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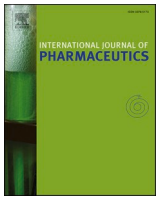

Strategies to improve the stability of amorphous solid dispersions in view of the hot melt extrusion (HME) method

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ABSTRACT

Oral administration of drugs is preferred over other routes for several reasons: it is non-invasive, easy to administer, and easy to store. However, drug formulation for oral administration is often hindered by the drug's poor solubility, which limits its bioavailability and reduces its commercial value. As a solution, amorphous solid dispersion (ASD) was introduced as a drug formulation method that improves drug solubility by changing the molecular structure of the drugs from crystalline to amorphous. The hot melt extrusion (HME) method is emerging in the pharmaceutical industry as an alternative to manufacture ASD. However, despite solving solubility issues, ASD also exposes the drug to a high risk of crystallisation, either during processing or storage. Formulating a successful oral administration drug using ASD requires optimisation of the formulation, polymers, and HME manufacturing processes applied. This review presents some important considerations in ASD formulation, including strategies to improve the stability of the final product using HME to allow more new drugs to be formulated using this method.

1. Introduction

Around 40 % of commercial drugs and 90 % of drugs currently being developed have poor water-soluble properties. As a result, the drugs are poorly absorbed when taken orally, leading to insufficient concentrations in the blood to generate effective drug effects (Ueda et al., 2018). (Ueda et al., 2018). The low solubility limits the dissolution rate of the drugs, ultimately limiting their bioavailability. In such situations, it is necessary to increase the drug dose to achieve the therapeutic concentration range, resulting in several clinical safety and commercial cost-effectiveness concerns. Altering the solubility of drugs in water is arguably the most significantly studied area in pharmaceutical science to address this problem. Several approaches have been proposed to solve this issue. Salt formation, prodrug formation, particle size reduction, complexation, micelles, microemulsions, nanoemulsions, nanosuspensions, solid-lipid nanoparticles, and solid dispersions are among the most successful methods in improving drug solubility (Vo et al., 2013).

The amorphous solid dispersion (ASD) technique has been applied to drug candidates to improve solubility. Chiou and Riegelman defined solid dispersion as "a solid state inert carrier or matrix containing one or more active pharmaceutical ingredient (API) dispersed and can be prepared via fusion, solvent or melting-solvent" (Chiou and Riegelman, 1971). The amorphous form of a drug represents a disorganised structure with a large free energy force, which increases the apparent water solubility, dissolution rate, and oral absorption (Zhang et al., 2012). The

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