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# Effect of polymer type on the surface energy of acetaminophen solid dispersions prepared by melt method

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ABSTRACT

Many newly developed active pharmaceutical ingredients (APIs) have very low solubility in aqueous media. The preparation of solid dispersions (SDs) is one way of avoiding this problem. However, compound wettability and thus solubility are influenced by surface energy. In this study, we used inverse gas chromatography (IGC) to evaluate the surface energies of prepared SDs, and compared them with those obtained for physical mixtures (PMs). SDs containing different weight ratios of crystalline acetaminophen and one of three polymers (Kollidon® 12 PF, Kollidon® VA 64 or Soluplus®) were prepared by the melt-quenching of corresponding PMs. In all cases, as the polymer content increased, the surface energy decreased significantly. For the SDs and PMs containing Soluplus®, this decrease in surface energy showed the same non-linear trend. In the cases of Kollidon® 12 PF and Kollidon® VA 64, the trend was linear, with the SDs showing a steeper decrease in surface energy than the corresponding PMs. Typically, such decreases are ascribed to the dissolution of the crystalline structure of an API. Our results suggest that in the case of the Kollidons, the steeper decrease is caused by another mechanism, namely, strong API-Kollidon interaction leading to the less wettable surface of SDs.



## 1. Introduction

An increasing number of poorly water-soluble drugs and their formulation are currently one of the biggest challenges for the pharmaceutical industry (Knopp et al., 2016). Especially, the low solubility and thus dissolution rate is a characteristic for an anti-inflammatory and analgesic drugs (Malviya et al., 2010). A low bioavailability after oral administration is usually caused by drug release which is crucial and limiting step for drugs with low solubility in biological fluids and high permeability (Malviya et al., 2010; Singh et al., 2011). The preparation of drug-polymer dispersions is a strategy to improve the dissolution of poorly soluble drugs (Janssens and van den Mooter, 2009; Qian et al., 2010). The solid dispersions can be defined as molecular mixtures of poorly water-soluble drugs in an inert hydrophilic polymeric carriers that are amorphous. Drug release from these binary mixtures is mainly affected by the polymer properties and thus, the addition of a surfactant is often important to ensure the drug release from such systems (Gumaste et al., 2016; Singh et al., 2011). The advantage of formulation of poorly soluble compounds as solid dispersions includes complete removal of drug crystallinity because it is generally known that the amorphous form is more soluble than its crystalline counterpart (Janssens and van den Mooter, 2009; Rumondor et al., 2009). Another advantage of solid dispersions is the size of the primary particles formed after the disintegration of the dosage forms which can limit the rate of dissolution of conventional capsules or tablets (Serajuddin, 1999). The solid dispersions can decrease the drug particle size into the molecular level (Vo et al., 2013). In addition, there is also the possibility to facilitate the development into preferred solid dosage forms, which can lead to lower manufacturing cost, smaller pill burden, improved physical and chemical stability or possibility of combination dosage form compared with liquid or semi-solid formulations (Qian et al., 2010). Moreover, Adler et al. (2016) or Gautschi et al. (2015) focused on an exploration of the feasibility of lipid-based solid dispersions which can be necessary approach to formulate challenging oral drugs.

However, there is still some uncertainty which is connected to the characterisation of such systems (Qi et al., 2008). Inverse gas chromatography can be used to describe the surface properties in terms of the dispersive component of the surface energy and of the acid-base or acceptor-donor character, because the surface energy

*Abbreviations:* API, active pharmaceutical ingredient; IGC, inverse gas chromatography; K12, Kollidon® 12 PF; K64, Kollidon® VA 64; PM, physical mixture; SD, solid dispersion; Sol, Soluplus®; STD, standard deviation.

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can noticeably affect the behaviour of pharmaceutical solids during processing or use (Grimsey et al., 2002; Schultz et al., 1987). In the case of pharmaceutical, this evaluation can help predict physico-chemical properties of particulate and fibrous materials, such as powder surface energies, acid/base/polar functionality of surfaces, diffusion kinetics, solubility parameters, surface heterogeneity or phase transformation caused by temperatures or humidities (Newell et al., 2001b; Thielmann and Levoguer, 2001). On the other hand, IGC has been also widely used to characterize the miscibility of the polymer mixtures containing a pair of amorphous homopolymers or a pair of amorphous-semicrystalline polymers in terms of interactions between polymers or polymer and solute, solubility parameters, sorption and mixing molar heat, decrease of melting point or contact energy parameters (Al-Saigh, 1997). The surface characteristics of the solid dispersions measured by IGC are characterised by the retention behaviour of probe. The probes of known properties are injected into the column containing the material of interest and the retention times are measured at infinite dilution leading to the low surface coverage and Henry's law is obeyed (Grimsey et al., 2002; Lavielle and Schultz, 1991; Schultz et al., 1987). It ensures only the interactions between the probes and the solid material (Schultz et al., 1987).

