as compared to plain gel of Aceclofenac. Both the transferosomal and liposomal gel showed better anti-inflammatory action and analgesic action than marketed gel of Aceclofenac (Marketed gel).

Key words: Nanocarrier, Arthritis, Transdermal drug delivery, Permeation, NSAID.

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1. Introduction
Arthritis is a major cause of disability, particularly in older individuals. More than 30 percent of females have some degree of osteoarthritis by age 65. The symptoms and signs of arthritis and related conditions include pain, stiffness, swelling, muscle weakness, and limitation of movement of the joints. Nonsteroidal anti-inflammatory drugs and corticosteroids are most widely used and effective drugs for treatment of arthritis[1]. Nonsteroidal anti-
inflammatory drugs (NSAIDs) that act by inhibiting cyclooxygenase and the formation of prostaglandins, are known to cause GI toxicity, leading to peptic ulcers, unwanted antiplatelet effects (nonselective inhibitors of cyclooxygenase), cardiotoxicity, renal toxicity and anaphylactic reactions in selected patients. The currently available oral dosage forms of NSAIDs like tablet and capsules etc are more likely to produce above mentioned adverse effects of these drugs. The intravenous administration of these drugs leads to distribution throughout the whole body and rapid clearance, thus a high and frequent dosing is necessary to achieve an effective concentration of drug at inflamed target sites. Moreover, the activities of drug in many different tissues increase the risk of adverse effects in patients. Topical delivery of drugs can be a suitable option and is associated with advantages such as avoidance of hepatic first-pass metabolism, improved patient compliance and ease of access, provides a means to quickly terminate dosing, sustained therapeutic drug levels, possible self – administered, non-invasive (no needles or injections needed), avoids food related interaction, reduction of doses as compared to oral dosage forms and intravenous therapy and most important is avoidance of GI adverse effects.

The topical drug delivery also suffers from some shortcomings such as poor permeability through skin, unpredictable drug release and skin irritation. These shortcomings can be overcome if we develop a drug delivery system in particular carriers, with enhanced localization to the target site and sustained drug release.

Drug targeting approach:- Most of the current therapies for RA do not achieve target specificity and to reach effective drug concentrations in affected joint tissues, high dose of drug must be administered, which may lead to significant adverse systemic side effects [10]. Currently anti-inflammatory drugs are mainly delivered by transdermal iontophoresis [11,12]. New drug application (NDA) of Alza corporation for iontophoretic fentanyl containing transdermal analgesic have been approved by US FDA[12]. Iontophoresis is a special method of applying drug to and pushing it through the skin to reach the blood vessels and surrounding deeper tissues by electric transmission. A significant amount of Piroxicam was retained in the skin after transdermal iontophoresis from Piroxicam[13]. In order to increase penetration and a prolonged release, lipid nano/submicron emulsion can be used as a vehicle for topical delivery of drugs[14]. The most prominent advantage of drug carriers such as liposomes, transferosomes, and solid lipid nanoparticles over conventional drug delivery systems is the option to improve selective delivery of drugs to the site of action, so-called drug targeting which can be either passive or active.

Liposomes:-This drug delivery system include easy encapsulation of hydrophilic drugs into their core compartment and hydrophobic drugs into their lipid bilayer, excellent biocompatibility, ability to penetrate effectively into cell membranes, delivery of drugs into the cell compartments and diversity in modifying the surface properties by altering or introducing new components into the lipid bilayer[14,15]. For transdermal absorption of NSAIDs at the localized site of action, liposomes may be a useful tool [16,17]. A single topical application of Diclofenac liposomal suspension has shown concentrations of Diclofenac in transudate within 6 hours and
significantly attenuated carrageenan-induced local production of Prostaglandin. Results of this study suggest that DLS is readily absorbed transdermally and may be efficacious for reducing subcutaneous inflammation[18]. In another study, Diclofenac sodium loaded liposomes were prepared by thin film hydration technique using soya lecithin, cholesterol followed by sonication and then incorporation into 1% carbopol gel. The particle size, polydispersity index and zeta potential of liposomes were found to be 230 nm, 0.247 and -41 respectively and the entrapment efficiency was found to be 62%. The cumulative amount of drug permeated in 24 hour from the liposomal gel formulation was found to be 1176.7 μg/cm [19]. From the drug entrapment efficiency study of ketoprofen liposomal gel formulation, maximum drug encapsulation of 97.51% was observed in formulation, in which lipid and cholesterol were used in ratio of 1:2. Therefore, it can be interpreted that, in liposome preparation, cholesterol was found to act as fluidity buffer and provided stability and rigidity to liposome. The marketed gel of Ketoprofen released approximately 92% of drug within 24 hour, whereas the liposomal formulations showed 87% drug release in 24 hour. Liposomal formulations showed sustained drug release compared to normal gel, also an increase in release rate was observed after 12 hour[20].

