RESEARCH ARTICLE

Comparison Between Conventional Gel and Nanostructured Lipid Carrier Gel of Zaltoprofen: Preparation and *In-vitro*/*Ex-vivo* Evaluation

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ABSTRACT

This study aimed to compare conventional gel and loaded nanostructured lipid carrier gel of zaltoprofen (ZPF) to be administered topically for treatment of some inflammatory conditions like rheumatoid arthritis and osteoarthritis. ZPF-NLC dispersion was prepared by melt-emulsification and ultra-sonication technique, and the formula was composed of a 70:30 ratio of solid lipid (stearic acid) to liquid lipid (peppermint oil) in concentrations of surfactant (tween 80) and co-surfactant (PEG400) of 5% and 2.5% v/v respectively. Three different gelling agents were used to convert the ZPF-NLC dispersion into ZPF-NLC gel. Six NLC gels were prepared from different gelling agents: sepineo, carbopol 396, and carbapol 934 in different concentrations.

Many tests were done to select the optimum gel: determination of pH, spreadability, viscosity, and drug content in addition to the physical appearance assessment.

Many further tests were done for the optimum gel: particle size (PS), polydispersity (PI), and zeta potential (ZP) in addition to *in-vitro* release and *ex-vivo* permeation studies of this optimum gel compared with conventional gel. A kinetic release study was also done to determine the mechanism of release.

Among all the prepared formulas, formula 5 (F5) obtained from carbopol 934 as a gelling agent with a concentration of 1% is considered the optimum one. Its PS was in the nano-size range (209.2 ± 1.3 nm), and it was homogenously distributed (its poly-dispersible index was 0.231 ± 0.2), its pH was 6.38 ± 0.08, it showed good spredability of 6.3 ± 0.5 cm and viscosity of (51200 ± 2.6 at 50 rpm) with best drug content of 94.4 ± 0.2%. This gel showed good stability (its zeta potential equal to -41.32 ± 0.8 mV). Its *in-vitro* release profile showed prolonged release, and this would preserve drug concentration on the skin for about eight hours. It was significantly higher ($p < 0.05$) than that of the conventional gel. Its *ex-vivo* permeability study in rat skin showed drug permeation of about 3.16 times higher than that of the conventional gel.

Finally, The present study confirmed the potential of this technique for preparing the zaltoprofen as a topical gel showing the enhancement in its deposition in the skin compared to the conventional one.

Keywords: Nanostructure lipid carrier (NLC), pH Determination, Surfactants.

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INTRODUCTION

Nanostructure Lipid Carrier (NLC)

NLCs are colloidal carriers consisting of a solid and liquid lipids mixture as a hybrid structure of an average size of 40–1000 nm; it consists of a lipid matrix of a specialized nanostructure (Figure 1) established by Müller *et al.*[1] This specific kind of nanostructure aids in enhancing drug solubility, drug loading, and drug bioavailability. Also, NLCs are prepared using lipids with less ordered arrangements to give more drug loading of molecules in the matrix structure.[1,2]

MATERIALS FOR NLCs

The important ingredients for NLCs include lipids (liquid and solid), surfactant, co-surfactants, and water.

Lipids

Lipids are considered the main constituents of NLCs that affect drug loading ability, stability, and controlled release profile of the preparation.[3] They are essential ingredients in NLCs for building the inner cores. To overcome the problems associated with polymorphism and lipid crystallinity, a binary combination of two various lipid structures, a solid lipid, and a liquid lipid, was utilized to formulate NLCs.[4]

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A. Liquid Lipids or Oils

Digestible oils derived from natural sources are the most frequently used in NLCs preparation. These lipids are well accepted and established for human use. Most used oils are bio-compatible, and biodegradable.[5] Examples are soya bean oil, palm oil, peppermint oil, coconut oil, olive oil, almond oil, oleic acid, etc.

