European Journal of Pharmaceutics and Biopharmaceutics 84 (2013) 555–565

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Stabilisation of amorphous drugs under high humidity using pharmaceutical thin films

Yuen Chuen Ng [a], Ziyi Yang [a], William James McAuley [b], Sheng Qi [a,*]

[a] School of Pharmacy, University of East Anglia, Norwich, UK
[b] Department of Pharmacy, University of Hertfordshire, Hatfield, UK

ARTICLE INFO

Article history:
Received 31 October 2012
Accepted in revised form 14 January 2013
Available online 9 February 2013

Keywords:
Amorphous
Crystallization
Phase separation
Solid dispersions
Polymer coating
Stabilisation
Pharmaceutical thin films

ABSTRACT

In this study, the stabilization effects of three polymers on four model drugs (felodipine, fenofibrate, carbamazepine, and celecoxib) under saturated humidity were investigated. Three different types of thin films (solid dispersions, drug films with a polymer film coating and drug films laid on top of polymer coated surfaces) were prepared and compared with films containing the drug alone. ATR-FTIR spectroscopy, polarised light microscopy (PLM), scanning electron microscopy (SEM) and nano-thermal analysis (nano-TA) were performed on the model systems after storage under saturated humidity. The recrystallisation tendency of the drug in the drug containing thin films was found to be strongly related to the intrinsic crystallization tendency of the drug film alone and the strength of drug–polymer interactions. Additionally, under high humidity, the glass transition temperature of the polymer is no longer an indicator of its drug stabilization capability. Instead, it is the hygroscobicity of the polymer that appears to be the most important parameter. Amongst the polymers tested in this study, EUDRAGIT E PO was found to have the greatest inhibitory effect on crystallization, whilst PVP K30 was found to have the least protective effect; presumably because of its hygroscopic nature.

1. Introduction

There is a growing interest in formulating drugs into thin films for uses such as buccal/sublingual oral strips/films as well as for medical implants, medical device coatings, and for wound healing applications [1–4]. For example, an increasing number of fast dissolving oral films for drug delivery have been marketed to provide dosage forms which can enhance absorption, compliance, and convenience [1]. Polymer coated coronary stents which have bioactive agents incorporated into the polymer are able to slowly release drug molecules and avoid negative effects associated with coagulation or the immune response [2]. These drug-eluting stents cannot only widen blood vessels, but also release therapeutic agents for the treatment for cardiovascular patients and have now been clinically tested for the prevention of stroke [2]. The dimensions of these endovascular thin film coated devices are such that the technology is suitable for use in the trachea, oesophagus and bile duct, and it has now been developed into a platform for the development of other devices for dealing with problems associated with diseases other than vascular disease [2,3]. For most of these applications, the drug is loaded into the polymer film via different dispersion techniques which are exposed to either high humidity or a wet/moist environment during their use. Therefore, it is essential to gain a fundamental understanding of the stability of these pharmaceutical thin films under high humidity. The present study is particularly focused on understanding the physical stability of pharmaceutical thin films with 5–10 μm thicknesses under high humidity. In particular, the stabilization capability of polymer-based solid dispersion thin films containing amorphous drugs is explored in comparison with the effect of polymer coatings or modification of underlying substrate surfaces on the recrystallisation tendency of amorphous drug layer.

Amorphous drugs often have higher dissolution rates than their crystalline forms, but lower physical stability during storage [5]. Addition of crystallisation inhibitors such as polymers to the amorphous drug to form amorphous molecular dispersions is a common method to minimise/prevent drug recrystallisation [6–8]. In solid solutions (often referred as amorphous molecular dispersions), it is believed that polymers can decrease the molecular mobility of the drug, therefore reducing the driving force for crystallisation and improving the physical stability of amorphous drugs [6–8]. In these systems, it has been reported that the stability of the amorphous drug is highly dependent on the miscibility of the components [9] and drug–polymer interactions such as formation of hydrogen bonds [6,10]. However, the stability of these amorphous dispersions can be disrupted by environmental factors such as humidity and temperature [9,11–14]. Moisture induced phase separation where the drug and polymer separate into domains, fol-

* Corresponding author. School of Pharmacy, University of East Anglia, Norwich, Norfolk NR4 7TJ, UK. Tel.: +44 (0) 1603592925.
E-mail address: sheng.qi@uea.ac.uk (S. Qi).

0939-6411/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejpb.2013.01.008

lowed by crystallisation of the drug is well known [11,12]. In the case of felodipine and PVP, it has been reported that water competes with the drug for hydrogen bonding sites on the polymers thus altering the driving force for crystallisation [11,12]. For pharmaceutical thin films which are different from other conventional solid dosage forms, stabilisation strategies other than forming solid dispersions have not been widely explored. The main aim of this study is to compare and contrast three different stabilisation approaches for amorphous drugs under high humidity. These are the formation of solid dispersions, layering a thin polymer coating on top of an amorphous drug layer and layering an amorphous drug layer on top of a polymeric film.

