Enhanced Bioavailability of Exemestane Via Proliposomes based Transdermal Delivery

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ABSTRACT: Exemestane, a novel steroidal aromatase inactivator used in the treatment of advanced breast cancer has limited bioavailability (42%) due to poor solubility, extensive first-pass metabolism, and also the absorption is dependent on formulation type and food. The present study is aimed to evaluate the feasibility of proliposomes for transdermal delivery of exemestane. The prepared proliposomes were characterized for size, zeta potential, and entrapment efficiency. The size of the vesicles was found to be between 440 and 700 nm with high entrapment efficiency for the formulation containing greater amounts of phosphatidylcholine. Differential scanning calorimetry and Fourier transform infrared studies were performed to understand the phase transition behavior and mechanism for skin permeation, respectively. The drug release across cellophane membrane follows zero-order kinetics by diffusion. *Ex vivo* permeation enhancement assessed from flux, permeability coefficient, and enhancement ratio were significantly higher for proliposome gels compared with control. A significant improvement in the bioavailability (2.4-fold) was observed from optimized proliposome gel compared with control (oral suspension). The stability data reveal that the formulations are more stable when stored at 4°C. In conclusion, proliposomal gels offer potential and prove to be efficient carriers for improved and sustained transdermal delivery of exemestane. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:3208–3222, 2011

Keywords: proliposomes; cholesterol; liposomes; exemestane; stratum corneum; permeability; flux; transdermal; pharmacokinetics; bioavailability

INTRODUCTION

Transdermal drug delivery serves as a surrogate for oral route of administration to improve the bioavailability of drugs. Apart from avoidance of first-pass metabolism, the enormous surface area of the skin, easy administration, and termination of action make the transdermal route of delivery more attractive.[1] However, the major challenge in transdermal delivery is facilitating drug permeation across the skin impeding the barrier function of stratum corneum (SC), which is the rate-limiting step for absorption.[2]

Drug delivery systems using colloidal vesicular carriers such as liposomes, niosomes, ethosomes, transferosomes, elastic liposomes, and so on proved to have distinct improvement in transdermal delivery.[3,4] Among them, the liposomes have gained much interest and often been considered to be potential candidates for drug delivery. In spite of many advantages, the success rate of liposomes is limited because of significant problems in the general application of liposomes for drug delivery such as aggregation, sedimentation, phospholipid hydrolysis, and oxidation.[5,6] The proliposome concept introduced by Payne et al.[7] has resolved many of the stability issues pertaining to the liposome dispersions. Proliposomes, a semisolid liquid crystal (gel) product, composed of drug and lipid portion (lecithin and cholesterol) with minimum quantities of ethanol and water.[4] The formulation upon application onto the surface of skin get hydrated with water from skin under occlusion and renovate liposomes, which favor the drug delivery via the SC.[8,9]

Several mechanisms could be explained for the ability of liposomes to modulate the diffusion across skin. The fusion of vesicles on the surface of the skin can lead to the establishment of large concentration

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gradients of the intercalated drug across the skin and hence enhanced skin permeation.[10] Furthermore, the vesicle intercalation into the intercellular lipid layers of the skin might result in fluidization and disorganization of the regular skin structure and thus obviate the barrier function of SC.[3] However, the size and composition of vesicles,[11] nature of drug, and biophysical factors[10] are the important factors to be taken into consideration, which contribute for efficient vesicle–skin interaction.

Exemestane is a potent third generation steroidal aromatase inactivator used in the treatment of advanced breast cancer in postmenopausal women. The bioavailability of exemestane is limited to only 42% due to poor solubility and extensive first-pass metabolism and further the absorption is highly variable, which is dependent on formulation type and food.[12] The current oral therapy with exemestane pose problems such as unpredictable dissolution and absorption, poor patient compliance with common adverse effects such as body weight change, fatigue, dizziness, hot flushes, arthralgia, and myalgias.[13] Earlier, attempts were made to improve the oral bioavailability of exemestane from proliposome beads,[14] cyclodextrin inclusion complexes,[15] and self emulsifying drug delivery systems (SMEDDS).[16] As the physicochemical characteristics of exemestane (log p 3.5, low-molecular weight 296.41 g/mol) are similar to the ideal requirements of a candidate for transdermal drug delivery and further the transdermal application of exemestane has not been investigated so far, we have made an endeavor to formulate proliposome-based transdermal gels to improve the bioavailability and to maintain sustained drug levels with minimal fluctuations in plasma. Moreover, the site-specific application is also feasible for proliposomal gels so as to obtain high local concentration of exemestane near the vicinity of cancerous breast tissue and thereby risk of systemic side effects can be reduced.[17] Furthermore, if any untoward reactions occur, the termination of drug action is also equally possible by simple removal of the formulation. Therefore, the present systematic study encompasses the formulation *in vitro* and *ex vivo* characterization of exemestane proliposome gels. Furthermore, the pharmacokinetic study was carried out in albino Wistar rats to assess the feasibility of these systems for efficient transdermal delivery.

MATERIALS AND METHODS

Materials

Exemestane was a kind gift sample from Dr. Reddy's laboratories, Hyderabad, India. Soy phosphatidylcholine [(PC), Phospholipon 90G] was generously donated by Lipoid, Ludwigshafen, Germany. Cholesterol was obtained from E. Merck (Mumbai, Maharashtra, India). Stearylamine (SA) was procured from Sigma (St. Louis, Missouri). Dialysis membrane [DM-70; molecular weight cutoff (MWCO) 12,000 Da] was purchased from Himedia (Mumbai, Maharashtra, India). All other chemicals used were of analytical grade and solvents were of high-performance liquid chromatography (HPLC) grade. Freshly collected double distilled water was used all throughout the experiments.

Preparation of Proliposomes

The preparation of proliposomes was carried out by using the method reported elsewhere with slight modification.[18] Accurately weighed amounts of lipid mixture (1 mM) comprising of PC and cholesterol at various ratios (1:0, 2:1, 1.5:1, 1:1, and 1:1.5, respectively) were taken in a clean and dry, wide mouthed glass vial. The drug was added to the lipid mixture followed by the addition of 400 mg of absolute ethanol. After ensuring the homogenous dispersion of the ingredients, the vials were tightly sealed in order to prevent the evaporation of the solvent and warmed in a thermostatic water bath at 55°C–60°C for about 5 min with intermittent shaking until the ingredients were dissolved. To the resultant transparent solutions, about 160 μL double-distilled water maintained at the same temperature was added stream wise while warming in the water bath till a clear or translucent solution was obtained, which upon cooling formed a yellowish translucent liquid or yellowish translucent gel or a white creamy proliposomal gel. The obtained gels were stored in the same closed glass vials for overnight in dark for characterization. The positively charged vesicles were prepared by adding 100 μM of SA (10 mol % of total lipid) to the proliposome formulation comprising of PC and cholesterol in 2:1 ratio and processed as described above. The composition of different proliposomal formulations is represented in Table 1.

Formation and Morphological Evaluation

The formation and morphology of the liposomes were evaluated by optical microscopy. For the morphological evaluation, the proliposomal gels were hydrated with 7 mL of phosphate-buffered saline (pH 7.4), mixed gently, and final volume was adjusted to 10 mL with the same vehicle. The liposomes formed after hydration was observed at a magnification of 450× through an optical microscope (Coslabs micro, Ambala, Haryana, India).

For transmission electron microscopy (TEM) studies, a drop of the final liposome dispersion formed after hydration was placed onto a carbon-coated copper grid, forming a thin liquid film. The film on the grid was negatively stained by adding immediately a drop of sodium phosphotungstate solution (2%, w/v);

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