Solid Lipids

These are solid forms at room temperature. They will be melted in high temperatures (e.g. >80°C) during the formulation method.[6] These solid lipids are preferred to be biodegradable, well-tolerated, accepted for human use.[7] There are many solid lipids used in preparation of NLC, e.g., stearic acid, theobroma oil, palmitic acid, glyceryl monostearate, glyceryl behenate, and others. The most usually used one is stearic acid. It is mainly surface-active, especially food-active compound carrier; it is an endogenous saturated long-chain fatty acid. It is biocompatible with body fluid and human tissues and has lower toxicity than its synthesized counterparts.[8] E.g., surfactants are tween 20, 40, 80, Span 20, 80, Poloxamer 188, Poloxamer 407 and others.

Surfactants

There are substances that are adsorbed at interfaces and minimized the surface interfacial tension between two immiscible components or liquids. When used in small amounts, they improve colloidal activity and, therefore, stability by reducing the aggregation rate, so-called surface-active agents. The surfactant used should be non-irritating, biocompatible and cost-effective. Lipophilic or ampiphillic emulsifiers are widely used in NLCs fabrication.[4]

Co-surfactants

There are substances added to enhance drugs solubility by decreasing the interfacial tension to point below that of the surfactants. Because of the limited mobility of surfactants to cover the surface of nanoparticles during the recrystallization of solid lipids, there might be chances of increasing the particles size or aggregation. Stabilizers of ionic or non-ionic type will aid in the system stabilization due to creation of dynamic micelles that lead to lower the interfacial tension.[9] Some examples of co-surfactants are polyethylene glycol (PEG), butanol, butyric acid and others.

Topical Benefit of NLCs

Improvement Occlusion of Skin

The formation of oil film on skin surface and consequent occlusive action is stated for lipid molecules. By utilizing so fine oily molecules formed from low melting point and highly crystalline lipids, a superior occlusive effect is gained.[10]

Improvement Hydration and Elasticity of Skin

The decrease of trans-epidermal water loss resulted from the occlusive effect will cause an elevation of hydration the skin after topical applying of a NLC. Müller *et al.* noticed a pronounced elevation of dermal hydration by preparing the cream as NLC compared to conventional cream.[9]

Improvement the Dermal Permeation and Drug Targeting

The subcutaneous layer of normal skin contains about 20% of water content; this keeps an efficient wall from dermal permeation of different substances. Skin hydration after applying NLC results in a decrement of accumulation of corneocytes and an elevation in corneocytes' gaps' volume because of its dermal hydration ability. This will facilitate the dermal permeation and absorption of the drug into the deep skin layers.[11]

Improvement of Chemical Stability of Chemically Labile Compounds

Improvement in chemical stability after incorporation into lipid nano-carriers was proven for many cosmetic actives, e.g., Ascorbyl palmitate.[12]

Improve Benefit/Risk Ratio

Systemic side effects and skin atrophy resulting from usual prednicarbate cream application could be prevented if the drug is prepared as lipid nanoparticles. Predinicarbate absorption could be improved and collected in the desired site with a low concentration in the dermis.[9,13]

Zaltoprofen (ZPF)

Zaltoprofen, a propionic acid derivative related to the clinical class of (NSAIDs), possesses superior inhibition action to bradykinin than all other NSAIDs. It is a unique compound that also has inhibitory activity on bradykinin-induced nociception, whereas others (like Ibuprofen and diclofenac) are not efficient.[14]

It is prescribed to treat acute and chronic inflammation and used in arthritic conditions like rheumatoid arthritis, osteoarthritis, in addition, to relieve of post-operative pain and also in tooth extraction, injury, and treatment of acute upper respiratory infection.[15]

MATERIALS AND METHODS

Materials

Zaltoprofen was obtained as a gift sample from Shanaghai Research Institute of Chemical Industry Testing Co., Ltd, China. Peppermint oil was purchased from Reagent World, Inc. Ontario, USA. Stearic acid was purchased from Xinwang, China. Tween 80 was supplied from Hopkin & Williams LTD. Chandwell Heath. Essex. England. PEG 400 was supplied by Provizer Pharma, India. Albino rat weight: 250–300 g were obtained from animal house, College of pharmacy.

