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Acid-base interactions in amorphous solid dispersions of lumefantrine prepared by spray-drying and hot-melt extrusion using X-ray photoelectron spectroscopy

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ABSTRACT

This study investigates drug-excipient interactions in amorphous solid dispersions (ASDs) of the model basic compound lumefantrine (LMN), with five acidic polymers. X-ray photoelectron spectroscopy (XPS) was used to measure the extent of the protonation of the tertiary amine in LMN by the five acidic polymers. The extent/efficiency of protonation of the ASDs was assessed a function of polymer type, manufacturing process (hot-melt extrusion vs. spray drying), and drug loading (DL). The most strongly acidic polymer, polystyrene sulfonic acid (PSSA) was found to be the most efficient polymer in protonating LMN, independently of manufacturing method and DL. The rank order for the protonation extent of LMN by each polymer is roughtly the same for both manufacturing processes. However, protonation efficiency of polymers of similar acidic strength ranged from ~0% to 75% (HPMCAS and Eudragit L100-55, respectively), suggesting an important role of molecular/mixing effects. For some polymers, including Eudragit L100 55 and HPMCP, spray-drying resulted in higher protonation efficiency compared to hot-melt extrusion. This result is attributable to a more favorable encounter between acid and base groups, when exposed to each other in solution phase. Increasing DL led to decreased protonation efficiency in most cases, particularly for polyacrylic acid, despite having the highest content of acidic groups per unit mass. These results indicate that the combined effects of acid strength and mixing phenomena regulate the efficiency of acid-base interactions in the ASDs.

1. Introduction

Over the last two decades or so, amorphous solid dispersions (ASDs) have become an increasingly widespread approach to enhance the dissolution rate of emerging poorly water soluble drugs, partly in response to the development of high throughput screening and combinatorial chemistry (Janssens and Van den Mooter, 2009). However, a major challenge for the use of ASDs is the chemical and physical instability of drugs in the amorphous state, with the latter being arguably the more significant issue. A successful ASD formulation has the active pharmaceutical ingredient (API) molecularly dispersed into polymer chains, while maintaining the APIs in the amorphous state during manufacturing, dissolution and long-term storage (Newman et al., 2012). A number of stabilization mechanisms for ASDs have been discussed over the years. More recently, the use of strong intermolecular interactions such as acid-base interactions between the drug and the polymer(s) has attracted considerable interest, as a means for stabilizing and improving the performance of ASDs (Kojima et al., 2012; Liu et al., 2012; Sarode et al., 2013; Sathigari et al., 2012; Singh et al., 2013; Song et al., 2015a; Wegiel et al., 2013; Weuts et al., 2005). It has been shown that the strong acid-base interactions result in a highly stable dispersion in the solid state, with an increased dissolution rate (Song et al., 2015b).

Among the various techniques for preparing pharmaceutical ASDs, spray-drying (SD) and hot melt extrusion (HME) are the two

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major approaches used in large scale for industrial manufacturing (Agrawal et al., 2013). Each of these two methods relies on a number of processing parameters that allow to "tune" the properties of amorphous product. For example, the choice of solvent, inlet temperature, feed rate and solution concentration are key parameters for SD (Paudel et al., 2013). In comparison, process temperature, residence time and screw rotation speed (shear forces) are the important parameters for HME processing (Lang et al., 2014; Saerens et al., 2014). However, there is little published information on how the choice of preparation method can influence the physical attributes of the resulting ASDs. One recent study showed that these two manufacturing processes can have different impact on the physicochemical properties of ASDs. Specifically, the choice of processing method can influence the extent of hydrogen bonding between drug and polymer in ASDs (Agrawal et al., 2013). As there has been a significant surge of interest on using ionic polymers to stabilize amorphous drugs in ASDs, it is important to investigate how different manufacturing processes can influence the proton exchange interactions between drugs and polymers in such dispersions.

X-ray photoelectron spectroscopy (XPS) has proven a powerful tool for surface chemistry characterization with a remarkable sensitivity for all elements, with the only exceptions of hydrogen and helium. Despite a limited number of reports on its applications to pharmaceutical systems, XPS has recently shown remarkable potential for exploring intermolecular drug-polymer interactions in ASDs (Song et al., 2015b). Specifically, XPS has excellent sensitivity for the assessment of protonation extent by measuring the shifts in binding energy (E_B) of the selected atoms (Stevens et al., 2014). For example, a positive 1 s N E_B shift value of 2 eV is observed for the protonation of an aromatic nitrogen in theophylline as well as for an aliphatic nitrogen in the piperidine group. In contrast, a positive 1 s N E_B shift of 1–2 eV indicates the presence of hydrogen bonding (Stevens et al., 2010). This level of informative detail shows that XPS is a very effective analytical technique for characterizing acid-base interactions in solids.

