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Microwave processed solid dispersions for enhanced dissolution of gemfibrozil using non-ordered mesoporous silica

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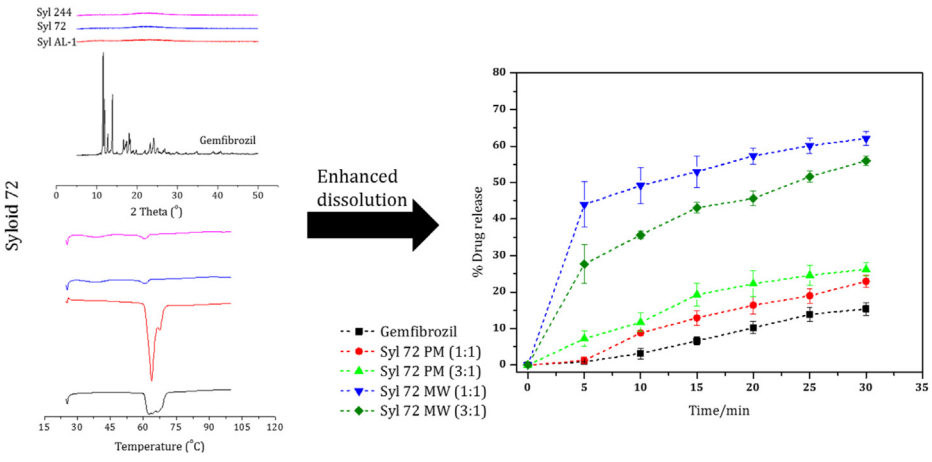
HIGHLIGHTS

- Microwave heating has shown promise in solid dispersion formulation using melt method.
- Non-ordered mesoporous silica carriers have the ability to enhance the dissolution rate of poorly soluble drug like gemfibrozil.
- Mesoporous silica pore volume and surface area play a key role in drug loading and subsequent release from the carrier system.
- Transformation of crystalline to amorphous form of drug was confirmed by X-ray diffraction and differential scanning calorimetry.
- Syloid-72 silica showed highest enhancement of drug dissolution as compared with Syloid Al-1 and 244 silica.

GRAPHICAL ABSTRACT



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ABSTRACT

This study describes the application of three non-ordered mesoporous silicas (Syloid AL-1, Syloid 72 and Syloid 244) in improving the dissolution rate of a poorly aqueous soluble drug, namely gemfibrozil. For this purpose, solid dispersions were formulated using a robust and controlled microwave heating method. Prepared formulations were subjected to solid state characterisation and dissolution behaviour. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) results confirmed that microwave heating method incorporated gemfibrozil in an amorphous form in Syloid 72 and Syloid 244. This was attributed to a large pore volume and diameter compared with Syloid AL-1 which has a small pore volume. Presence of more crystalline drug in the case of Syloid AL-1 based formulations was attributed to larger surface area where drug was adsorbed in layers as confirmed by the scanning electron microscopy. DSC and XRD results also confirmed stability of formulations when stored for 3 months under stressed conditions (40 °C and 75% RH). FT-IR results show lack of interaction between silica and the drug in all cases. It was also noted that all three silica types improved the dissolution behaviour of gemfibrozil when compared with dissolution properties of pure

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drug. The surface properties of Syloid 72 were found optimum as it enhanced the rate of dissolution of gemfibrozil from microwave processed formulation far better than physically mixed formulations and those prepared with Syloid AL-1 and Syloid 244.

1. Introduction

Most of the new chemical entities with potential pharmacological effects show limited physicochemical (aqueous solubility and stability) and biopharmaceutical (dissolution rate and permeability) properties which significantly limit their oral bioavailability [1]. Since crystalline structures have high lattice energy, any method that can reduce this energy by creating less ordered or amorphous structures will aid in enhancing the solubility and ultimately dissolution profile of poorly soluble compounds [2]. Formation of amorphous structures involve various techniques including hydrotropy, cyclodextrin complexation, micellar solubilisation, pH modification, solid dispersions, nanosuspensions, spherical crystallisation, and some other techniques [3–5]. These modalities have certain benefits and limitations, and yet there is no universal solution because of varying physicochemical properties of APIs. In recent years, porous materials such as mesoporous silica have gained considerable attention in enhancing the dissolution rate of poorly soluble compounds [6–8]. These highly porous and sophisticated forms of silica have a meso-scaled pore size that is ranged from 2 to 50 nm [9]. These porous silicas are available in various ordered [10–12] and non-ordered forms [13–16]. Both types of mesoporous silica materials are routinely used as potential carriers for various active pharmaceutical ingrediants. The surface chemistry of ordered and non-ordered silica is similar, consisting of siloxane groups (—Si—O—Si—), with the oxygen on the surface, and of three forms of silanol groups (—Si—OH) [17,18]. However, ordered silica has honeycomb like uni-directional and uniform pore structure as compared with non-ordered silica [7,17,19].