Methods

Preparation of Zaltoprofen Nanostructured Lipid Carrier (ZPF-NLC)

ZPF-loaded NLCs were produced by melt-emulsification and ultra-sonication techniques. This method shows superiority over other techniques, as it is considered the most cost-effective and less time-consuming technique for producing NLC formulations.[16]

Briefly, the lipid phase composed of the solid lipid and liquid lipid along with the drug (ZPF) was melted at 5°C above solid

lipid melting point with continuous stirring in a beaker on a hot plate magnetic stirrer. The aqueous phase was prepared by dissolving the surfactant and co-surfactant in distilled water. Both phases were heated up to 5°C above solid lipid melting point under magnetic stirring. Then the hot aqueous phase was added drop by drop to the melted oily phase in hot plate magnetic stirring at 600 rpm for 15 minutes and the primary emulsion was homogenized by probe-ultrasonic (ultrasonic processor UP200Ht hielscher, Germany) with amplitude of 80% pulses were maintained to 10 seconds, and the sonication was carried for 5 minutes. Ultimately, after homogenization, the resulting o/w nano-emulsion was cooled at 4 ± 0.5°C for 15–20 minutes by placing the container on an ice bath, then the ZPF-NLC dispersions were formed.[17,18] The NLC dispersions were lyophilized for long term stability, mannitol as a cryoprotector (5% w/v) was added. The samples were frozen at -78°C for 10 hours, followed by lyophilization for 36 hours. The lyophilized formulation was used for gel preparation. Table 1 showed the type and amount of constituent used in ZPF-NLC preparation.

Preparation of Zaltoprofen-Loaded NLC Based Gel

Different gelling agents were used to convert the NLC dispersion into the NLC gel: sepineo, carbopol 396, and carbapol 934. Six gel formulas were prepared from these gelling agents (Table 2). In brief, (1 or 2% w/v) of gelling agent (carbopol 934 or carbopol 396) was dispersed in distilled water and allowed to hydrate for 4 to 5 hours, glycerin (10% w/v) was added gradually into aqueous dispersion, 0.5% of methyl paraben was also added as a preservative. Lyophilized ZPF-NLC of the optimum formula powder equivalent to 1% w/v has been then incorporated into the gel and stirred at 1200 rpm for 2 hours.[19,20]

The dispersion was neutralized with few drops of triethanolamine (TEA), sufficient amount of water has been added for constructing final weight of gel up to 100% as was described in Table 3. While for gels prepared by gelling agent sepineo, about (1 or 2) % v/v of sepineo was dispersed in distilled water and left hydrate for 4 to 5 hours, and then 1% w/v of the lyophilized ZPF-NLC was incorporated into the gel and stirred at 1200 rpm for 2 hours (Table 4).[19,20]

The ZPF conventional gel was prepared in a way similar to the method of the optimum gel preparation but except dispersing the drug directly in the gel preparation (without being prepared as NLC dispersion). The purpose of the prepared conventional gel was to compare the result of the in-vitro release and ex-vivo permeation studies with optimum prepared ZPF-NLC gel because no marketed gel of zaltoprofen has been produced yet.

Evaluation of Zaltoprofen-loaded NLC Based Gel

Physical Appearance:

The ZPF-NLC gel formulations were examined visually for the color, appearance, consistency, and homogeneousness, in addition to the determination of pH, spreadability, and viscosity.

pH Determination

pH of the NLC gels was measured by a digital pH meter. One gram of every prepared gel was dispersed in 30 mL of the distilled water. pH value has been measured by getting the electrode near the formulation surface and permitting it to equilibrate for about one minute.[21] The measurements of pH of each formulation were done in triplicate.