In this study, we used five acidic polymers to formulate ASDs of a poorly water soluble drug, lumefantrine (LMN), used as model compound. The polymers used in the study include hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropylmethylcellulose phthalate (HPMCP), poly(methacrylic acid-co-ethyl acrylate) or Eudragit L-100-55, polyacrylic acid (PAA), and polystyrene sulfonic acid (PSSA).The ASDs were prepared using both SD and HME with 20% and 40% drug loading (DL). The amorphous state of LMN in the ASDs was verified using powder X-ray diffraction (PXRD) analysis. Scanning electron microscopy (SEM) was used to qualitatively characterize the surface morphology of the ASDs. Finally, XPS was used to assess the extent of protonation of LMN by each polymer in the corresponding ASDs, and to explore the effects of polymer type, manufacturing processes, and DL on the extent of acid-base interactions in the ASDs obtained. Table 1 lists the relevant structural and acid-base parameters of LMN and the different polymers used in this study. The chemical structures of LMN and the repeating units in the different polymers are shown in Fig. 1.

2. Experimental

2.1. Materials

Dichloromethane (DCM) and methanol were purchased from Macron Fine Chemicals (Center Valley, PA). Lumefantrine was obtained from Attix Corporation (Toronto, Canada). HPMCAS (Aqoat® AS-MF) and HPMCP (HP-55) were obtained from Shin-Etsu Chemical Company (Tokyo, Japan). Polyacrylic acid (PAA, MW = 450,000) and Polystyrene sulfonic acid were obtained from Sigma-Aldrich Corporation (St.Louis, MO). Eudragit® L100-55 was obtained from Evonik Industries AG (Essen, Germany).

2.2. Spray drying (SD)

LMN and polymers (except PAA) were completely dissolved in a 1:1 (v/v) mixture of DCM and methanol. The drug:polymer ratio in the solutions used were 20:80 and 40:60 (w/w), corresponding to DL of 20% and 40% (DL20% and DL40%), respectively. A Buchi B190 (Flawil, Switzerland) spray drier was used to spray dry the clear LMN-polymer solutions prepared with a solids (drug:polymer mixture) content of 2% (w/v) under the following processing

Table 1
Characteristics of lumefantrine and acidic polymers functional groups relevant for hydrogen bonding and proton exchange.

Material	Functional Group	mmol of functional group per g	pK_a	Hydrogen Bond Donor	Donor Strength	Hydrogen Bond Acceptor	Acceptor Strength (pK_{BHX})[a]
Lumefantrine	R_3–N	1.9	8.5	N	–	Y	Strong (triethylamine 1.98)
HPMCAS	R–O–R	8.8	–	N	–	Y	Medium (diethylether 1.01)
	R–C(O)–O–R	2.5	–	N	–	Y	Medium (ethyl acetate 1.07) [b]
	R–OH	1.8	–	Y	Strong	Y	Medium (ethanol 1.02)
	R–C(O)–OH	1.0	4.5	Y	Very Strong	Y	Medium (ethyl acetate 1.07)[b]
PAA	R–C(O)–OH	13.9	4.5	Y	Very Strong	Y	Medium (ethyl acetate 1.07)[b]
Eudragit L100-55	R–C(O)–OH	5.8	4.5	Y	Very Strong	Y	Medium (ethyl acetate 1.07)[b]
	R–C(O)–O–R	5.8	–	N	–	Y	Medium (ethyl acetate 1.07) [b]
HPMCP		2.0	2.9	Y	Very Strong	Y	Medium (acetophenone 1.11)[c]
	R–OH	Negligible	–	Y	Strong	Y	Medium (ethanol 1.02)
PSSA	Ar–S(O)$_2$–OH	5.4	−1.5	Y	Very Strong	Y	Low (methyl methanesulfonate 0.71)

The strengths used the following scale: Weak < 0.75 < Medium <1.5 <Strong <2.25 <Very Strong (Bernard and Taylor, 2011).
[a] H-bond acceptor strength was determined using the pK_{BHX} scale (Laurence et al., 2009).
[b] No values were found for COOH acceptors, (Laurence et al., 2009) but it was approximated to ethyl acetate carbonyl.
[c] No values were found for similar COOH acceptors, but it was approximated to acetophenone carbonyl (Laurence et al., 2009).