RESEARCH ARTICLE

Fabrication of Transdermal Gel Embedded with Solid Lipid Nanoparticles of Indomethacin

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ABSTRACT

Rheumatoid/osteoarthritis is one of the most common causes for lacking behind in the health sector. Medication in the form of tablets are already available in the market but has disadvantages. When these medicines are taken orally it cause heartburn and discomfort. The introduction of transdermal drug delivery is expected to solve this problem of side effects associated with oral delivery of drug. In the present study, indomethacin was loaded in solid lipid nanoparticles (SLN) which are then embedded in Carbopol gel for transdermal application. The solvent evaporation ultrasonication method was used for making SLNs.

The formulation was evaluated for various parameters such as; particle size and zeta potential of SLN using zetasizer as an instrument and gel formulations were evaluated for pH, spreading coefficient, viscosity, visual appearance and clarity.

Gel-embedded SLN formulation was found to be a potential transdermal drug delivery system for NSAIDs like indomethacin to treat ailments like rheumatoid arthritis or osteoarthritis.

Keywords: Nanoparticles, Rheumatoid arthritis, Solid lipid nanoparticles, Transdermal drug delivery system, Transdermal gel.

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INTRODUCTION

The non-invasive topical drug administration of drugs usually has higher patient compliance.[1] Indomethacin is widely used as a non-steroidal anti-inflammatory drug (NSAID) for treating rheumatoid arthritis and osteoarthritis.[2] Indomethacin has been widely used in the management of patients affected by rheumatic diseases and dermatitis. The risk associated with conventional oral use of indomethacin as an NSAID is the irritation and ulceration of the gastrointestinal mucosa.[3] The main challenge in topical delivery is to overcome the protective skin barriers. Recently, various novel delivery systems like polymeric nanoparticles, niosomes, liposomes and microemulsions have been used used for effective transdermal drug delivery systems (TDDS). Hence there was a need for novel TDDS for NSAIDs. Drug delivery through a transdermal route also prevents first pass metabolism.[1] Solid lipid nanoparticles (SLN) found popularity as novel TDDS among formulation scientists because its versatile nature and stability. The fine particle size of SLN is responsible for bio-adhesion to the stratum corneum thereby improving drug delivery to the skin.[4] In the current study, drug-loaded SLNs are incorporated into the transdermal gel to improve its efficacy. Those side effects could be minimized through site-specific drug delivery.

MATERIALS AND METHODS

Materials

Softisan -142 (Solid lipid) was provided as a gift sample by IOI oleochemical GmbH Germany. Tween 80 (Surfactant), acetone (Solvent 1), diethyl ether (Solvent 2), carbopol- 940 (Polymer) all of these were procured from Loba Chemie, Mumbai, Maharashtra, India. Triethanolamine (Buffer) was procured from Ultimate Chem India Pvt. Ltd, India. Indomethacin (Drug) was a kind gift from Joshi pharma company India. Other reagents were of analytical grade.

Method of Preparation of SLN

There are various methods for the formulation of drug loaded Solid Lipid Nanoparticles (SLN).[5,6] Solvent emulsification evaporation is a convenient and simple method of making SLN.[7,8] The drug was found poorly soluble in water but in organic solvent acetone, whereas the solid lipid was soluble in diethyl ether (organic). Hence, two different solvents were used for making indomethacin-loaded SLN through the technique of double solvent emulsification evaporation.[9] The solvents were selected based on the solubility of the drug and the solid lipid in it. Probe ultrasonicator Figure 1 was used for high shear agitation, which works on the Principle of ultrasound waves breaking the larger particles into smaller ones.[10] The

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Figure 1: Probe Sonicator.

Figure 2: Indomethacin-SLN loaded carbopol gel.

organic phase slowly added to the emulsifier (tween 80) solution along with ultrasonication. Evaporation of organic solvent was carried out overnight.

Formulation of Drug-Loaded SLN

The basic formula of drug-loaded colloidal SLN consists of three components besides the drug; the solid lipid, the emulsifier, and the aqueous phase (distilled water). To study its effect on particle size, nine formulations (F1-F9) were made with three different levels of emulsifier (Tween 80) concentration and time of sonication. Small quantities (1–2 mL) of organic solvents were used for each formulation.[11,12] The concentration of the drug in all nine formulations were kept constant. Table 1 indicates a combination of various ingredients and sonication time for all nine formulations.