Determination of Spreadability

The prepared gels' spreadability was determined after 24 hours from gel preparation by measuring the diameter of spreading of 1 gram of the gel that is located between 2 horizontal plates approximately (20 × 20 cm^2) after 1min. The standard weight that has been tied on the upper plate has been 220 grams. The spreadability has been estimated from the equation below:

$$\text{Spreadability} = M * L / T$$

Table 1: Material used in preparation of ZPF-NLC with their amounts

Material	*Amount*
Solid lipid (Stearic acid)	210 mg
Liquid lipid (Peppermint oil)	90 mg
Drug (Zaltoprofen)	80 mg
Surfactant (Tween 80)	5% (v/v)
Co-surfactant (PEG 400)	2.5% (v/v)
Distilled water	12 mL

Table 2: Formulas of ZPF- loaded NLC incorporated into gel

Formula no.	*Sepineo*	*Carbapol 396*	*Carbapol 934*
F1	1 %	–	–
F2	2%	–	–
F3	–	1%	–
F4	–	2%	–
F5	–	–	1 %
F6	–	–	2 %

Table 3: Formulation of ZPF-NLC gels by using carbapol 934 or carbapol 396 as gelling agents

No.	*Ingredients*	*Quantity*
1	Gelling agent (carbapol 396 or carbapol 934)	1 or 2 % w/v
2	Glycerin	10 % w/v
3	Methyl Paraben	0.5 % w/v
4	Lyophilized ZPF- NLC	1 % w/v
5	Triethanolamine (TEA)	Fewdrops (0.5%v/v)
6	Distilled water	Up to 100 mL

Table 4: Formulation of ZPF-NLC Gels by using sepineo as a gelling agent

No.	*Ingredients*	*Quantity*
1	Gelling agent (*sepineo*)	1 or 2 % v/v
2	Lyophilized ZPF- NLC	1 % w/v
3	Distilled water	Up to 100 ml

In which M represents the Weight tied to the upper slide (g), T represents the Time taken (s), and L represents the length of the glass slide (cm).[20]

Determination of Viscosity

Viscosity measurement of the prepared ZPF-NLC gels of different gelling agents was carried out using a spindle (no. 7). The viscosity of the gel (100 gram) was at a constant velocity that was 50 rpm.

Drug Content Estimation

Precisely weighed 1 gram of the ZPF-NLC gels transferred to 100 mL volumetric flask having 20 mL of the phosphate buffer pH 7.40. The volumetric flask was shaken for approximately 30 minutes, and the volume was completed to 100 mL with the phosphate buffer solution. After appropriate dilution, the content of ZPF was determined by UV-visible spectrophotometer at the λmax of the drug-using phosphate buffer pH 7.4 calibration curve.[19]

Measurement of Polydispersity (PS) and Polydispersity Index (PI)

The average PS and PI of the size distribution of the optimum ZPF-based gel was determined. The formula has been diluted 1:1000 with an aqueous phase to get suitable kilo counts per second (kcps). The analysis has been carried out at 25ºC with a 90º detection angle. Every one of the values that have been reported represents the average of three measurements.[21]

Measurement of Z-Potential (ZP)

ZP of the optimum NLCs gel was measured using the zetasizer. The dispersion was diluted as mentioned in the previous paragraph.[21]

In-vitro Drug Release for Zaltoprofen NLC Gel

The *in-vitro* drug release profile of ZAL-NLC gel and the conventional ZPF gel was done by Franz diffusion cell with a surface area of 3.14 cm^2. About 0.5 g of gel (equivalent to 5 mg of ZPF) was placed on the dialysis membrane of the donor compartment and fixed on it. The dialysis membrane (which has 2.4 nm pore size and a molecular weight cut-off from 12000 to 14000 Da) has been soaked overnight in the phosphate buffer pH 7.40. The receptor compartment was filled with the same buffer. The Franz diffusion cell was sited over a magnetic stirrer and stirred using the magnetic bar at 500 rpm. The temperature was kept constant at 32°C during the process. Sample of 1 mL was withdrawn at predetermined intervals of time (0.15, 0.3, 1, 2, 3, 4, 5, 6, 7, and 8 hours) and substituted by an equal volume of fresh phosphate buffer. After suitable dilution, samples have been examined for the concentration of the drug by the UV spectrophotometer at λmax of the drug, the release studies were carried out in triplicates.[22,23]

