European Journal of Pharmaceutics and Biopharmaceutics 122 (2018) 62–69

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Influence of PVP molecular weight on the microwave assisted *in situ* amorphization of indomethacin

Maria Doreth[a], Korbinian Löbmann[a,*], Petra Priemel[a], Holger Grohganz[a], Robert Taylor[b], René Holm[a,c], Heidi Lopez de Diego[d], Thomas Rades[a,e]

[a] Department of Pharmacy, Faculty of Health, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark
[b] Sirius Analytical Instruments Ltd., Station Rd, Forest Row RH18 5DW, United Kingdom
[c] Drug Product Development, Janssen Research and Development, Johnson & Johnson, Turnhoutseweg 30, 2340 Beerse, Belgium
[d] Analytical Development & Compliance, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark
[e] Department of Pharmacy, Faculty of Science and Engineering, Åbo Akademi University, Turku, Finland

ARTICLE INFO

Keywords:
In situ amorphization
Microwave
Glass solution
Solid dispersion
PVP
Amorphous
Indomethacin

ABSTRACT

In situ amorphization is an approach that enables a phase transition of a crystalline drug to its amorphous form immediately prior to administration. In this study, three different polyvinylpyrrolidones (PVP K12, K17 and K25) were selected to investigate the influence of the molecular weight of the polymer on the degree of amorphization of the model drug indomethacin (IND) upon microwaving. Powder mixtures of crystalline IND and the respective PVP were compacted at 1:2 (w/w) IND:PVP ratios, stored at 54% RH and subsequently microwaved with a total energy input of 90 or 180 kJ. After storage, all compacts had a similar moisture content (~10% (w/w)). Upon microwaving with an energy input of 180 kJ, 58 ± 4% of IND in IND:PVP K12 compacts was amorphized, whereas 31 ± 8% of IND was amorphized by an energy input of 90 kJ. The drug stayed fully crystalline in all IND:PVP K17 and IND:PVP K25 compacts. After plasticization by moisture, PVP K12 reached a T_g below ambient temperature (16 ± 2 °C) indicating that the T_g of the plasticized polymer is a key factor for the success of *in situ* amorphization. DSC analysis showed that the amorphized drug was part of a ternary glass solution consisting of IND, PVP K12 and water. In dissolution tests, IND:PVP K12 compacts showed a delayed initial drug release due to a lack of compact disintegration, but reached a higher total drug release eventually. In summary, this study showed that the microwave assisted *in situ* amorphization was highly dependent on the T_g of the plasticized polymer.

1. Introduction

Due to the introduction of high-throughput screening and combinatorial chemistry in the early 90s [1], it is estimated that the majority of low molecular weight ('small molecule') drugs in the pipeline of the pharmaceutical industry today are poorly water soluble [2–4]. To make such compounds 'druggable', tailor made enabling formulations are often needed [5].

It is well known that the amorphous form of a drug possesses a higher apparent solubility and a faster intrinsic dissolution rate compared to the crystalline form [6]. As such, polymeric glass solutions are a promising approach to improve the solubility and dissolution characteristics of small molecule drugs [7–9]. In a glass solution, the drug is present in its amorphous form and molecularly dispersed in an amorphous polymer network, commonly formed by a hydrophilic polymer [10]. The function of the polymer in a glass solution is primarily to stabilise the amorphous form of the drug physically [11]. Polymers with a high glass transition temperature can limit the molecular mobility of the drug within these systems and hereby prevent, or at least slow down, recrystallization of the amorphous drug [12], which is a major concern when formulating amorphous drugs. The stability of such systems is, however, highly dependent on the storage temperature and humidity. On the one hand, high temperatures (and plasticization due to moisture) can increase the mobility of the polymer chains, and thus, facilitate recrystallization of the amorphous drug [13]. On the other hand, a too low temperature can reduce the solubility of the drug in the polymer and facilitate drug nucleation [14]. Although some drugs have been introduced to the market in form of glass solutions