LUV dispersions containing Indomethacin was prepared by extrusion method using dipalmitoyl-L-alpha-phosphatidylcholine and cholesterol and observed a high percentage of entrapped drug (approximately 84%). Furthermore, in-vivo findings revealed that the anti-inflammatory effect was more prolonged when Indomethacin was delivered from a liposomal gel formulation rather than from a gel formulation without liposomes. In particular, the Indomethacin-loaded gel formulation LUV-A showed a sustained release, possibly related to an interaction between LUV lipids and stratum corneum lipid structure [21]. Piroxicam liposomes were prepared by thin film hydration technique using phospholipids and cholesterol. Liposomes were characterized by electron transmission microscopy, and the mean structure diameter was found to be 278 nm. The encapsulation efficiency obtained was 12.73%. The topical anti-inflammatory effect was evaluated in vivo by the cotton pellet granuloma method [22]. The encapsulation of Piroxicam produced an increase of topical anti-inflammatory effect. In addition it was also observed that, anti-inflammatory effect can be achieved using lower drug concentrations when formulated as liposomal gel [22-24]. Liposomal gel of dex-ibuprofen prepared by rotary evaporation followed by sonication using phosphatidylycerol and cholesterol with particle size of 5.40 μm and entrapment efficiency of 61% showed sustained drug delivery for 12 hours[25]. In a study, liposome preparation consisted of a combination of methyl prednisolone, phospholipid and cholesterol. Phospholipids were a combination of hydrogenated soybean phosphatidylcholine (HSPC), polyethylene glycol coated distearoyl phosphatidyl ethanolamine (PEG-DSPE) and cholesterol. HSPC/ cholesterol/PEG-DSPE-2000 at mole ratio of 55:40:5. In the work, methyl prednisolone derivative encapsulated in a liposome was essentially retained in said liposome for 6 months; liposomes were uniformly sized to a selected size range between 70-100 nm, preferably about 80nm (AU 2005/281351A1). Charge-inducing lipids, such as phosphatidylglycerol can be incorporated into the liposome bilayer to decrease vesicle-vesicle fusion and to
increase interaction with cells, while cholesterol and sphingomyelin can be included in formulations in order to decrease permeability and leakage of encapsulated drugs. At neutral pH buffers can decrease hydrolysis. Addition of an antioxidant, such as sodium ascorbate can decrease oxidation etc. A preferred formulation according to one invention was that comprising phosphatidylcholine (PC) such as egg PC (EPC) or hydrogenated soy PC (HSPC) as a the liposome forming lipid (US 2008/0003276 A1).