Kinetic Analysis of Drug Release

To determine the kinetics of drug release from the optimum NLC loaded gel, the results gained from in-vitro release studies was fitted to different kinetic models such as Zero-order model (percentage cumulative drug released versus time), First-order model (log percentage cumulative drug remained versus time), Higuchi diffusion model (percentage cumulative drug released versus square root of time), Hixon-Crowell model (cube root of percentage cumulative drug remaining versus time). The model with the highest correlation coefficient (R^2) is considered the best fitted one.[20,24] And Krosmeyer Peppas model (percentage cumulative drug released versus square root of time) and the (n) value, this model characterizes the release mechanism ($n < 0.45$ for Fickian transport and $n = 0.45–0.89$ for non-Fickian transport).[25]

Ex-Vivo Skin Permeation Studies

The skin of rodents (rats, guinea pigs, mice) is considered the most usually used skin in the ex-vivo permeation percutaneous study because of its small size, relatively low cost in addition to its availability. Among different rodents, the rat skin is the most similar to human skin structure; so, it is the most commonly used rodent model.[26]

1. Preparation of Rat's Skin for Permeation Study

After scarifying them, albino rats of 250–300 grams were used to take their skin for ZLP-NLC gel permeation study. The hairs were shaved from the abdominal area by an electric clipper. The excised skin was treated with isopropyl alcohol to remove the subcutaneous fat, and then it was washed with distilled water and checked for any likely damage during the removal.[27]

Permeation for ZPF-NLC Gel

The *ex-vivo* permeation studies of ZPF-NLC optimum gel and ZPF conventional gel were evaluated using Franz-diffusion apparatus with a 3.14 cm^2 diffusional area. The rat skin has been set between the donor and receptor chambers of the diffusion cell. The rat skin was adjusted with the stratum corneum layer facing the donor chamber and dermis-faced receptor chamber. The rest of the study was accomplished in the same way prescribed in the previous section of in-vitro release study. The cumulative amount of drug permeated per square cm of the skin was calculated and plotted versus time. The flux was calculated from the slope of linear part of the cumulative amount of the ZLP permeated per unit area (μg/cm^2) against a time per hour plot.[19]

Flux (μg/cm^2 h^{-1}) has been specified with the use of the equation (1):

$$J = \frac{Q}{(A \times t)} \qquad \text{eq. (1)}$$

Where, J = flux (μg/cm^2 h^{-1}), Q represents the quantity of the compound that traverses membrane in time (t), A= diffusion area (cm^2). The permeability coefficient (Kp) has been computed through dividing J by the value of the initial concentration of the drug in the donor cell (C_o) by applying the following formula, eq (2).[27]

$$Kp = \frac{J}{Co} \qquad \text{eq. (2)}$$

Statistical Analysis

To investigate the significance of difference between the results of studied formulations, the one-way analysis of variance (ANOVA) test was used by StatPlus in excel. The significance level was set at α 0.05, which was considered statistically

significant (P <0.05). All the results were illustrated as the mean values ±standard deviation (SD) in three replicates (n=3)

RESULTS

Preparation of Zaltoprofen-loaded NLC Based Gel

Three gelling agents were used to convert the NLC dispersion into gel: sepineo, carbopol 396, and carbapol 934. The preparation method and composition of different gel formulations was described previously in Tables 3 and 4.

