Journal of Drug Delivery Science and Technology 30 (2015) 232–241

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Research paper

Competence of raloxifene hydrochloride loaded liquisolid compacts for improved dissolution and intestinal permeation

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ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
15 October 2015
Accepted 31 October 2015
Available online 6 November 2015

Keywords:
Liquisolid compacts
Raloxifene HCl
Non-volatile liquids
Liquid retention potential
Dissolution
Ex-vivo permeation

ABSTRACT

The primary purpose of this research is to formulate raloxifene hydrochloride (RXH) loaded liquisolid compacts for improved dissolution behavior and intestinal permeation. Owing to their higher drug solubility, Cremophor® EL, Capmul PG-8 and Transcutol P were selected as suitable non-volatile liquid vehicles to develop desired formulations. The liquisolid formulations were obtained by allowing liquid vehicles with varying drug concentrations to get absorbed onto carrier and coating material taken at different ratios (R = 5; R = 10). Avicel PH 102 and Aerosil PH 200 displayed good liquid retention potential values confirming appropriate load factor and thus, resulting in liquisolid powders with good flow properties exemplifying their caliber as efficient solid carrier and coating materials in developing liquisolid compacts. FT-IR spectra illustrated no significant interaction between drug and carrier. The DSC and PXRD studies demonstrated the absence of crystalline form of drug in liquisolid powders. Further, the enhanced dissolution performance of RXH from liquisolid systems suggested the transformation of the drug to molecular/amorphous state. *Ex vivo* rat intestinal permeation studies revealed an improvement in drug absorption from formulation unraveling the ability of non-volatile liquid vehicles of liquisolid systems in enhancing the intestinal permeation of dissolution rate limited RXH.

1. Introduction

About 60% of pharmaceutical actives exhibits low systemic exposure upon oral ingestion owing to poor dissolution and/or limited absorption across the gastro intestinal membrane (BCS class II, III and IV drugs) [1]. In view of addressing these issues, formulation scientists focused on development of oral delivery systems to augment the rate and extent of absorption of hydrophobic therapeutic entities. Numerous traditional and modern approaches like eutectic mixtures, solid dispersions, molecular inclusion complexation, drug derivatization, micronization or nanonization, colloidal delivery systems, self emulsifying formulations, solid lipid nanoparticles etc were investigated to enhance dissolution quality of drugs [2–5]. Among them, one of the promising techniques to resolve the solubility concern is "liquisolid compacts", a derivative of 'powdered solution technology' that can be used for liquid medication. A non-volatile liquid with drug in a dissolved form is adsorbed onto the carrier and coating material to obtain free flowing powder with good compressibility property [6–9]. The carrier used in the liquisolid compacts should possess porous surface with high adsorption properties towards the liquid medication without hindering the micromeritics of powder. The coating material is used to cover the surface and impart flowability to the powder ensuring the content uniformity while manufacturing a tablet dosage form. In accordance, the quantities of carrier and coating materials are important as they can affect the dissolution behavior of the drug and can be calculated from the flowable liquid retention potential (Φ value) [10]. Based on the carrier to coat ratio (R), the load factor (Lf) which affect the micromeritic properties to the liquisolid powders were determined by using the following equation.

$$\mathbf{L_f = \Phi_{CA} + \Phi_{CO}(1/R)} \quad (1)$$

where Φ_{CA} and Φ_{CO} are the flowable liquid retention potential of the

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http://dx.doi.org/10.1016/j.jddst.2015.10.020
1773-2247/

carrier and coating material respectively

The Equation (2) helps to know the amount of carrier (Q) and can be applied in Equation (3) in order to calculate the required amount of coating material (q). In view of the final weight of liquisolid compact, the R value of 5 and 10 were used.

$$\mathbf{L_f = W/Q} \quad (2)$$

$$\mathbf{R = Q/q} \quad (3)$$

The liquisolid compacts containing insoluble drugs promote dissolution by promoting the wetting process which can improve the net effective surface area and thereupon an increase in the availability of drug for dissolution media. The selection of non-volatile solvent is a prime factor to be taken into consideration because the presentation of drug in solubilised state depends on the solvent capacity of the non-volatile liquid vehicle.

Osteoporosis in post menopausal women is the serious disorder around the world due to low mineral density in bone. Selective estrogen receptor modulator (SERM) class of drugs were considered as one of the most potential actives in maintaining osteoporosis and in prolonged hormonal replacement therapy in females [11]. On the other hand, the oral delivery of raloxifene HCl, an SERM class active, was inadequate owing to poor oral bioavailability (<2%) caused by low aqueous solubility (0.25 mg/L) [12]. Keeping this in view, the present research was focused to formulate liquisolid compacts using non-volatile liquid vehicles (Cremophor® EL, Capmul PG-8 and Transcutol P) to improve the dissolution characteristics of raloxifene HCl. Further, ex-vivo permeation study was carried to assess their potential on enhancing the permeation of raloxifene HCl across rat intestine.