Mesoporous materials have different surface chemistries in term of pore size, volume and surface area. These interesting properties can be exploited for effective drug loading and tuning the release rate of loaded drugs [20]. In addition to that, method by which drug is loaded into mesoporous materials also influences the release behaviour. Drug loading is usually done by impregnation technique in which either silica is immersed in concentrated drug solution or drug solution is added drop-wise to silica followed by its removal by evaporation. However, this technique has several downfalls such as low drug loading due to competition between drug affinity to solvent and the porous material, and residual solvent removal from the formulations which may lead to recrystallisation or degradation of actives within porous material [12]. One common approach to replace wet methods is heating the drug to its molten form in the presence of excipient, which has proved to be superior over conventional loading methods [21]. Heating source also has some effects on the performance of solid dispersions [22]. Previously, we reported successful inclusion of fenofibrate in a series of ordered/non-ordered silica through the application of novel microwave heating methods [13]. The results confirmed the remarkable enhancement in the extent of dissolution of fenofibrate from silica based solid dispersions. This approach worked well for fenofibrate but warrants further investigation to make full use of the microwave technique to develop mesoporous silica based formulations.

Herein, we report the effect of the silica's properties (Table 1) along with the microwave method of formulation on the release rate of a poorly water soluble drug, namely gemfibrozil (Fig. 1).

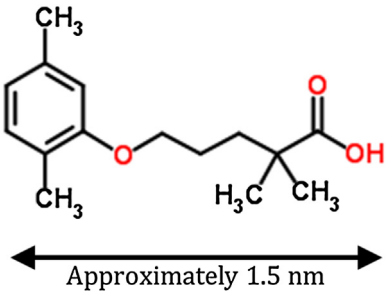

Fig. 1. Structure of gemfibrozil.

Gemfibrozil effectively decreases serum triglycerides and very low density lipoproteins-cholesterol (VLDL) and increases high-density lipoprotein-cholesterol (HDL), thus acts as a lipid regulating agent [23–25]. Microwave assisted solid dispersions of gemfibrozil with three types of silica were formulated. The formulations were characterised for their solid state properties using a combination of techniques including differential scanning calorimetry (DSC), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), and scanning electron microscopy (SEM). This was followed by evaluating release behaviour of the formulations in an acidic dissolution medium.

2. Material and methods

Syloid® silica excipients were received as a gift samples from W.R. Grace & Co., (St. Neots, UK). Gemfibrozil was purchased from Sigma-Aldrich (Dorset, UK). Sodium lauryl sulphate was sourced from Sigma-Aldrich (Dorset, UK) with a minimum purity of 99%. De-ionised water was used throughout the experiments.

2.1. Physical mixtures of silica and gemfibrozil

Gemfibrozil was tumble mixed with three Syloid silica samples (from here onwards, Syloid silica will be abbreviated as Syl AL-1, Syl 72 and Syl 244) at 1:1 and 3:1 silica to drug mass ratios for 5 min until a homogenous mixture was achieved. Sample were then stored in an air tight container until further investigations.

2.2. Single-mode microwave processed solid dispersions

Microwave processed solid dispersions were prepared according to previously described method [22,26]. Briefly, 500 mg of each physically mixed sample of gemfibrozil with three silica at two different silica to drug ratios was placed in an alumina crucible in the bespoke microwave heating system with the fibre optic probe positioned directly in the sample. Microwave heating system was operated and controlled by the software. The software was programmed to continuously modify the microwave power such that the sample was heated slightly above the melting temperature of the drug, maintained isothermally for 20 min and then cooled to room temperature, after which the sample was removed and stored in air tight containers until further investigations.