Evaluation of ZPF-NLC Based Gel

Physical Appearance

The visual inspection of ZPF-NLC gels was found to be transparent. For the homogeneity, the prepared gels were examined visually, they appeared clear, smooth in texture, and no aggregations were seen for all the prepared ZPF-NLC gels.

Determination of pH

The pH of the prepared NLCs loaded gel was measured, and it was found to be between 6.02 ± 0.07 to 7.02 ± 0.03 that lies in the normal skin pH range (4.5–7) as shown in Table 5.

Determination of Spreadability

Spreadability was measured for all the prepared NLC gels (Table 5), it found to be between 3.8 ± 1 to 6.3 ± 0.5 cm for the optimized gel formula (F5), which indicates excellent spreadability as the large diameter signifies good spreadability

Determination of Viscosity

The viscosities of all gel preparation were determined and mentioned in Table 5. They were ranged from 43200 ± 1.5 to 57300 ± 2.2.

Determination of Drug Content

The drug content was measured for all the prepared NLC loaded gel formulations and represented in Table 5. It was found to be between 70.4 ± 0.3 to 94.4 ± 0.2, indicating good content of ZPF with the best drug content for F5.

Based on the compatibility with the NLC dispersion, esthetic appearance, and the ease of spreadability in addition to results of viscosity and drug content, carbapol 934 was selected as the best gelling agent, and the concentration of 1% w/v was the best, so F5 was chosen as the optimum prepared gel formula, and it was therefore subjected to more investigations.

Determination of Particle Size and Polydispersity Index

The PS and PI of the F5 gel (optimum gel formula) were found to be 209.2 ± 1.3 nm and 0.231 ± 0.2, respectively, as shown in Figure 2, indicated that the prepared gel was within the nano-size range and it was homogenously distributed.

Determination of Zeta-potential

The ZP of the optimum gel formula was found to be –41.32 ± 0.8 as shown in Figure 3, indicted the stability of the ZPF loaded NLC gel as the zeta potential value higher than -30 mV show good physical stability.[28]

In-Vitro Drug Release for Zaltoprofen NLC gel

The *in-vitro* release profile was done for the optimum gel formula and the conventional ZPF gel. The cumulative percent drug release from the ZPF-NLC loaded gel (F5) was much higher than that of the conventional gel in all the study period, as shown in Figure 4. This might be because of the NLC gel containing the drug-loaded lipid particles that concentrated on the skin and remained localized for that period.[19]

There was a significant difference (p < 0.05) between ZPF released from NLC gel and conventional gel. The study revealed a significantly higher release of ZPF from ZPF-NLCs

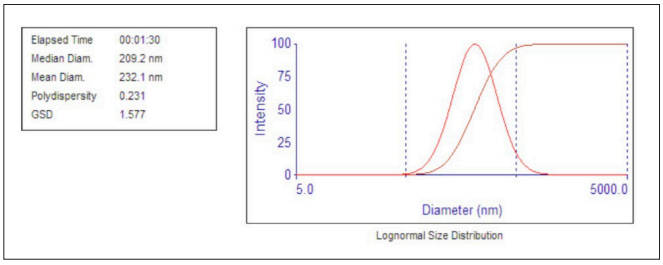

Figure 2: The PS and PI of the optimum gel (F5)

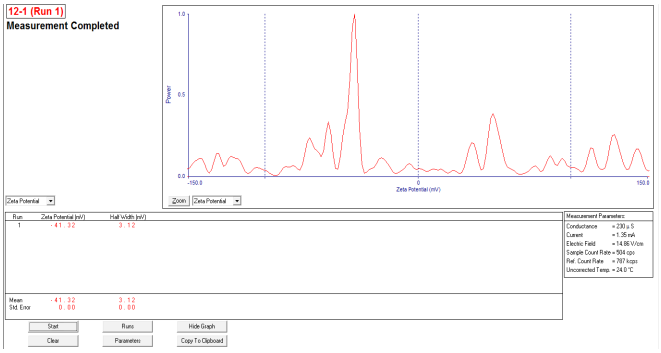

Figure 3: Zeta Potential of the optimum formula (F5)