**Transferosomes:** These are ultra deformable vesicle, elastic in nature which can squeeze itself through a pore which is many times smaller (1/10th) than its size owing to its elasticity. These are applied in a non-occluded method to the skin and have been shown to permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. Transferosomes are made up of a phospholipid component along with a surfactant mixture (Sodium Cholate, Spans and Tweens)[26,27]. The ratio and total amount of surfactants which acts as edge activator controls the flexibility of the vesicle. The unique property of this type of drug carrier system lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic drugs. These ultra deformable drug carriers trespass the intact skin spontaneously, probably under the influence of the naturally occurring, transcutaneous hydration gradient. The ‘moisture seeking’ tendency (hydro taxis) of transferosomes permits the carrier to bring more than 50% of the epicutaneously administered drug across the skin barrier[27]. In a study on Ibuprofen transferosomes the best formulations were observed with the use of Span 80 and Tween 80 where vesicle size was found to be 962 nm and 2250 nm respectively, and zeta potential (negatively charged) for Span 80 and Tween 80 was found to be -16.1 and -17.5 respectively. The %EE of ibuprofen in the vesicles was 47.8 and the elasticity of both increases with increase in surfactant conc. and were found to be 34.4 and 26.5, in vitro skin permeation studies were carried by human cadaver skin using Franz diffusion cell, and drug release after 24 hrs and flux was found 2.5824 and 1.9672 μg/cm²/hr respectively[26]. It is evident from one of the studies, where transfersomes of Diclofenac sodium were prepared using soya Phosphotidylcholine by suspending lipids in aqueous phase containing drug and thereafter sonication, size achieved was in the range of 100-200 nm Diclofenac association with ultra deformable carriers have a longer effect and reach 10-times higher concentrations in the tissues under the skin in comparison with the drug from a commercial hydrogel. In rats, a single epicutaneous application of 2 mg of Diclofenac per kg bodyweight in highly deformable carriers produced at least 4 times higher drug concentration in the treated muscles than a drug-loaded hydrogel[28]. Ketoprofen transferosome formulation has been granted marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007; the product is under the trademark Diractin of IDEA AG (Munich) U.S. Pat. No. 6,165,500 (Idea AG) describes an adaptable bilayer vesicle comprising a phospholipid combined with edge activators which include alcohols and surfactants such as cholates or polyoxyethylene ethers. These ultra deformable particles are termed Transferosomes and are suitable for delivering hydrophilic and lipophilic agents through the hydrophilic pores in the skin. Transferosomes ranging from
200 to 600 nm in size physically appear as milky emulsions. For dermal delivery applications, a particle sizes in the range of 100 to 200 nm is preferred. A pharmaceutical composition was prepared which comprises of a bilayer membrane vesicles suspended in a liquid medium. The components were bilayer forming lipid, an amphipathic analgesic drug and a surfactant capable of self-aggregation in the suspension medium, surfactant selected were preferably nonionic such as polyethylene glycol-sorbitan-long fatty chain ester, a polyethylene glycol-long fatty chain ester or ether and a polyhydroxyethylene-long fatty chain ester (EP 1551370 B1).

**Objective and scope of work**

The objective of the present work was to provide a dosage form for localized action of drugs used in treatment of arthritis to the affected tissues for prolonged period and to avoid side effects in non-target organs. To achieve this, it was hypothesized that if we incorporate the Nonsteroidal anti-inflammatory drugs in Nano drug carriers such as liposomes and transferosomes, and then incorporate them in topical gel formulation we can achieve size and characteristics for better permeation and release of drug through transdermal route to provide localized action. We planned to perform the optimization of carrier composition by experiment design and evaluation of prepared formulations to achieve desired permeation and release of drug through transdermal route in addition to formulation factors.

The present study provides a novel approach in order to achieve a targeted drug delivery with minimization of side effects in arthritis, a very prevalent disease among elderly which leads to disability. The treatment of arthritis by conventional methods produces many side effects in long run due to which treatment cannot be continued for a long period.

### 2. Materials and Methods

The phospholipids 1-2 disteroyl-sn-glycerol-3-phosphoethanolamine, Na, 1-2 disteoyl-sn-glycerol-3-phosphate monosodium salt & hydrogenated Phosphotidylcholine were procured from Lipoid, Germany. Carbomers, cholesterol and sorbitan monoesters were purchased from Qualichem Ltd. Mumbai, Maharashtra. All the chemicals were of analytical grade.

**Preparation of vesicles**

Multilamellar vesicles were prepared by the established method of hydration of thin film prepared by rotary vacuum evaporation. The phospholipids, cholesterol and Aceclofenac 10 mg were dissolved in chloroform and methanol mixture in ratio of 9:1. After formation of thin film, it was hydrated with 20 ml of Phosphate buffer. The process variables, temperature, RPM and time of operation were varied based on 3 factor, 3 level general factorial design and based on the quality of film produced, the process was optimized.

The vesicles were reduced in size by probe sonication. The method of 5 sonication cycle each of 2 minutes at amplitude of 60% using 13 mm standard probe was applied as it produced transparent vesicular dispersion with reproducibility and uniformity in vesicle size.

**Evaluation of Formulation**

**Determination of particle size & zeta potential of vesicles**

The sizes of the vesicles were determined by dynamic light scattering method (Malvern Instruments Ltd. UK).
Morphology of vesicles
The shape and morphology of vesicles were determined by Transmission electron microscopy. For analysis 2 drops of sample was placed on carbon support film, dried and then 1% solution of Urenyl acetate was used for negative staining.