* Corresponding author at: University of Copenhagen, Department of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark.
E-mail addresses: maria.doreth@sund.ku.dk (M. Doreth), korbinian.loebmann@sund.ku.dk (K. Löbmann), petra.priemel@sund.ku.dk (P. Priemel), holger.grohganz@sund.ku.dk (H. Grohganz), robert.taylor@sirius-analytical.com (R. Taylor), rholm@ITS.JNJ.com (R. Holm), HLD@Lundbeck.com (H. Lopez de Diego), thomas.rades@sund.ku.dk (T. Rades).

http://dx.doi.org/10.1016/j.ejpb.2017.10.001
Received 23 May 2017; Received in revised form 2 October 2017; Accepted 2 October 2017
Available online 03 October 2017

[15], physical stability during long-term storage remains a challenge [16].

'*In situ* amorphization' is a concept that addresses this particular issue [17–20]. The idea behind *in situ* amorphization is (1) to amorphize a drug within the given formulation and (2) to allow amorphization to take place immediately before the administration of the formulation. This implies that simple, non-industrial amorphization techniques need to be used. The deliberate '*in situ* amorphization' has so far been realised with two different approaches. Priemel et al. demonstrated *in situ* amorphization of crystalline indomethacin (IND):Eudragit® E PO compacts at drug-to-polymer ratios of 3:1, 1:1 and 1:3 (w/w) when these were placed into 900 mL phosphate buffer for 1 h [18]. At the chosen pH of 6.8, Eudragit® E PO, which is a weakly basic polymer, can slightly swell but not dissolve. When placed into the phosphate buffer, the compact's appearance turned from white to yellow, which indicated that IND turned amorphous. Physicochemical characterization of the dried compacts and dissolution tests at pH 4.1 confirmed the assumption that indeed an *in situ* amorphization had occurred. The authors reported a dissolution advantage of the *in situ* amorphized samples under gastric pH conditions (pH 4.1) compared to samples not exposed to phosphate buffer, i.e. compacts containing the drug in its crystalline form. Doreth et al. developed this approach further using only 50 mL of water for the *in situ* amorphization process [20], demonstrating that also ibuprofen and naproxen were suitable candidates for *in situ* amorphization with Eudragit® E PO. In both studies by Priemel et al. and Doreth et al., it was assumed that water had two functions: (1) to plasticize the polymer, giving the polymer chains flexibility and creating space within the polymer network and (2) to dissolve a (small) part of the drug, which enables the integration of the drug into the polymer network on a molecular level.

Using a different approach, Doreth et al. achieved a partial *in situ* amorphization of indomethacin by microwave irradiation of a compact, containing initially crystalline IND and the hygroscopic polymer polyvinylpyrrolidone K12 (PVP K12) at a 1:2 (w/w) IND:PVP K12 ratio, using a household microwave at different power-time combinations [20]. The authors demonstrated that *in situ* amorphization was dependent on the moisture content within the compacts and the energy input by microwave irradiation. After microwaving the compacts, which had the highest moisture content (9.8% w/w) with high energy input settings (90 kJ), up to 80% of the initially crystalline drug turned amorphous. The intrinsic dissolution behavior of the *in situ* amorphized samples was significantly improved compared to physical mixture compacts containing the crystalline drug and showed a similar intrinsic dissolution behavior compared to a fully amorphous quench cooled glass solution of the same components.

