



Preparation and impregnation of deep eutectic solvents containing zileuton onto adsorbents to elicit the biopharmaceutical attributes

Purushottam Gangane^a, Akshay Sahare^a, Sachin More^b, Amol Warokar^c, Maheshkumar Borkar^d, Pankaj Dangre^{e,f,*}

^a Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, MS, Nagpur, India

^b Department of Pharmacology, Dadasaheb Balpande College of Pharmacy, Besa, MS, Nagpur, India

^c Department of Pharmaceutical Chemistry, Dadasaheb Balpande College of Pharmacy, Besa, MS, Nagpur, India

^d Department of Pharmaceutical Chemistry, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Mumbai, Maharashtra 400056, India

^e Department of Pharmaceutics, Datta Meghe College of Pharmacy (DMIHER), MS, Wardha 442001, India

^f Department of Pharmaceutics, K K Wagh College of Pharmacy, MS, Nashik 442001, India

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ABSTRACT

Deep eutectic solvent (DES) is a contemporary and eco-friendly solvent recently exploited to modulate the solubility of drugs. Herein, we developed DESs for an increment of solubility and bioavailability of zileuton (ZLT). ZLT is an anti-inflammatory drug categorized as an inhibitor of the enzyme 5-lipoxygenase commonly prescribed for treating chronic bronchial asthma. However, its therapeutic uses are limited owing to its poor water solubility. Several stable DESs were developed and assessed for viscosity, pH, and solubility. The DES comprising ChCl: EG (1:3) exhibits an excellent ZLT solubility (57.27 ± 0.14 mg/mL). The molecular and electrostatic interaction was assessed through a conductor-like screening model for real solvents (COSMO-RS). Further, ¹H NMR analysis, FTIR, and digital microscopy were used to investigate the molecular transition in the chosen DES-ZLT. The DES in a liquid state possesses several drawbacks, such as instability, volatility, and dose precision. Therefore, a wet impregnation approach utilizing inert carriers such as Aerosil-200 and Avicel PH-102 was performed for the solidification of liquid DES. The solidified DES-ZLT was characterized by DSC and PXRD techniques and indicated the existence of ZLT in a highly dissolved state. Furthermore, solid DES-ZLT showed a significant increment in the dissolution studies, resulting in a 2.91 fold rise in oral bioavailability of ZLT. Hence, the presented study proves a well-organized and proficient development of a solid DES system to ameliorate the solubility and stability aspects of ZLT, which could provide the template for promising drugs that lack therapeutic effectiveness owing to solubility issues.

1. Introduction

Zileuton (ZLT) is chemically known as 1-(1-(Benzo[b]thiophen-2-yl)ethyl)-1-hydroxyurea. It is a 5-lipoxygenase (5-LOX) inhibitor. ZLT is mainly employed clinically to treat asthma; it prevents the production of downstream 5-LOX products. ZLT reduces the enzymatic activity of 5-LOX. Particularly, it inhibits leukotriene LTB₄, LTC₄, LTD₄, and LTE₄ formation [1]. ZLT is not only a selective inhibitor of 5-LOX; in an animal model of brain ischemia, it has also been shown to decrease 5-LOX expression [1–3]. Although ZLT has various therapeutic advantages, its use in clinical settings is limited due to its low oral bioavailability (22.1 %) [4]. A restricted solubility in water, slow dissolution rate, less

stability in the stomach, and oxidation sensitivity are all possible causes of limited bioavailability, resulting in decreased ZLT absorption [5,6].

Green solvents are becoming more popular for the solubilization of potential drugs due to their good safety, low degree of toxicity, and biodegradability [7]. Furthermore, green solvents might be an exciting method for green chemistry as a suitable vehicle for the solvation of hydrophobic drugs. These techniques place a premium on environmentally and economically sustainable solutions [8,9]. Deep eutectic solvents (DESs) can improve drug solubility and dissolution more effectively than ionic liquids (ILs), making them viable green solvent substitutes [10]. However, DES has certain drawbacks, including hygroscopicity, stability, high viscosity, and considerable volatility. These

* Corresponding author at: Department of Pharmaceutics, K K Wagh College of Pharmacy, Nashik, Maharashtra 442001, India.

E-mail address: pankaj_dangre@rediffmail.com (P. Dangre).

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