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Original Research Paper

Development of amorphous dispersions of artemether with hydrophilic polymers via spray drying: Physicochemical and *in silico* studies

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ABSTRACT

Artemether (ARM) is a poorly water soluble and poorly permeable drug effective against acute and severe falciparum malaria, hence there is a strong need to improve its solubility. The objective of the study was to enhance the solubility and dissolution rate of ARM by preparation of solid dispersions using spray-drying technique. Solid dispersions of ARM were prepared with Soluplus, Kollidon VA 64, HPMC and Eudragit EPO at weight ratios of 1:1, 1:2, 1:3 using spray drying technology, and characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry (DSC), and X-ray powder diffraction (XRD) to identify the physicochemical interaction between drug and carrier, as well as effect on dissolution. The prepared solid dispersion of ARM with polymers showed reduced crystallinity as compared to neat ARM, which was confirmed by DSC and XRD. Drug/polymer interactions were studied *in-silico* by docking and molecular dynamics which indicated formation of van der Waals type of interactions of ARM with the polymers. Based on solubility studies, the optimum drug/Soluplus ratio was found to be 1:3. The dissolution studies of formulation SD3 showed highest drug release up to 82% compared to neat ARM giving only 20% at 60 minutes. The spray-dried products were free of crystalline ARM; possessed higher dissolution rates, and were stable over a period according to ICH guidelines. These findings suggest that an amorphous solid dispersion of ARM could be a viable option for enhancing the dissolution rate of ARM.

Abbreviations: ARM, artemether; SDs, solid dispersions.

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1. Introduction

Artemisinin is an important class of antimalarial drugs, structurally characterized by incidence of a sesquiterpene lactone with a peroxide bridge and is the active constituent of the Chinese medicinal herb *Artemisia annua* [1–3]. Different types of active metabolites of artemisinin have been synthesized, viz. artemether, artesunate, and arteether are currently in use or under clinical trials [4].

β-Artemether [5] is one of the artemisinin derivatives which has been proven to be effective against acute uncomplicated and severe falciparum malaria [6]. ARM is active against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. ARM is also indicated in the treatment of cerebral malaria. ARM, having the chemical structure as shown in Fig. 1, shows rapid onset of schizontocidal action and is metabolized in the liver to a demethylated derivative, dihydroartemisinin. However, the therapeutic potential of ARM is markedly delayed due to its low oral bioavailability. The low bioavailability of ARM results from its poor aqueous solubility [5], resulting in poor absorption upon oral administration. This is due to a large fraction of the drug that remained undissolved to reach absorption site. Under such conditions, the bioavailability can be increased by using a water-soluble formulation [6].

IUPAC name: [7]-[8a-beta,9-alpha,12-beta,12aR]-decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[9]-1,2-benzodioxepin.

Formulation scientists are working on different approaches to enhance the dissolution rate of poorly soluble drugs includes, solid dispersions prepared by spray-drying [7,8], freeze-drying [9], mechanical milling [10], hot melt extrusion [11,12], supercritical fluid extraction [13,14], co-crystal formation [15,16], inclusion complexation using cyclodextrins [17], microencapsulation [18], and particle size reduction [19,20]. However, most of these approaches face demerits of scale up issues or economic challenge.

Literature reports that solid dispersion [21] using water-soluble polymers showed good improvement in dissolution rate and bioavailability. Researchers have established various approaches for dissolution rate enhancement of ARM with PEG 6000 and PVP by solvent evaporation and lyophilization method [22], ARM with PEG 4000 and PVP K25 by freeze-drying and melt extrusion method [23], and ARM inclusion complexes with hydroxypropyl β-cyclodextrin [2] microencapsulation [18]. In addition, spray drying technology has also explored for solubility enhancement ARM using polyvinylpyrrolidone as a carrier [21], also by making microparticles of ARM [24] and using polyethylene glycol as hydrophilic polymer [25]. The ARM–Soluplus SD system has been developed using hot melt extrusion technology for improving the dissolution rate of ARM [5].

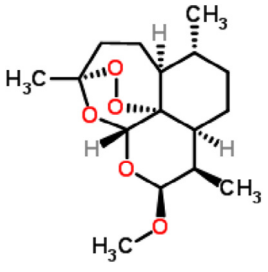

Fig. 1 – Chemical structure of ARM.

Spray drying is known to produce predominately-amorphous material due to the instantaneous transition between liquid and solid phases. In spray drying, the drug–polymer solution is atomized and dispersed into hot gas, which causes the solvent to evaporate and leads to the generation of spherical solid particles [26]. Spray drying is the most universally used industrial process as the product from spray drying process meets the highest quality standards with reference to the particle size, shape, homogeneity, and uniform distribution of products. Different types of particles can be produced by this technology [27,28]. The wide variety of processing parameters [25] makes it a powerful technique to tune the physical state [29] and the particle morphology of pharmaceutical systems [30].

The present study aims to elucidate the potential of enhancing the solubility and dissolution rate of ARM using hydrophilic polymers like Soluplus, Kollidon VA 64, HPMC and Eudragit EPO by spray-drying technology. Kollidon VA 64 is a water-soluble vinylpyrrolidone–vinyl acetate copolymer. Low viscosity HPMC is an odorless and tasteless, white or creamy-white fibrous or granular powder. It is partly O-methylated and O-cellulose [31]. Soluplus is a polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, a new polymer with amphiphilic properties [5]. Eudragit EPO is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate. It is a white powder with a characteristic amine-like odor.

The chemical interaction of ARM with the polymers triggering enhancement in solubility of ARM was simulated *in silico* by means of docking and molecular dynamics [18]. The docking analysis mimics the drug binding to proteins to understand the interactions occurring at the molecular level. This approach has found relevant applications in material science, particularly in the area of drug–polymer interactions [32]. Some authors have exploited *in silico* studies to predict and rationalize the design of drug delivery systems as well [33–35]. In the present study, we attempted to study the interactions between ARM and the respective polymers viz. Soluplus, Kollidon VA 64, HPMC and Eudragit EPO by combining docking and molecular dynamics study [18]. The analysis of the molecular phenomena involved in the recognition capability of polymeric complex represents clearly an intricate but fascinating research topic, which has been implicated from the results.

In the present study, we attempted to simulate the interactions between ARM and the respective hydrophilic polymers combining several computational techniques. In particular, the polymers were simulated as functional oligomers simplifying the whole composition and structures and therefore maintaining the recognition properties.

ARM solid dispersions were prepared by spray drying technology from various ratios of Soluplus, Kollidon VA 64, HPMC and Eudragit EPO as hydrophilic polymeric carriers. Furthermore, the study undertakes to investigate solid-state characterization using differential scanning calorimetry (DSC),