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Original Research Paper

Exploring the potential of porous silicas as a carrier system for dissolution rate enhancement of artemether

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ABSTRACT

Malaria is a parasitic and vector determined blood-conceived infectious disease transmitted through infected mosquitoes. Anti-malarial drug resistance is a major health problem, which hinders the control of malaria. A Results of a survey of drug-resistant malaria demonstrated safe proclivity to nearby all anti-malarial regimes accessible except from artemisinin and its derivatives. Artemether is a BCS class IV drug effective against acute and severe falciparum malaria; hence there is a strong need to improve its solubility. Silica is one of the most widely studied excipients. Silica can be used in solubility enhancement by preparing its solid solution/dispersion with the drug. The objective of this research was to improve dissolution rate of Artemether using non-precipitated porous silica (Aeroperl 300 Pharma) and precipitated silica like EXP. 9555, EXP. 9560, and EXP. 9565. Specific surface area calculated from BET method of porous silicas viz. APL 300 (A), Exp. 9555 (B), Exp. 9560 (C), Exp. 9565 (D) was found to be 294.13 m^2/g (A), 256.02 m^2/g (B), 213.62 m^2/g (C) and 207.22 m^2/g (D) respectively.The drug release from the developed formulation was found to be significantly higher as compared to neat ARM. This improved solubility and release kinetics of ARM may be attributed to high surface area, improved wettability and decreased crystallinity. Solid-state characterization of the developed optimized formulation F3 was carried out with respect to FTIR chemical imaging, XRD, SEM, and DSC. All the porous silicas which we have explored in the present context showed a significant capability as a carrier for solubility enhancement of ARM.

Abbreviations: ARM, Artemether; PS, porous silica; ARM:PS system, artemether:porous silica system.

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1. Introduction

Drugs with poor aqueous solubility have low or erratic absorption and, subsequently poor bioavailability [1]. Some of the drugs that belong to class IV of the biopharmaceutical classification system are characterized by poor permeability and low aqueous solubility [2,3]. Current statistics report that because of the low aqueous solubility, up to 40% of new chemical entities fail to reach the market despite revealing potential pharmacodynamic activities.

Many potential compounds often drop out on the way of pharmaceutical development because of their insufficient oral bioavailability. Consequently, a lot of efforts have been made to increase dissolution rate of such drugs. Different approaches to enhance the dissolution rate of poorly soluble drugs include solid dispersions prepared by spray-drying [4–6], freeze-drying [7], mechanical milling [8,9], hot melt extrusion [10,11], supercritical fluid precipitation [12,13], co-crystal formation [14], inclusion complexes using cyclodextrins [15], liquid antisolvent precipitation [16], loading onto porous carriers [17], amorphous solid dispersions by hot melt extrusion [18]. However, most of these technologies face demerits of scale up issue and economic challenge.

Malaria is a parasitic and vector determined blood-conceived infectious disease transmitted through infected mosquitoes. Anti-malarial drug resistance is a major health problem, which hinders the control of malaria. Results of a survey of drug-resistant malaria demonstrated safe proclivity to nearby all anti-malarial regimes accessible except from artemisinin and its derivatives. Artemisinin is an important type of antimalarial drug, structurally characterized by incidence of a sesquiterpene lactone with a peroxide bridge [19,20]. Different types of artemisinin derivatives have been synthesized viz. artemether, artesunate, arteether, which are currently in use [21].

Artemether [ARM] (chemical structure as shown in Fig. 1) is a potent antimalarial agent accessible for the treatment of severe multiresistant malaria and is included in the WHO list of essential medicines. It is active against *Plasmodium vivax* as well as chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. ARM shows rapid onset of schizontocidal action and is metabolized in the liver to a demethylated derivative, dihydroartemisinin, which is indicated in the treatment of cerebral malaria. However, the therapeutic potential of ARM is significantly delayed due to its low oral bioavailability because of its poor aqueous solubility [22,23].

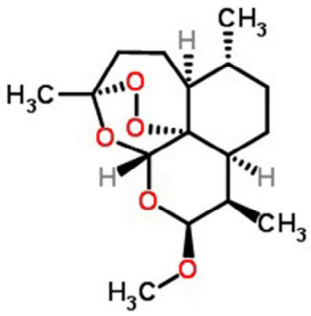

Fig. 1 – Chemical structure of ARM.

Solvent evaporation method involves preparation of a solution containing both carrier material and drug, and the removal of the solvent resulting in the formation of the solid powder mass. Preparation of SDs using solvent evaporation has been successfully explored for the dissolution rate enhancement of poorly water-soluble drugs [24–26]. In present study, the potential of various porous silica to improve the dissolution of ARM has been studied. Silica is one of the most widely studied excipients. It exists in amorphous to highly ordered crystalline states. Silica is generally regarded as safe [27]. The amorphous silica has many applications in pharmaceutics and drug delivery such as glidant (flow promoter), carrier, thickener and viscosity modifier, adsorbent and preservative. Various reports are available in the literature implementing its use in solubility enhancement by preparing its solid solution/dispersion with the drug. For example solid dispersion formulations using porous silicas [24,25] and bicalcutamide using Aeroperl 300 (APL300) [28].

In this context, we have explored the use of porous silicas like non-precipitated silica as APL 300 and precipitated porous silicas viz. EXP. 9555, EXP. 9560, EXP. 9565 as a carrier and adsorbent to formulate ARM:PS systems. All porous silicas had an inert amorphous material consisting of colloidal silicon dioxide with a significantly high pore volume and consistent spherical shape. Silica exists in amorphous to highly ordered crystalline states. It also has excellent flow and compressibility properties. Porous silicas in the ARM:PS system can potentially resolve formulation issues associated with solid dispersions. In addition, porous silicas are less likely to promote reversion of amorphous drug to crystalline state on storage of solid dispersion due to its non-crystalline nature [28,29]. Solid dispersion prepared using hydrophilic excipients often face softness and tackiness issues. To overcome such issues the use of large amount of excipients is reported [30,31]. The use of such excipients at higher amount often resulted into large tablet weights, which is not acceptable practically. Hence, in this research work we have explored different types of porous silicas as a carrier system for dissolution rate enhancement of poorly water-soluble drugs. ARM loading into porous silica by solvent evaporation method was explored at various ratios. Molecular state of drug in the prepared samples was evaluated using differential scanning calorimetry and powder X-ray diffractometry. Surface morphology study was carried out using scanning electron microscopy. The apparent solubility and dissolution behavior of ARM:PS systems were evaluated further.

2. Materials and methods

2.1. *Materials*

Artemether was obtained as a generous gift from IPCA Pvt. Ltd. Mumbai, India. Aeroperl 300 pharma and other porous silicas viz. EXP. 9555, EXP. 9560, EXP. 9565 were obtained from Evonik Industries, Germany. Hard gelatin capsules IP were obtained as a gift sample from ACG Associated Capsules Pvt. Ltd. India. All other chemicals and solvents used were of analytical grade and were procured from Merck India Ltd. All the materials were used as received.