However, there is still the question that relates to the fact whether the probe can interact with one or both of the components in the binary systems. There are several assumptions that could describe the problem. The first assumption could be that the probes interact preferentially with the highest energy sites (Gamble et al., 2013). For example Newell et al. (2001a) described that even very small amounts of amorphous material significantly affect the surface energy due to its higher energy sites. Other assumption is that the measured energy is reduced due to one component which can create a barrier to interaction probes with the highest energy sites. And the final assumption could be that probes can interact with the both components equally (Gamble et al., 2013). And thus, it can be explained by the availability of the surface. Gamble et al. (2013) demonstrated that the probes interact preferentially with the lower surface available drug substance. Ho et al. (2010) proposed the passivation of strong binding sites or high energy sites by fine particles. Kołodziejek et al. (2013) determined surface energy for ternary systems of hybrid materials and it was described that most of the materials had comparable values of the dispersive component. However, the surface activity of the hybrid materials is influenced by the type of polymer or the weight ratio of the components.

The aim of this study was to evaluate the surface energy of the solid dispersions and to compare them with corresponding physical mixtures. IGC was used to characterisation of these binary mixtures. Acetaminophen was used as a model active pharmaceutical ingredient and Kollidon® 12 PF, Kollidon® VA 64 and Soluplus® were used as a polymeric carriers for drug. The dispersive component was calculated according to approach of Schultz et al. (1987) using a series of *n*-alkanes.

## 2. Materials and methods

### 2.1. Materials

Acetaminophen was obtained from Zentiva, k.s. (Prague, Czech Republic). Kollidon® 12 PF (K12), Kollidon® VA 64 (K64) and Soluplus® (Sol) were obtained from BASF Pharma (Ludwigshafen, Germany). Hexane, heptane, octane and nonane were of analytical grades and were obtained from Sigma-Aldrich (Prague, Czech Republic).

### 2.2. Preparation of solid dispersion

A solid dispersion containing 50%, 33% or 25% (w/w) acetaminophen was prepared using a melt method. 2 g physical mixture was weighed into an evaporating dish and then placed on a special metal holder. The holder was placed on a magnetic stirrer with heating. The physical mixture was heated above melting or glass transition temperatures of components until it melted. The melted liquid had to be stirred gently using a glass rod. This was to prevent phase separation and to aid mixing of the molten mixture. The melted mixture was then cooled and the final solid mass was crushed using a pestle and a mortar.

### 2.3. Inverse gas chromatography

The surface characteristics of the solid dispersions and physical mixtures were studied using the instrumented gas chromatograph (Shimadzu, Japan) which was equipped by mass detector QP 2010 (Shimadzu, Japan). The flow rate of the carrier gas, dry helium, was 2.32 mL $min^{-1}$. About 300 mg of the solid sample was uniformly packed in a pre-silanized glass column so there were no visible cracks, hollows or channels in the body of the powder. The sample column was blocked with silanized glass wool at each end. The column was placed in a column oven of the gas chromatograph and conditioned at 40 °C for 30 min in flowing helium before each measurement to remove residual moisture adsorbed on the powder surface. After this conditioning the temperature of the column oven was cooled down to 30 °C and then the probes were repeatedly injected in split mode of injector. In order to achieve infinite dilution condition, the probes (200 μL) were introduced to the injection port of the column using a 1 mL syringe. For the probes injections, evacuated Tedlar® bags (200 mL of nitrogen and 75 μL of solvent) were used. Series measurements with different gas phase probes allow the characterization of the surface energy of the solid sample. Hexane, heptane, octane and nonane were used as nonpolar probes which were carried into the column by helium and the retention time was detected.

The dispersive component of the surface energy was determined by Schultz et al. (1987) approach which is based on the retention parameters of these nonpolar probes. The net retention volume of the probe ($V_N$) was calculated using the following Eq. (1):

$$V_N = j \cdot D \cdot (t_R - t_0) \quad (1)$$

where $j$ is the James-Martin compressibility correction factor, $D$ is the flow rate of the carrier gas in the column, $t_R$ is the gross retention time (the maximum of the probe peak) of the solute and $t_0$ is the dead-time of non-interacting, non-adsorbed solute (nitrogen in our case). The specific retention volume ($V_g^0$) was used to eliminate the dependence of $V_N$ on the quantify of the stationary phase and the temperature and can be expressed by the following Eq. (2) (Ho and Heng, 2013):

$$V_g^0 = \left(\frac{V_N}{m_S}\right) \cdot \left(\frac{273.15}{T}\right) \quad (2)$$

where $m_S$ is the mass of the sample and $T$ is the experimental temperature. The combination of Eqs. (1) and (2) yields Eq. (3):

$$V_g^0 = \frac{j}{m_S} \cdot D \cdot (t_R - t_0) \cdot \frac{273.15}{T} \quad (3)$$

The standard Gibbs free energy change of desorption ($\Delta G_D^0$) or adsorption ($\Delta G_A^0$) is related to the $V_N$ and can be calculated from the following Eq. (4):

$$\Delta G_D^0 = -\Delta G_A^0 = RT \ln V_N + K \quad (4)$$