In most cases for amorphous drug films, drug crystallisation is a heterogeneous process, and the growth of crystals is often favourable at the free surface; so called surface-enhanced crystallisation [15]. The surface not only provides a favourable site for crystal nucleation, but also accelerates crystal growth rate [16,17]. Several studies have found that crystallisation of drugs in amorphous systems is faster at the free surface than in the bulk because of the gain in molecular mobility at the surface, which enhances crystallisation through upward crystal growth [18]. Therefore, when the surface is coated, drug molecules which would originally have been at the free surface will be in an environment similar to the bulk, be less mobile and therefore surface-enhanced crystallization would be expected to be inhibited [16,17]. Thus, direct use of polymer coatings to protect the free amorphous drug surface may be a suitable and simple approach for stabilising amorphous drugs against high humidity.

Although recrystallisation of glassy materials has been found to be rapid at free surfaces [18], there are other factors reported to affect the crystallisation process, including the surface properties of the solid substrate on which the glassy material is laid. For example, a previous study showed that the choice of substrate can dramatically affect the crystallization kinetics of poly(ε-caprolactone) [19]. Another study showed that a thin coating of an impure metal on the solid substrate could significantly alter the rate of crystallisation of an amorphous thin film [20]. It has also been suggested that the rate of crystal growth may be associated with density and roughness of the substrate [21]. Therefore, the third approach investigated in this study to stabilise amorphous drugs was to modify the solid substrate surface.

In order to appropriately examine the relative merits of the three amorphous drug stabilization methods, four model drugs (carbamazepine, celecoxib, felodipine and fenofibrate) were selected which have an intermediate to high tendency of recrystallisation according to a recently proposed classification system [22,23]. Additionally, three different polymers, PVP K30, EUDRAGIT E PO, and Soluplus, were used. These polymers have different hygroscobicities and viscosities enabling investigation of the effect of different polymers on the crystallisation of the drugs from thin films.

2. Materials and methods

2.1. Materials

Celecoxib, felodipine, fenofibrate and EUDRAGIT® E PO were given as generous gift from Evonik (Darmstadt, Gerrmany). PVP Kollidon® 30 (K 30) and Soluplus® were obtained from BASF (Ludwsigshafen, Germany). Ethanol and Dichloromethane were bought from Sigma–Aldrich (Poole, UK). Carbamazepine was purchased from Acros (Geel, Belgium) with a melting temperature of 189–192 °C, indicating that it is the stable form I polymorph.

2.2. Preparation of spin-coated thin films

Three different drug stabilization approaches were employed in this study through changing the architectures of the films. For approach I, a solid dispersion film of the drug and polymer was prepared. Approach II involved coating the surface of a freshly prepared drug thin film with a thin polymer film, whereas for approach III, the solid substrate surface was modified with a polymer coating prior to the laying of the pure drug thin film on top. All thin films with the different configurations were prepared by spin coating. Prior to spin coating, solutions were prepared by dissolving the drugs, polymers and mixtures of drugs and polymers with different drug–polymer ratios in a 1:1 mixture of ethanol and dichloromethane with solid concentrations of 15% (w/v). Spin-coated thin films were manufactured on a Spincoat G3P-8 (Specialty Coating Systems, Indianapolis, US). Three drops (about 200 μl) of the solutions were transferred onto microscope glass slides, which were then continuously spun at a rotation speed of 2000 rpm. Layered films were prepared by spin coating the glass slides twice with the pure drug or pure polymer solutions in turn. The first spin-coated layer was left to dry for 5 min before the second coating was applied. Freshly prepared samples were characterised immediately. Ageing studies were carried out by storing the slides in a saturated humidity chamber for up to 96 h before testing. The chamber with saturated humidity was created by equilibrating an air-tight sealed chamber with damp tissue paper saturated with deionised water for 24 h. Pure drug films were also prepared as a control and were stored in a 0%RH chamber (with the presence of P_2O_5) for comparative purposes.

2.3. Attenuated Total Reflection-Fourier Transform Infrared (ATR-FTIR) Spectroscopy

ATR-FTIR spectroscopy was used to investigate the physical state of the drug in thin films and to characterise drug–polymer interactions. Spectra were collected in absorbance mode using a 1FS/66S spectrometer from Bruker Instruments equipped with a Golden Gate ATR accessory (Specac Ltd., Coventry, UK). Sixty-four scans were collected at a resolution of 2 cm^{-1} for each sample over the wavelength region 500–4000 cm^{-1}. Each sample was examined in triplicate.

2.4. Polarised light microscopy (PLM) and scanning electron microscopy (SEM)

PLM studies were conducted using a Leica DM LS2 polarised light microscope (Wetzlar GmbH, Germany) connected to a video capture system. For SEM, the spin-coated films were sputter coated with Au/Pd. The images of the surface morphology of the thin films were taken using a Phillips XL20 SEM (Phillips Electron Optics, Netherlands).

2.5. Nano-thermal analysis (nano-TA)

Nano-thermal analysis was performed using a Nano Thermal Analyzer (Anasys Instruments, Santa Barbara, USA) with a Veeco diCaliber scanning probe microscope head (Veeco, CA, USA) and a ThermaLever™ nanoprobe (Anasys Instruments, Santa Barbara, USA). The ThermaLever™ probes have a tip radius similar to that found with conventional AFM probes, therefore providing comparable lateral resolution. This detection area varies depending on the thermal and mechanical properties of the material being investigated although it is generally accepted to be at a maximum of 100 nm in diameter and in some cases can be as low as 10 nm [24,25]. The ThermaLever™ probes used have an approximate length of 200 μm and width of about 2 μm. The tip height is typi-