Table 5: pH, spreadability, viscosity and % drug content of the different ZPF-NLCs based gel

Formula Number	*pH*	*Spreadability (cm)*	*Viscosity (cp)(50 rpm)*	*% Drug Content*
F1	6.54 ± 0.22	6.1 ± 0.5	43200 ± 1.5	88.3 ± 0.6
F2	6.02 ± 0.07	4.7 ± 1.5	46700 ± 2.1	92.4 ± 0.2
F3	7.02 ± 0.03	5.3 ± 0.5	53800 ± 1.3	70.4 ± 0.3
F4	6.63 ± 0.12	3.8 ± 1	57300 ± 2.2	82.4 ± 0.4
F5	6.38 ± 0.08	6.3 ± 0.5	51200 ± 2.6	94.4 ± 0.2
F6	7.01 ± 0.12	4.8 ± 0.5	53100 ± 1.8	86.4 ± 0.2

Each value represents the mean ± SD (n=3).

gel (84.3 ± 2.64%) than the conventional ZPF gel (36.8 ± 3.46%) at the end of the 8 hour. The result also agreed with the reports that the SLNs and NLCs improve the dermal localization of several topical therapeutic agents.[29]

One of the reasons to employ the NLC approach for topical delivery of the drug was to improve its dermal localization to reduce its systemic side effect and enhance the localized treatment of diseases. This was also noticed by Agrawal *et al.* in their study of methotrexate NLC preparation as topical delivery to minimize the toxic side effect of the drug on the patient of psoriasis.[30]

Kinetic Release of Optimum ZPF-NLC Gel

The release data for the optimum ZPF-NLC gel (F5) was fitted to the different kinetic models to compute the regression co-efficients (R^2) to determine the drug release mechanism. These kinetic models with their (R^2) values were shown in Table 6. The table clearly showed that the optimum gel followed Higuchi kinetics because it had the highest R^2 value (0.982).

The fundamental of diffusion, according to the model, was based on Fick's laws of diffusion that describes the transport of molecules by the concentration gradient, but in non-Fickian type, the drug release varies with time (t) according to the power law, which has been given in Table 7. The release of zaltoprofen from the optimum gel formulation had shown upper case II transport mechanism (Table 7) because n value was more than 1, this result was the same as was obtained by Nighojkar *et al.* in their study of formulation development of betamethasone-NLC enriched gel.[31]

Ex-Vivo Skin Permeation Studies

1. Preparation of Rat's Skin for Permeation Study

Skins of the abdominal area of healthy albino rats were obtained after scarifying them, and then the obtained skin was preserved in phosphate buffer pH 7.4 solution until use within few days.

2. Permeation for ZPF-NLC Gel

The *ex-vivo* drug penetration studies were performed for zaltoprofen NLC optimum gel and conventional gel (Figure 5). The cumulative amount of drug permeated through rat skin was 80.5 µg/mL from ZPF conventional gel compared to 400 µg/mL from ZPF-NLC gel in the first hour. At the end of the 8th hour, the amount of ZPF permeated from the conventional gel was only 980 µg/mL compared to 3100 µg/mL of drug permeated from the NLC gel, the drug permeated from the optimum gel was about 3.16 times higher than that of the conventional gel. The flux of the optimum gel was about six-folds more than of conventional gel. The diffusion parameters of both gels were summarized in (Table 8).

