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Research paper

Surface composition and contact angle relationships for differently prepared solid dispersions

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ABSTRACT

Solid dispersions are promising drug delivery forms which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution behavior and the bioavailability of the drug. One important aspect and a prerequisite in understanding the drug dissolution mechanism from solid dispersions is a better analytical monitoring of the solid dispersion surface properties, such as powder surface composition and water adsorption properties. In this paper, we have considered chemical and structural surface analysis data for solid dispersions processed by spray drying or roto-evaporation and compared these data with information obtained by contact angle measurements. Firstly, we establish the usefulness and suitability of X-ray photoelectron spectroscopy (XPS) for determination of surface chemical composition and scanning electron microscopy (SEM) for determining the structure of solid dispersions composed of different types of carriers, drugs and drug concentrations. Secondly, we measure contact angles of solid dispersions to describe wettability, to finally establish a link between the surface chemical composition, the powder structure and the wetting behavior. These experimental methods offer a rapid screening tool for the selection of carrier, drug concentration and/or process in early development. In addition, they provide a useful tool for investigating structural aspects of solid dispersions which have intrinsic relevance for drug dissolution and stability.

1. Introduction

Enhancement of the bioavailability of poorly water soluble drugs has been one of the main targets of drug development during the last decade and will continue in the upcoming years. Several techniques have been developed concerning enhancement of the dissolution rate of these drugs, including particle size reduction [1], salt formation [2] and preparation of solid dispersions [3].

Solid dispersions can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties [4]. During the solid dispersion preparation, the aim is to disperse the drug homogenously within the carrier matrix and to encapsulate the hydrophobic drug to ensure complete wetting, fast carrier dissolution and improved drug stability [4,5]. Solid dispersions of different characters exist. In this study, we are using amorphous carriers to originate amorphous solid dispersions. These can be classified as solid amorphous solutions, solid amorphous suspensions and a mixture of both [4]. As the drug concentration is increased, the characteristics of the solid dispersions tend to shift towards solid suspensions.

Despite the intense research on solid dispersions, only a very limited number of commercial products have been developed. One of the primary reasons is the poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties. The rate at which a solid oral drug delivery system dissolves depends on many parameters, and occurs in a series of steps: wetting, solvent penetration, disintegration, swelling (if applicable) and dissolution of components. Each of these areas is complex, and their respective roles in the dissolution process need to be considered separately. In this work, we have focused on the relationship between surface properties and wetting. The powder surface composition is expected to play an important role in the wetting process, as it influences the overall hydrophobicity of the powder. In particular, high surface coverage of hydrophobic drug is assumed to give poor wetting properties with large contact angles. The amount of drug at the powder surface is further believed to significantly influence dissolution and physical drug stability. The importance of contact angles and wettability on dissolution rate is discussed in several studies [6–8]. In one recent study by Chokshi et al. [9], it was reported that the contact angles of solid dispersions correlate to improved intrinsic dissolution data for a poorly water soluble drug. In another study, Buckton [10]

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describes the Noyes–Whitney model which infers a direct proportionality between the dissolution rate of drug and the effective surface area of a powder (determined partly by wettability). There are some reports in the literature which describe structure–activity relationships of powders which refer to solubility and wettability [11]. They claim that the structure of molecules is linked to both wettability and solubility, but the mechanism by which the structure affects wettability and solubility is different. This relates to the fact that wetting is a reflection of the functional groups that are present at the surface of the solid, but solubility relates to the structure of the entire molecules respectively powder. It follows that it should be possible to alter the structure of a powder to independently manipulate wettability and solubility. However, what is lacking so far is a more detailed description of the solid dispersion structure including aspects such as drug distribution, surface properties, wetting and its impact on the molecular disintegration during dissolution.

There are several ways to prepare solid dispersions, such as melting or solvent methods [3,14]. The latter method consists of the solubilization of the drug and carrier in a volatile solvent which is later evaporated. In this study, we have compared solid dispersions prepared by two solvent methods; rotary evaporation, which is a slow drying technique, in combination with milling, and spray drying, which is a fast drying technique that directly produces a powder. The properties of the prepared solid dispersions may depend greatly on the preparation technique. The possibility to alter the structure of a powder to manipulate wettability is presumably relevant for drying processes, which have a significant impact on the surface composition of powders, in particular when one or more surface-active components are present.