Method of Preparation of Carbopol Gel

The weighted quantity of Carbopol-940 (1-g) was soaked in distilled water (100 mL) for 24 hours. The solution was covered

Figure 3: Diluted SLN Formulations.

Figure 4: ZetaSizer Instrument.

and stored in a dark room temperature around 25 + 2°C. After keeping the solution to form gel, remove any bubbles that were entrapped in the gel carefully.[13,14] After removing the bubbles, add propylene glycol (10 g) and isopropyl Alcohol (10 g). Triethanolamine (0.5 g) (TEA) was added to gel formulation to adjust its pH, dropwise[15] SLN colloidal suspension was incorporated into the gel Figure 2.

Dynamic Light Scattering (DLS)

Sample preparation was done before proceeding for DLS tests. Prepared formulations were kept in the beakers and subjected to a normal laser beam using laser presenter device. The presence of fine colloidal (particles) in the medium create Tyndall effect.[16] The nanoformulation suspension were diluted (20 times) with distilled water Figure 3. The laser beam was used to check if the nanoformulations were diluted enough until the laser light passed through without changing its color. Thereafter, DLS analysis was done to confirm particle size using Malvern zeta sizer instrument Figure 4. The diluted sample was added to square polystyrene disposable cuvettes (DTS0012) for measurement of particle size.[17]

Table 1: Formulation of drug loaded SLN (Drug; Indomethacin, Solid lipid; Softisan-142, Emulsifier; Tween 80)

Formulations	*DRUG (gm)*	*Solid lipid (gm)*	*Emulsifier (mL)*	*Distilled water (mL)*	*Time of sonification (min)*
F1	0.15	0.75	0.5	15	2
F2	0.15	0.75	1	15	2
F3	0.15	0.75	1.5	15	2
F4	0.15	0.75	0.5	15	4
F5	0.15	0.75	1	15	4
F6	0.15	0.75	1.5	15	4
F7	0.15	0.75	0.5	15	6
F8	0.15	0.75	1	15	6
F9	0.15	0.75	1.5	15	6

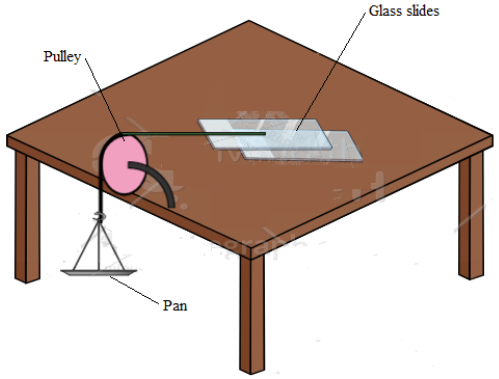

Figure 5: Spreadability test assembly.

Whereas DTS1070 were employed for the measurement of zeta potential.[18] The study was done at 25°C.

pH Determination

The pH was determined using a digital pH meter (Manti Lab). Calibration of the digital pH meter was done using a standard buffer. Sample was prepared by dissolving 1-gm of gel to make 10 mL of solution using distilled water. Digital pH meter was used to test pH of the sample.[19,20]

Viscosity Measurement of Gel

The viscosity of the obtained gel was checked & determined with the help of Brookfield viscometer (Fungi lab instrument). The prepared solution was put into a Nessler's cylinder and was analyzed at room temperature. Spindles L4 was used with 50 rpm for the viscosity measurement.[13]

Spread-Ability of Gel

The test was performed with the help of a setup using two glass slides and a paper pan with a capacity upto 50 gm of weight. A glass slide fixed to the tabletop, whereas another slide was placed above it and was attached to the weight. One end of the string is attached to the surface the top slide whereas other end string attached to the paper pan. The string passes over a small pully attached to the corner of tabletop.[15,20,21] The setup for the spreadability test is arranged as shown in the Figure 5. Then 1-gm of gel is sandwiched between the two slides. weight of 50 gm was added to the pan and the time taken for the top slide to slip smoothly without any hurdles was recorded. The spreadibility (S) of gel was calculated using the formula:

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

where, M = Weight used to pull the slide
L = Length of glass slides in cm
T =Time taken for gel to slide smoothly on two slides.