It is important to notice that for the production of conventional glass solutions, hygroscopic polymers and polymers with a low T_g are often problematic, as absorbed moisture can lower the T_g of the polymer and a low T_g increases molecular mobility [21–24]. The risk of drug recrystallization would thus be enhanced. Considering this, the use of Eudragit® E PO (T_g 54 °C [19]) and polyvinylpyrrolidone K12 (T_g 110 °C; highly hygroscopic [20]) would likely be unsuitable for the development of a conventional glass solution. However, for an *in situ* amorphized glass solution, the long term physical stability of the amorphized product is of minor importance as the amorphization could in principle happen immediately before administration. Conceptually, the *in situ* amorphization process might even benefit from a low T_g of the polymer as molecular mobility is required for the amorphization process and moisture is required to transfer energy from the microwaves to the compact. In the above mentioned microwave study it was shown that a higher moisture content of the compacts was advantageous for the microwave assisted *in situ* amorphization [20]. It is, however, unknown to which extent the T_g of the polymer contributes to the success of the *in situ* amorphization. Hence, in this study, the effect of the molecular weight (and thus T_g) of PVP on microwave assisted *in situ* amorphization was investigated. Compacts of the crystalline BCS II drug IND and three PVPs with different molecular weights (PVP K12, K17 and K25, with molecular weights of 2000–3000 g/mol, 7000–11,000 g/mol and 28,000–34,000 g/mol, respectively) at a 1:2 (w/w) IND:PVP ratio were conditioned at 54% RH for a minimum of two weeks and subsequently microwaved at 300 W for 5 or 10 min, resulting in a total energy input of 90 kJ and 180 kJ, respectively. To get a deeper understanding of the importance of the polymer and its interaction with water, the relation between molecular weight, glass transition temperature and plasticization on the resulting *in situ* amorphization of the initially crystalline drug in the compacts was studied. Understanding of the influence of these factors may help identifying new drug-polymer systems for microwave assisted *in situ* amorphization.

2. Materials and methods

2.1. Materials

γ-indomethacin (IND) was purchased from Fagron (Copenhagen, Denmark). The three different grades of polyvinylpyrrolidone, Kollidon® 12 PF (PVP K12), Kollidon® 17 PF (PVP K17) and Kollidon® 25 (PVP K25) were a gift from BASF (Ludwigshafen, Germany). Magnesium nitrate hexahydrate was obtained from VWR International BVBA (Leuven, Belgium). Sodium chloride, 0.5 M hydrochloric acid, and 1 M sodium hydroxide solution were obtained from Fisher Scientific (Loughborough, United Kingdom). Sodium dihydrogen phosphate and sodium acetate trihydrate were purchased from Sigma-Aldrich Company Ltd (Dorset, United Kingdom). All materials were used as received.

2.2. Methods

2.2.1. Preparation of compacts

Physical powder mixtures (PM) were prepared by mixing IND and PVP (K12, K17 or K25) gently with mortar and pestle at a 1:2 (w/w) IND:PVP ratio. 100 mg of the PM was subsequently compacted, using a custom-made manual press (Sirius Analytical Instruments Ltd., Forest Row, United Kingdom) and an 8 mm die assembly with flat faced punches. Compacts were produced at a compaction force of 29 MPa and were compressed for 1 min. After compaction, the compacts were stored at ambient temperature in a desiccator containing a saturated solution of magnesium nitrate, resulting in a relative humidity of 54% RH, for a minimum of two weeks.

2.2.2. Microwaving process

For the microwaving process, a household microwave oven NN-DF383BGPG from Panasonic (Hamburg, Germany) was used, containing an in-built mode stirrer to assure an even microwave distribution. The microwave oven was equipped with the inverter technology, allowing a real power reduction without pulsing the radiation on and off as commonly used in household microwaves [25–27]. Compacts were placed upright standing on a polypropylene watch glass into the microwave. Polypropylene cannot absorb microwave radiation and hence, does not heat up during microwaving. Passive heating through conduction between the sample holder and the compact could hereby be avoided. Samples were microwaved with 300 W for either 5 or 10 min, resulting in a total energy input of 90 and 180 kJ. A beaker with 150 mL of tap water, glass beads and a glass rod was additionally placed in the cooking chamber of the microwave. As the samples had a comparatively low amount of radiation absorbing matter, the additional water could absorb the surplus radiation, preventing it from returning to the microwave oven's energy source and thus, damaging the magnetron.

2.2.3. Light microscopy

To capture visual changes of the samples after storage and