Entrapment efficiency
Drug loaded Vesicles in phosphate buffer saline pH 7.4, were centrifuged at 15000 rpm for 15 minutes at 4°C on Remi Lab Centifuge. The supernatant was collected and again centrifuged at 15000 rpm for 15 minutes and the drug content of supernatant was analyzed after dilution to determine unentrapped drug content. The residue at bottom was soaked in methanol for 30 minutes and then agitated, and analyzed for the entrapped drug content.

Evaluation of drug loaded Liposomes and Transferosomes in transdermal gel
Release studies
In-vitro and Ex vivo diffusion studies: (IAEC Approval no. PhD/13-14/23 dtd. 14th December 2013)
In vitro diffusion studies was performed using Franz diffusion cell and dialysis membrane (himedia) having pore size of 2.4 nm followed by excised skin samples. The excised skin of dorsal side of 5-6 weeks old Rat was mounted on donor compartment after removing hair. It was then clamped between the donor and the receptor chamber of modified diffusion cells with the stratum corneum facing the donor chamber. Then, 0.2 g of gel containing Aceclofenac was applied on the skin in donor chamber. The receptor chamber was filled with 20 ml of With Phosphate buffer saline pH 7.4 as diffusion media in receptor compartment. The receptor medium was maintained at a temperature of 37 ± 0.5°C and stirred at 600 rpm throughout the experiment.

Aliquots of 5 ml were sampled from the receptor compartment at time interval of 1 hr and then immediately replaced with the same volume of pure medium. Aliquots were withdrawn at specific time intervals and drug release was studied. All samples were analyzed by UV spectroscopy method. Cumulative corrections were made to obtain the total amount of drug released at each time interval. The cumulative amount of drug released across the Rat skin was determined as a function of time.

Permeation flux
The permeation flux for experimental batches of liposomal gel, transferosomal gel and plain drug gel were determined. Permeation flux is the slope of percentage drug release v/s time. It is expressed as μgcm⁻²/hr⁻¹

Refractive index
Refractive index was measured using Abbs refractrometer, dolphin at BIP, Baroda.

Determination of pH
The pH of gels was checked by using a digital pH meter at room temperature. Initially, the pH meter was calibrated using standard buffers of pH 7 and then 10 gm of gel was weighed and dispersed in 25 ml of distilled water and then electrode of pH meter was dipped in the dispersion and the pH was noted.

Spreadability
0.5 g gel was placed within a circle of 1cm diameter (pre marked glass slide) over which a second glass slide was placed. A weight of 2 g was allowed to rest on the upper glass slide for 1min. The increase in the diameter due to spreading of the gel was noted. Spreadability was then calculated by using the formula:
S = M.L / T
Where, $S =$ Spreadability, $M =$ weight attached to upper slide, $L =$ length of spread, $T =$ time taken.

**Gel strength**

The apparatus for measuring gel strength consist of plunger having pan to hold weights at one end and the other end was immersed into gel. Formulated gels were placed in glass bottle where marking was done 1cm below the filling mark. The weight required for the plunger to sink to a depth of 1 cm through the prepared gel was measured for each formulation.

**Extrudability**

Prepared gel was filled in tube and sealed. 3 Markings were done at interval of 1.5 cm from bottom of tube. The tube was pressed at marking using Pfizer hardness tester with 1 kg/cm², the weight of gel in continuous ribbon expelled is measured for each formulation.

**Rheological studies**

The viscosity of gels was determined by using Brookfield helipath (LVDV 2) viscometer. The gel was placed in the sample holder and no. 96 spindle was lowered perpendicularly into the sample. The spindle was attached to viscometer and then it was allowed to rotate at a constant optimum speed at room temperature. The readings of viscosity of the formulation were measured at different rpm.

**Plasma Profile of drug administered through drug carriers incorporated transdermal gel**

Approval to carry out pharmacokinetic studies was obtained from the Institutional Animal Ethics Committee. Approval no- AEP. PhD/13-14/23. These studies were performed on optimized Liposomal gel (M3), Transferosomal gel (F3) and marketed gel. Male Wistar rats were stores under standard laboratory conditions (temperature 25 ± 2°C and relative humidity of 55 ± 5%). The rats were kept in cages (6/cage) and feded with standard laboratory diet. About 15 cm² of skin was shaved on the abdominal side of rats in each group. They were fasted for the period of 12 h for observations of any unwanted effects. The rats were divided into 3 groups, each containing 3 rats. Group I received M3 transdermally, group II received F3 transdermally and group III received plain gel. The rats were anaesthetized using light ether anesthesia and blood samples (0.5 ml) were withdrawn from the tail vein of rat at 0 (pre-dose), 30 minutes, 1, 2, 3, 4, 6 and 8h and kept in micro centrifuge tubes in which 6 mg of EDTA was added as an anticoagulant. The blood collected was mixed with the EDTA properly and centrifuged at 5000 rpm for 25 min for separation of plasma. The separated plasma was stored at -21°C until drug analysis was carried out using high performance liquid chromatographic (HPLC) method.

