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Original Research Paper

Development and evaluation of lafutidine solid dispersion via hot melt extrusion: Investigating drug-polymer miscibility with advanced characterisation

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ABSTRACT

In current study, immediate release solid dispersion (SD) formulation of antiulcer drug lafutidine (LAFT) was developed using hot melt extrusion (HME) technique. Amphiphilic Soluplus® used as a primary solubilizing agent, with different concentrations of selected surfactants like PEG 400, Lutrol F127 (LF127), Lutrol F68 (LF68) were used to investigate their influence on formulations processing via HME. Prepared amorphous glassy solid dispersion was found to be thermodynamically and physicochemically stable. On the contrary, traces of crystalline LAFT not observed in the extrudates according to differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM) and Raman spectroscopy. Raman micro spectrometry had the lowest detection limit of LAFT crystals compared with XRD and DSC. Atomic Force microscopy (AFM) studies revealed drug-polymer molecular miscibility and surface interaction at micro level. 1H–COSY NMR spectroscopy confirmed miscibility and interaction between LAFT and Soluplus®, with chemical shift drifting and line broadening. MD simulation studies using computational modelling showed intermolecular interaction between molecules. Dissolution rate and solubility of LAFT was enhanced remarkably in developed SD systems. Optimized ratio of polymer and surfactants played crucial role in dissolution rate enhancement of LAFT SD. The obtained results suggested that developed LAFT has promising potential for oral delivery and might be an efficacious approach for enhancing the therapeutic potential of LAFT.

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1. Introduction

Pharmaceutical drug development research using hot melt extrusion (HME) has attracted increasing attention as novel strategy to produce delivery system with enhanced bioavailability as well as solubility of dissolution rate limited APIs [1–3]. This technology employs the application of high shear and high temperature to formulate drug-polymer molecularly dispersed systems, can be termed as solid dispersions (SD) or solid solutions [4]. HME is an industrially scalable continuous manufacturing technique without the necessities of additional drying or process fragments [5]. The distinctiveness of the procedural features allows the fabrication of various drug delivery systems. HME technology has many advantages over traditional processing techniques such as spray drying or co-evaporation, which involves organic solvents [6]. Homogeneous mono-phase systems with the drug molecularly dispersed in the polymer matrix, is challenging delivery, as such systems are intrinsically metastable [7]. The formation of melt extrusion involves the exchange of heat energy during HME process and followed by instant cooling of the melt which affects thermodynamic and kinetic properties of forming solid dispersion variance [8]. Use of highly water soluble carrier in solid dispersion always increases the chances of crystallization due to swelling behavior when comes in contact with the aqueous GI fluid [9]. Therefore, surface active agents or surfactants used as inhibitors for recrystallization. HME has the unique property to maintain the amorphous state of the drug after the formation of solid dispersion. Literature cited various methods for preparing amorphous solid dispersion such as melt method, solvent evaporation, cyclodextrin inclusion complex, cryo milling which explained the importance of solid dispersion type of formulation strategy [10].

Lafutidine (LAFT) a newly developed histamine H2-receptor antagonist, inhibits daytime (i.e., postprandial) as well as nighttime gastric acid secretion in clinical studies. It is practically insoluble in water and has low bioavailability. LAFT has a very low aqueous solubility, which impairs its dissolution in upper gastric fluid producing problems to prepared systems [11]. Overall, these characteristics hinder its therapeutic application by delaying the absorption rate and thereby onset of action or activity [12]. Together solubility, permeability and dissolution rate of a drug are essential factors for determining its oral bioavailability [13]. Literature reports generally revealed the fact that drug materials with a very low aqueous solubility will show dissolution rate limited absorption and hence poor bioavailability. Improvement of aqueous solubility in such a case is a valuable assignment to improve therapeutic efficacy [14]. However there is no literature on the enhancement of solubility of LAFT by hot melt extrusion method reported. Subsequently there is a need to deliver LAFT in formulation with increased solubility and improved dissolution profile.

For the current study we selected polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) a novel polymer with amphiphilic properties and explored its solubilizing potential using HME technology. Soluplus® has been especially developed for hot melt extrusion process. It offers exceptional capabilities for solubilization of BCS class II and class IV drugs, with the extensive possibility of making SD by hot-melt extrusion [15]. Its bulk density is low and has high molecular weight with excellent flow properties. The prime objective was to prepare stable SD systems of low T_g and water insoluble drug LAFT using an optimized ratio of drug-polymer-surfactant blends [16]. The next part involves physicochemical characterization using various analytical techniques to understand the drug–polymer molecular interactions. Six-month stability according to the ICH guideline studies was performed and supported by DSC, XRD, dissolution studies.

2. Materials and methods

2.1. Materials

LAFT was obtained as a generous gift from Alkem Laboratories Ltd., India. Soluplus®, a hydrophilic graft copolymer of polyvinyl caprolactam–polyvinyl acetate–polyethylene, Lutrol F127 and Lutrol F68 were kindly donated by BASF Corporation, Mumbai, India (Head office Ludwigshafen, Germany). PEG 400 of analytical grade was procured from Sd. Fine Chemicals, Mumbai, India. All other chemicals used were of analytical grade or equivalent quality.

2.2. Methods

Calculation of solubility parameter (δ), glass transition temperature (T_g) and Flory–Huggins parameter (χ).

As an indicator of the drug-polymer miscibility, values of δ were calculated using the Hoftyzer and vanKrevelen group contribution method described by the following Eq. [17].

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (1)$$

where,

$$\delta_d = \sum F_{di}/V,\ \delta_p = \left(\sum F_{pi}^2\right)^{1/2}/V,\ \delta_h = \left(\sum E_{hi}/V\right)^{1/2}$$

Here i is the groups within the molecule, δ is the total solubility parameter, δ_d is the contribution from dispersion forces, δ_p is the contribution from polar interactions, δ_H is the contribution of hydrogen bonding, F_{di} is the molar attraction constant due to molar dispersion forces, F_{pi} is the molar attraction constant due to molar polarization forces, E_{hi} is the hydrogen bonding energy and V is the molar volume. The solubility parameters of polymer and surfactant combinations were calculated using the following Eq.

$$\delta_{1,2} = Vf_1\delta_1 + Vf_2\delta\rho_2 \quad (2)$$

where Vf is the volume fraction of each compound.

Miscibility of the drug with the polymer can be assessed based upon the shift in melting endotherm or T_g of the drug or can be predicted theoretically using the Gordon–Taylor equation based on the T_g, densities, and weight fractions of the components.

$$T_{gmix\ (HME\ system)} = w_1T_{g1} + kw_2T_{g2}/w_1 + kw_2 \quad (3)$$

$$K \approx T_{g1}\rho_1/T_{g2}\rho_2 \quad (4)$$