It has been shown for water-based solutions that the surface of a spray-dried powder is dominated by surface-active species in the formulation [15–18]. This effect on the surface composition is due to adsorption of the surface-active substance to the air/liquid interface of the spray droplet before it turns into a dry particle. If none of the materials is surface-active, the less soluble material dominates the surface. The fact that most solid dispersion of poorly soluble drugs is prepared form non-aqueous solvents does not change the mechanism in principle: the substance with the strongest affinity for liquid/air interface will tend to dominate the surface of the powder. Thus, in the case of solid dispersion preparation processes the migration of the hydrophobic drug towards the particle surface would render the powder surface hydrophobic with a large contact angle between the powder surface and the penetrating surface. In this case, retardation or inhibition of the drug dissolution could be expected. In order to improve the wetting, surfactants are frequently incorporated into the formulation to decrease contact angles and promote a better powder wetting. The competitive adsorption process between the components with different surface affinities might be different for slow and fast drying techniques, which might lead to differences in the surface properties related solely to the drying technique. These differences in enrichment or depletion at the powder particle surface relative to the bulk composition may have consequences for the wetting, dissolution and bioavailability for the final formulation.

In general, wettability is a measure of the ability of a bulk powder to imbibe a liquid under the influence of capillary forces, and it depends on particle size, density and porosity of the powder bed. The rate of ingress of water into a powder bed can be described by Washburn's equation [12,13], but, the wetting properties of powders are not straight forward to determine, and several attempts have been presented in the literature. In food industry, the most common procedure is to observe the time for a powder to sink from the surface into the liquid. In the pharmaceutical area, no pharmacopeia methods exist for describing the wettability of dispersed drug delivery forms such as solid dispersions, although this value has a significant impact on the method development of release studies. Several approaches have been reported which describe powder wettability by using the Wilhelmy plate technique [19] to determine an apparent contact angle of water insoluble powders by gluing the powder onto the Wilhelmy plate and measuring the contact angle. The difficulty here is to determine the actual perimeter of the powder covered plate, which is essential for the determination of the contact angle. Further, the influence of the glue on the powder is not clear. Lippold et al. [20] have tried to measure contact angles on different crystal faces, which is interesting since different crystallization protocols can give rise to different crystal habits, with relative differences between the sizes of the different crystal faces. This is thus a way to influence the wetting properties of a crystalline powder. However, this method is not applicable for small crystals or amorphous materials. Buckton et al. [21] used compressed tablets of pure drug powders to determine the contact angle of these powders. A similar method is used in this paper for analysis of the wetting properties of solid dispersions.

To correlate the observed wetting behaviors with surface chemical composition data, obtained by X-ray photoelectron spectroscopy (XPS) measurements, the Young–Laplace equation is suitable:

$$\gamma_s = \gamma_{sl} + \gamma_l \cos\theta \quad (1)$$

where γ_s, γ_l and γ_{sl} are the solid–vapor surface tension, the liquid–vapor surface tension and the solid–liquid surface tension, respectively. The suggestion is that the amount of drug on the surface would correlate to the contact angle with water via the surface energy of the powder compact, γ_s. The negative aspect of this is that according to Eq. (1) we ignore effects due to the γ_{sl} term, and also any effects due to the physical surface structure (roughness, pores, etc.). None the less this exercise can be seen as a step towards correlating surface chemical composition, itself determined by the drug and excipient components present and the production method used, to wetting properties.

The aim of this work is to establish a link between solid dispersion surface properties, i.e., chemical surface composition and wettability. In addition, we study the impact of formulation variables such as type of carrier, drug concentration and the preparation process on the encapsulation efficiency of the drug inside the powder bed. To this end, we consider chemical and structural surface analysis data for different processed solid dispersions composed of different types of carriers, drugs and drug concentrations and compare these data with information obtained by contact angle measurements with the view to assess relationships between them. Firstly, we establish the usefulness and suitability of experimental methods for the determination of surface chemical composition and structure of solid dispersions, secondly we measure contact angle of solid dispersion to describe wettability, and finally we attempt to establish a link between the surface chemical composition, the powder structure and the wetting behavior.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) (Dow Chemical, USA), polyvinyl pyrrolidone (PVP K30) (BASF, Germany) and hypromellose phthalate (HP50) (Shin-Etsu Chemical, Japan) have been used as carriers in combination with drug A and drug N (obtained from Novartis Pharma AG) to generate amorphous solid dispersions. Both the drug candidates represent a class of drugs which have increased industrial importance and which are frequently developed by the solid dispersion concept (for physical–chemical properties see Table 1). Poloxamer F68 (Uniqema Germany) was used as a surface-active