2. Materials and methods

2.1. Materials

Raloxifene HCl was a kind gift sample from Aurobindo Pharma Limited, Hyderabad, India. Polyoxyl-35 castor oil (Cremophor® EL) and tween 80 were purchased from Merck, Mumbai, India. Transcutol-P (Diethylene glycol monoethyl ether) was generously donated by Gattefosse, France. Propylene glycol monocaprylate (Capmul PG-8), Glyceryl Mono-dicaprylate1,2,3-propanetriol decanoic acid monoester (Capmul-MCM) and Propylene glycol dicaprylocaprate (Captex-200) were gifted by Abitec corporations, Cleveland, USA. Microcrystalline cellulose (Avicel® PH102), Colloidal silicondioxide (Aerosil® PH200) and Crospovidone were procured from Dr. Reddy's Laboratories, Hyderabad, India. All the chemicals used were of analytical grade and freshly collected double distilled water was used all throughout the study.

2.2. Methods

2.2.1. HPLC analysis

The quantification of Raloxifene hydrochloride in all the samples of this study was performed by using a High performance liquid chromatography (HPLC) system (Shimadzu, Japan) equipped with LC-10 AT solvent delivery unit and SPD-10 AVP ultraviolet detector. A mobile phase composition of acetonitrile and water containing 0.25% (v/v) triethylamine at pH 3.9 (35:65 (v/v)) was allowed to pass through Licrospeher, Merck, C18 reverse phase stainless steel analytical column (250 × 4.6 mm, 5 μm) with a flow rate of 1.0 ml/min at room temperature. The column effluent was examined for UV absorption at 285 nm with detector sensitivity set at 0.005 AUFS.

2.2.2. Solubility studies

Since the selection of non-volatile solvent as a vehicle is an essential factor for liquisolid compacts, solubility studies were executed out to demonstrate the solubility of raloxifene hydrochloride in different nonvolatile solvents i.e. Cremophor® EL, Capmul PG-8, Capmul-MCM, Captex-200, Transcutol P and Propylene glycol (PG). The excess amount of drug was added to various vehicles until saturated solutions were obtained and agitated for 48 h by placing on the mechanical shaker (Remi equipments, India) at room temperature. Later, the samples were subjected to centrifugation and the supernatants were filtered by passing through membrane filters (Millipore, USA). The filtrates were suitably diluted with mobile phase and quantified for raloxifene HCl with aid of HPLC. This study was executed in triplicate.

2.2.3. Estimation of the liquid-retention potential (Φ-value) for Avicel® PH102 and Aerosil® PH200

The flow property of the powder admixtures was assessed by 'angle of slide' measurement [13]. Various liquid vehicles (Capmul PG-8 and Transcutol P) were added in increment to 10 g of the carrier (Avicel® PH102) or coating material (Aerosil® PH200) and mixed uniformly. The resultant liquid/powder admixtures were placed on polished metal plates and was gradually raised until the liquid/powder admixture was about to slide. The angle of slide (θ) formed between the plate and the horizontal surface was noted and the flowable liquid-retention potential (Φ-value) of each liquid/powder admixture was calculated with Equation (4), as described earlier [14].

$$\Phi - \text{value} = \text{weight of liquid/weight of solid} \quad (4)$$

The Φ-value at an angle of slide (33°) was interpolated from the plot of Φ-value vs corresponding θ which denotes the flowable liquid-retention potential of liquid/powder admixture.

2.2.4. Formulation of liquisolid compacts and conventional tablets

Based on the Φ values for carrier and coating material, the liquid load factor was calculated for drug concentrations (20% w/w and 30% w/w) in different liquid vehicles (Cremophor® EL, Capmul PG-8 and Transcutol P) with carrier to coat ratio (R) of 5 and 10 respectively and was represented in Table 1. Raloxifene HCl (30 mg/tablet) was dispersed in appropriate amount of liquid vehicle with continuous mixing to produce a homogenous liquid medication. The resultant liquid medication was uniformly blended with calculated amount of Avicel® PH102 (carrier) and thereby Aerosil® PH200 (coating material) was added to dry the wet mass. Finally, crospovidone, a superdisintegrant (5% w/w) (previously sifted through #40 mesh ASTM) was added to the powder mass and mixed in a polybag for 10 min and was compacted into tablets by a 16 station rotary tablet press machine (Cadmach, Ahmedabad, India) [10,15]. For comparison, conventional tablets (DCT) without any liquid vehicle were prepared by direct compression method.

2.2.5. Micromeritic properties of prepared liquisolid powders

The micromertic behavior of powders is essential in conferring the content uniformity of the drug in formulation. The values of Angle of repose, Carr's compressibility index along with Hausner's ratio were measured to evaluate the flow properties of liquisolid powders [16]. In order to estimate the angle of repose, a fixed funnel method was exercised. The Carr's compressibility index [17] and Hausner's ratio were calculated from the bulk and tapped density of the liquisolid powders [18].

2.2.6. Evaluation of raloxifene HCl liquisolid compacts and DCT

For uniformity of tablet weight, 20 tablets were randomly