**Radioactive tagging experiment for skin permeation studies**

The radiolabeling of Compound was performed as per standard protocol. Scintigraphic images of pre-wash area and post-wash area were taken at the end of 1 hour, 2 hour and 3 hour after the gel application on individual rabbits.

**Anti inflammatory activity**

The anti inflammatory activity was carried out by carrageenan induced paw oedema method to compare the activity of Aceclofenac Liposomal gel, transferosomal gel and marketed gel using Plethysmometer. After 30 minutes of topical application of formulations on the right hind paw of rats, 0.1 ml of 1%w/v carageenan (in 0.9% saline
solution) was injected in the subplantar region of right hind paw of rats. The initial paw volume just after injection and subsequent readings up to 6 hours and then at 24 hrs were measured.

**Analgesic activity**
The time of latency was determined as the time period between the zero point, when the animal is placed on the hot plate surface, and the time when the animal jumps off to avoid thermal pain. Analgesic activity was determined for Liposomal gel, transferosomal gel and marketed gel of Aceclofenac.

**3. Result & Discussion**

The drug loaded liposomes and transferosomes were prepared for Nonsteroidal anti inflammatory drug Aceclofenac and further incorporated in transdermal gel formulation. The formulations were prepared by Experimental design using screened factors and their levels and by optimized process parameters.

The process of rotary vacuum evaporation at 50°C temperature and 90 rpm, for 20 minutes can produce a thin film which is uniform and translucent in appearance. Probe sonication for 5 cycles each of 2 minutes at amplitude of 60% using 13 mm standard probe can produce transparent vesicular dispersion with reproducibility and uniformity in vesicle size.

Among phospholipids, 1,2-disteroyl-sn-glycero-3-Phospho-ethanolamine,Na salt was found to be better for liposome preparation and among Surfactants, Span 60 was screened as suitable surfactant for transferosome preparation on the basis of size, drug entrapment efficiency and drug release. The excipients were found to be compatible with the drug based on the results of drug excipient compatibility studies. The transferosomes and liposomes batches were prepared based on experimental design using minitab software 16. Both the drug carriers were found in the nanometric range with size uniformity with good zeta potential value indicating stability of drug carrier suspension as presented in figure 1 & 2.

On the basis of formulation optimization based on drug entrapment efficiency and in vitro drug permeation studies, the optimized formulation of liposome was found to have a composition of phospholipid 109.9 mg, and cholesterol 27.68 mg with 100 mg Aceclofenac, whereas the optimized formula of transferosomes was found to have a composition of Phospholipid 91.41 mg, surfactant 25mg and cholesterol 35.60 mg in formulation with 100 mg Aceclofenac. The %drug entrapment of optimized formulation of transferosomes and liposomes were found to be 57.44 % and
51.02 % respectively which were very close to the target responses fixed in Response surface methodology. Similarly, permeation flux of optimized formulation of transfersomes and liposomes were found to be 28.69 and 26.88 µgcm⁻² hr⁻¹ respectively which were very close to the target responses fixed in Response surface methodology. Therefore optimized formulation was found to follow the prediction of possibility to meet the target responses of %drug entrapment and permeation flux. The details are presented in Table 1.

Table No. 1. Evaluation of Optimized batch of Transfersomal and Liposomal gel formulation of Aceclofenac

<table>
<thead>
<tr>
<th>Optimized formula</th>
<th>Size (nm)</th>
<th>Zeta potential</th>
<th>% drug entrapment</th>
<th>Ex-vivo Permeation flux (µgcm⁻² hr⁻¹)</th>
<th>Viscosity (cp)</th>
<th>pH</th>
<th>Spreadability (gm.cm/sec)</th>
<th>Gel strength (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfersomal gel</td>
<td>368</td>
<td>-39.12</td>
<td>57.44%</td>
<td>28.69</td>
<td>4768</td>
<td>6.4</td>
<td>1.446</td>
<td>22.80</td>
</tr>
<tr>
<td>Liposomal gel</td>
<td>517</td>
<td>-56.14</td>
<td>51.02%</td>
<td>26.88</td>
<td>4872</td>
<td>6.0</td>
<td>1.3989</td>
<td>23.57</td>
</tr>
<tr>
<td>Marketed gel</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17.46</td>
<td>5938</td>
<td>6.0</td>
<td>1.3595</td>
<td>17.23</td>
</tr>
</tbody>
</table>

