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ORIGINAL ARTICLE

Nanostructured lipid carriers for oral bioavailability enhancement of raloxifene: Design and *in vivo* study

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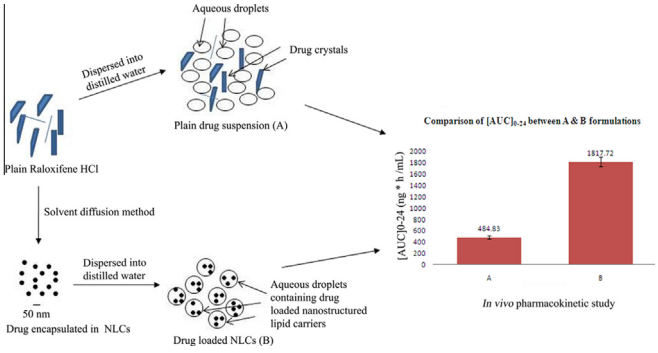
GRAPHICAL ABSTRACT



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ABSTRACT

The objective of present work was to utilize potential of nanostructured lipid carriers (NLCs) for improvement in oral bioavailability of raloxifene hydrochloride (RLX). RLX loaded NLCs were prepared by solvent diffusion method using glyceryl monostearate and Capmul MCM C8 as solid lipid and liquid lipid, respectively. A full 3^2 factorial design was utilized to study the effect of two independent parameters namely solid lipid to liquid lipid ratio and concentration of stabilizer on the entrapment efficiency of prepared NLCs. The statistical evaluation

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confirmed pronounced improvement in entrapment efficiency when liquid lipid content in the formulation increased from 5% w/w to 15% w/w. Solid-state characterization studies (DSC and XRD) in optimized formulation NLC-8 revealed transformation of RLX from crystalline to amorphous form. Optimized formulation showed 32.50 ± 5.12 nm average particle size and −12.8 ± 3.2 mV zeta potential that impart good stability of NLCs dispersion. *In vitro* release study showed burst release for initial 8 h followed by sustained release up to 36 h. TEM study confirmed smooth surface discrete spherical nano sized particles. To draw final conclusion, *in vivo* pharmacokinetic study was carried out that showed 3.75-fold enhancements in bioavailability with optimized NLCs formulation than plain drug suspension. These results showed potential of NLCs for significant improvement in oral bioavailability of poorly soluble RLX.

Introduction

The oral route is the most imperative route for administering varieties of drugs. It has been extensively used for both conventional and novel drug delivery systems. In spite of the wide success with some other routes for drug administration, the oral route is still most preferred route for its vast qualities.

Raloxifene hydrochloride (RLX) is a selective estrogen receptor modulator (SERM) with a proven estrogen agonist action on bone that leads to an improvement in bone mass [1] and a reduction in vertebral fractures [2]. RLX is poorly soluble drug as it belongs to class II category according to BCS classification. RLX has oral bioavailability of only 2% owing to extensive first pass metabolism. Therefore, it is necessary to increase the solubility and dissolution rate of RLX which lead to improvement in oral bioavailability [3].

Enhancement in oral bioavailability can be achieved by reducing the hepatic first pass metabolism. Such problem with conventional dosage form can be minimized by any suitable novel drug delivery system such as prodrug concept or by the use of novel lipid based system such as lipid nanoparticles, microemulsion [4] and Self emulsifying microemulsion drug delivery system [5].

Since last decade, various techniques have been studied to formulate nanoparticulate carrier systems [6]. Polymeric and solid lipid nanoparticles (SLNs) are two varieties of such nano carrier systems. Polymeric nanoparticles suffered with some drawbacks such as toxicity and unavailability of some good techniques for production of nanoparticles at large scale. Compared to polymeric nanoparticles, SLNs gain some advantages in terms of less toxicological risk because of natural origin lipids. Despite SLNs being good carriers, less capacity of drug loading and expulsion of the drug during storage may require to think of some good technique to overcome such problems. As an effect, nanostructured lipid carriers (NLCs) have been developed, which in some extent can avoid the aforementioned limitations. NLCs can be defined as a second generation of SLNs having solid lipid and liquid lipid (oil) matrix that create a less ordered or imperfect structure which helps in improving drug loading and decreasing the drug expulsion from the matrix during storage period [7,8]. In the present work, RLX loaded NLCs were developed by solvent diffusion method as this method has remarkable advantages such as use of simple equipment accessories, easiness in handling and quick manufacturing [9].

The aim of present research work was to develop stable RLX loaded NLCs formulation using solvent diffusion method and to evaluate *in vitro* characteristics and *in vivo* pharmacokinetic parameters of prepared formulation.

Material and methods

Materials

RLX was gifted from Aarti drugs Pvt Ltd, Mumbai, India. Dynasan 114 (Trimyristin) and Dynasan 118 (Tristearin) were gifted from Cremer Oleo GmbH & Co. KG, Germany. Glyceryl monostearate (GMS), Isopropyl myristate, oleic acid, polyvinyl alcohol (PVA) and stearic acid were purchased from Loba Chemie, Mumbai, India. Capmul MCM C8, Labrafil ICM 1944 CS and Labrafec CC were gifted from Abitec Corporation, Janesville, USA. All other reagents used in research work were of analytical grade.

Methods

Selection of solid lipid

Solid lipid was selected by checking the solubility of the drug in melted solid lipid by means of visible observation with the naked eyes under normal light [10–13]. Lipids used for this study were Dynasan 114, Dynasan 118, stearic acid and GMS. Weighed quantity of drug (50 mg) separately with various lipids (5 g each) was heated above the melting point of lipid in a temperature regulated water bath (Macro Scientific Work Pvt Ltd, Delhi, India) in 10 mL glass vials. After melting of lipid, the solubility of RLX in each lipid was observed visually under normal light [14,15].

Partition behavior of RLX in various solid lipids

Weighed quantity of drug (25 mg) was added into the blend of melted solid lipid (5 g) and hot water (5 g). Mixture was shaken on an isothermal orbital shaker (MSW-132, Macro Scientific Work Pvt Ltd, Delhi, India) at 70 ± 2.0 °C for 24 h to reach equilibrium followed by separation of aqueous phase through centrifugation at 5000 rpm for 5 min using cooling centrifuge (C-24 BL, Remi Instrument Pvt Ltd, Mumbai, India). Drug content was analyzed spectroscopically at 288 nm using UV visible spectrophotometer (UV-1800, Shimadzu, Japan) [13,16].

Selection of liquid lipid

Liquid lipid was selected based on the maximum solubility of the drug in different liquid lipids. Lipids used for this study