This enhancement of skin permeation in NLC gel was mainly due to the increased surface area and smaller particles (nanosize range) that would interface with skin corneocytes, more excellent skin occlusion characteristics, and superior hydration of the stratum corneum as compared with other dosage forms.[32] Besides, the lipid nanoparticles can deliver substances by interactions of the lipids used to prepare particles with the lipids of skin surface. Increasing the adhesiveness to the skin surfaces is a general characteristic of lipid nanoparticles that form an adhesive film leading to occlusion of particles to the skin's surface. In contrast, intact particles are generally unable to permeate the stratum corneum.[33]

Tween 80 used in the NLC as a surfactant, also had an important role, it may fluidize or loosen the stratum corneum

Table 6: The Regression Coefficients (R^2) of various release models for ZPF-NLC

F. code	*Zero order*	*First order*	*Higuchi*	*Hixon-Crowel*	*Korsmeyer-Peppas*	*Diffusion Exponent*
	(R^2)	(R^2)	(R^2)	(R^2)	(R^2)	*(n)*
F5	0.937	0.654	0.982	0.802	0.722	1.39

Table 7: Drug transport mechanism and diffusional exponents[31]

Diffusional exponent (n)	*Type of transport*	*Time-dependent*
0.5	Fickian diffusion	$t^{1/2}$
0.5 < n <1	Anomalous transport	t^{n-1}
1	Case II transport	Time independent
N >1	Super case II transport	t^{n-1}

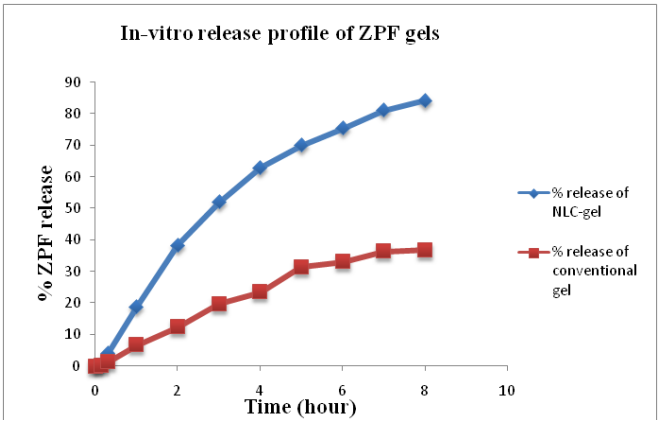

Figure 4: % Cumulative ZPF released profile from NLC gel and conventional gel

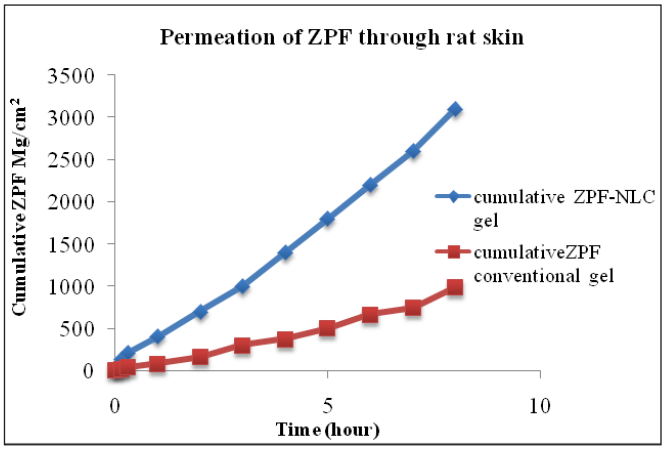

Figure 5: Comparative ex-vivo permeation study of ZPF-NLC gel and ZPF conventional gel

Table 8: Permeation parameters of ZPF NLC loaded gel and conventional gel at time 0.15 hours

Type of gel	*Flux ($\mu g/cm^2 h^{-1}$)*	*Kp (cm/h)*
ZPF-NLC	178.34	1.27
ZPF-conventional	25.85	1.27

lipid bilayer, thus leading to enhanced skin permeation.[34] The result of drug permeation from the prepared gel through the rat skin confirmed that zaltoprofen was highly permeated through the rat skin and could permeate through the human skin.

CONCLUSION

ZPF-NLC was successfully formulated by this technique as a topical gel to improve its permeation through the skin to avoid systemic side effects compared to conventional ones when treating special conditions like osteoarthritis and rheumatoid arthritis.

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