The optimized transfersomal gel and liposomal gel of Aceclofenac showed better drug permeation in ex-vivo studies through rat skin as compared to Plain drug gel. The transdermal drug permeation was found to be highest for transfersomal gel, whereas drug was found to be slightly retained in skin during permeation from liposomal gel formulation. The reason may be fusion of Phospholipids during diffusion through skin. Both the Transfersosomal gel formulation and Liposomal gel formulation showed sustained release of drug for more than 6 hrs. The details are given in Table 2.

Table No. 2. The Ex-vivo release data of Optimized batch of Transfersomal and Liposomal gel formulation of Aceclofenac

<table>
<thead>
<tr>
<th>Optimized Formula</th>
<th>In acceptor compartment</th>
<th>Retained On Surface Skin</th>
<th>In skin</th>
<th>Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfersomal gel</td>
<td>82.85%</td>
<td>10.02%</td>
<td>4.28%</td>
<td>2.85%</td>
</tr>
<tr>
<td>Liposomal gel</td>
<td>74.16%</td>
<td>12.89%</td>
<td>9.63%</td>
<td>3.32%</td>
</tr>
<tr>
<td>Marketed gel</td>
<td>59.04 %</td>
<td>26.88</td>
<td>3.76</td>
<td>10.32</td>
</tr>
</tbody>
</table>

Based on the pharmacokinetic studies, liposomal gel showed Cmax of 7.002µg/ml and a Tmax of 6 hrs. The plain gel of Aceclofenac as compared to liposomal and transfersomal gel, showed lesser Cmax but the same Tmax. The AUC
was found to be highest for transferosomal gel (67.14 µg.hr/ml) followed by liposomal gel (53.87 µg.hr/ml).

Both the liposomal gel and transferosomal gel were found to have better bioavailability as compared to marketed gel of Aceclofenac (42.92 µg.hr/ml). The details are given in Table 3.

Table No. 3. Comparative Pharmacokinetics Profile of Optimized batch of Transferosomal and Liposomal gel formulation of Aceclofenac

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (hr)</th>
<th>AUC0–t µg.hr/ml</th>
<th>AUCt∞ µg.hr/ml</th>
<th>AUCo–∞ µg.hr/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal gel</td>
<td>7.002</td>
<td>6</td>
<td>44.957</td>
<td>8.917</td>
<td>53.874</td>
</tr>
<tr>
<td>Transferosomal gel</td>
<td>8.879</td>
<td>6</td>
<td>56.419</td>
<td>10.724</td>
<td>67.143</td>
</tr>
<tr>
<td>Marketed gel</td>
<td>5.998</td>
<td>6</td>
<td>36.916</td>
<td>6.007</td>
<td>42.923</td>
</tr>
</tbody>
</table>

The anti inflammatory activity was measured by rat paw edema method using Plethysomometer and it was observed that Aceclofenac transferosomal gel showed maximum anti inflammatory action followed by liposomal gel.

Both the transferosomal and liposomal gel showed better anti-inflammatory action than marketed gel.

The analgesic activity was measured by Eddy's hot plate method and it was found that transferosomal gel has better analgesic action than marketed gel.

The rheological properties of gel formulation indicated a potential to withstand stress conditions of handling and packaging. The pH of the gel formulation was found to be compatible with the skin and the formulation was also found to be free of any toxic organic solvent.

The spreadability, gel strength and extrudability of the formulation were found to be satisfactory for ease of application.

It was found that statistically, there is no any significant difference found among the size, zeta potential and drug permeation profile from the batches at 0 month, 3 months and 6 months.

Conclusion

The prepared formulation of drug carriers incorporated in gel can be a novel approach for treatment of Arthritis through topical route through which the drug can permeate through skin and also show sustained release characteristics. The localized action of drug through novel drug carriers containing gel for prolonged period at the site of pain can provide more relief to patients as well as can reduce the side effects of drug associated with conventional oral route such as gastrointestinal disorders in particular dyspepsia, abdominal pain, nausea and diarrhea.

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