Formulation and Evaluation of Nanostructured Lipid Carriers of Tretinoin for Topical Delivery

N. M. Patel, P. Prabhu, V. M. Ghate
Shree Devi College of Pharmacy

Purpose
Incorporation of the drug into nanostructured lipid carriers can dramatically alter the pharmacokinetic properties of a drug, targeting the drug to a particular organ and/or enhancing the efficacy of the encapsulated drug. Tretinoin is a retinoid being a derivative of vitamin A with anti-ageing, anti-acne properties. Data from the preliminary clinical trials and the available marketed products suggest that tretinoin is effective as a topical anti-ageing medicament. It is also reported to be effective in reducing the signs and symptoms of various types of skin ageing such as the photo ageing and premature ageing. Hence the present study is aimed at formulating the nanostructured lipid carriers of tretinoin with the aim of reducing the skin irritation potential, increasing the drug loading capacity and prolonging the duration of action.

Methods
Nanostructured lipid carriers of tretinoin were prepared by hot melt microemulsion and hot melt probe sonication based methods. The hot melt was prepared by heating the drug with a blend of solid and liquid lipids: stearic acid and oleic acid with and without cholesterol. The prepared hot melt was poured into the hot aqueous surfactant solution and subjected to rapid cooling in the case of microemulsion based method. The hot melt was poured into the aqueous surfactant solution and subjected to probe sonication to obtain the product in the case of sonication based method. All the formulations were optimized to get the best entrapment efficiency.

Results
The SEM photographs showed that the tretinoin NLC was spherical in shape. It was found that the average particle size was 762.1 nm. The surface charge was confirmed by the measurement of the zeta potential for the unsonicated NLC and was found to be -25.3 mV and that of the sonicated NLC was -28.4 mV. The PDI value remained approximately around 0.483, indicated good dispersion of uniformly sized NLC’s. All the formulations followed the Higuchi model drug release profile. The DSC thermograms for the drug and formulation indicated that the drug was in an amorphous form in the NLC. The FTIR spectral data showed no change in the signal peaks and thus indicated no interaction between the drug and the excipients. Stability studies indicated that the formulations stored at refrigeration temperature and room temperature showed no significant changes in the drug content and in vitro drug release, after a period of 4 weeks. ANOVA test for the % drug release showed that the formulations showed extremely significant difference (***p<0.001) in the values when compared with the marketed product. This indicated that the NLC are capable of releasing the drug over a longer duration. The ANOVA test for the % drug content showed a non significant value (p>0.05) in the sonicated formulation. This indicated that the sonicated NLC is effective in entrapping the added dosage of the drug. In vivo skin irritation test was conducted on male wister rats and the results indicated no irritation or erythema after the repeated application for a period of 7 days compared to the application of marketed tretinoin gel which showed irritation and slight erythema within 3 days. This showed that the irritation potential of tretinoin conventional formulations was reduced by the incorporation into the NLC.

Conclusion
Tretinoin is employed topically in treating skin ageing and photo-ageing. However, the topical use of the marketed gel formulations is hampered by various drawbacks including the irritation potential, short duration of action and inappropriate dose application. In the current work, an attempt was made to formulate and evaluate tretinoin NLC using a mixture of stearic acid and oleic acid. The NLC prepared by two different methods: hot melt microemulsion and the hot melt probe sonication method. The NLC were prepared with the use of a blend of solid and liquid lipid with a suitable emulsifier. The NLC formulations also were prepared by the incorporation of cholesterol. The two methods of preparation were found to be simple, economical and effective in terms of drug entrapment. These NLC were then dispersed in the carbopol gel and further evaluation was carried out. The sonicated NLC showed ex vivo skin permeation of 59.78% after 360 min which indicated the prolongation of the drug release. The in vivo skin irritation studies showed no irritation or erythema for a period of 7 days in comparison to the marketed gel which showed irritation and erythema in 3 days. The tretinoin NLC developed in this study have successfully reduced the irritation associated with the marketed gel formulation, with implications for longer duration of drug action. The present study showed lot of promise to scale up the method and to investigate further so that the said formulation can become commercially successful.