RESULT AND DISCUSSION

DLS

For the nanoformulations, the Z-Average particle size was found to be in the range of 117.5 to 155.9 nm, whereas polydispersity index (PDI) was in the range of 0.264 to 0.538. The small particle size (less than 1000 nm) confirm the formulation of nanoparticles. The small particle size below

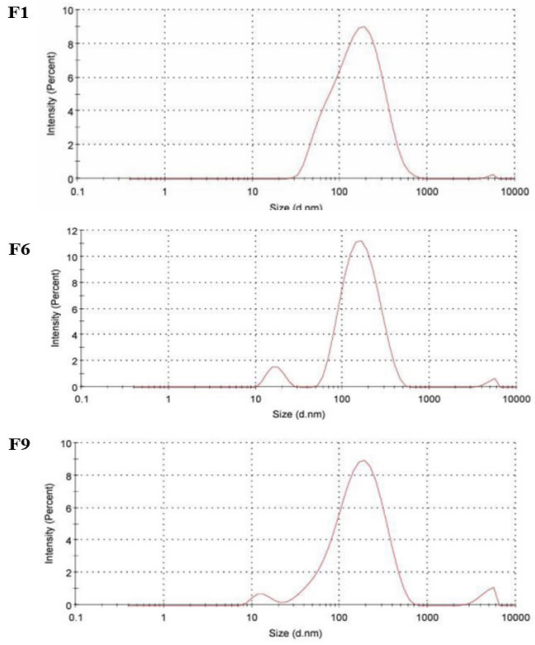

Figure 6: Particle size distribution of representative formulations.

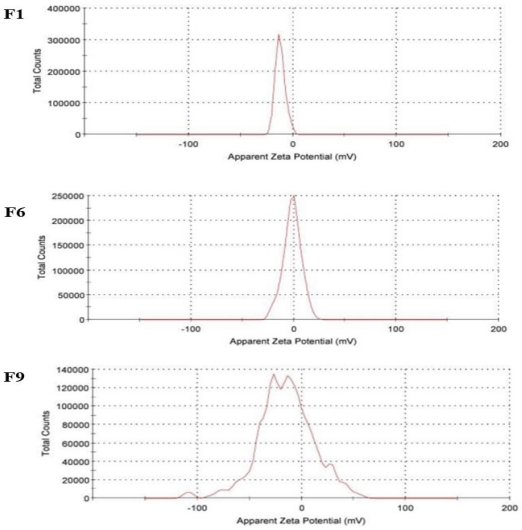

Figure 7: Zeta potential distribution of representative formulations.

200 nm is helpful for efficient drug delivery and permeation through gel structure. The small particle size help to keep the colloidal suspension stable because of the Brownian movement. Low PDI < 0.5 indicate the proximity of formulation toward monodispersed characteristic. Increase in time of sonication found to reduce particle size whereas it seldom shows effect on PDI. Figure 6 indicate the particle size distribution of representative formulations.

Zeta Potential

Zeta Potential for the nanoformulations was found to be in the range of -1.44 to -19.4 mV. High zeta potential stabilizes the colloidal suspension by keeping the particles apart through

electrostatic repulsion. Figure 7 indicates the potential zeta distribution of representative formulations.

pH Determination

The pH of all the formulations was checked with a digital pH meter and all the formulations were between the pH value of 5 to 6.8.

Viscosity of Gel

Average viscosity of the gel formulation was found to be 3011.6 ± 13.1 cP. Suitable viscosity is required for spreading of gel while using for topical application.

Spreadability of Gel

The average spreadability of all the gel embedded formulations was 5.95 ± 0.37. High spreadability indicate ease of application for topical use. At the same time, it should not be too high, otherwise it will flow and do not adhere at the site.

CONCLUSION

Indomethacin-loaded SLNs were prepared through ultrasonication solvent evaporation technique solvent. Nanoformulations were found in the acceptable size range 100-200 nm. SLNs were loaded in a carbopol gel. The drug-loaded SLN incorporated in a Carbopol gel could be a potential transdermal drug delivery system for NSAIDS.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHOR CREDIT

All authors contributed equally

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