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iGC SEA Case Study 610

Correlating Mixing Properties of Model Excipient-API Blends to Spreading Coefficients Determined via Inverse Gas Chromatography

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Blend stability of dry powder mixtures is important for optimizing pharmaceutical processing and formulation. The spreading coefficient is a term used to predict blend quality based on individual component surface energy values. In this study, Inverse Gas Chromatography (IGC SEA) was used to measure surface energy values for model drugs and excipients. The surface energy values were then used to determine the drug-excipient spreading coefficients. Finally, the spreading coefficients were compared to physical mixing performance.

Introduction

During pharmaceutical processing it is common to mix dry blends of different components. When the blend is either transported or dispensed the components may segregate. This can be particularly troublesome when the API is not dispensing uniformly. This can lead to dosage irregularities during production. Therefore, predicting blend stability of different mixtures can be valuable in optimizing product processing and formulation.

In this study, the surface energy values of individual blend components were used to predict mixing behaviour. These values were compared to mechanical mixing results. The blend characteristics were determined by content uniformity, in order to test for how well the two powders initially mix upon blending. Also, loss on tapping was performed, to test how well the powders maintain a blend upon the input of energy without segregating.

Theory

IGC SEA is a well-known tool for the characterization of particulates [1], fibres [2] and films [3]. IGC SEA involves the sorption of a vapour (probe molecule) with known physico-chemical properties onto an adsorbent stationary phase with unknown physico-chemical properties. This approach inverts the conventional relationship between mobile and stationary phase found in analytical chromatography. The stronger the interaction of the vapour phase (known properties) with the unknown adsorbent (unknown properties), the more energetic the surface and the longer the vapour phase retention time. For this reason a range of thermodynamic parameters can be derived from the retention behaviour. A detailed explanation of the theory is given in Reference [1].

IGC SEA is commonly used to obtain surface energy values for powders. The surface energy is analogous to the surface tension of a liquid. In

practical terms, the higher the surface energy is the more reactive the surface will be. The surface energy parameter can be divided into a dispersive and a specific component. The dispersive surface energy can be directly calculated from the retention times of a series of injected n-alkanes [4]. The specific contribution of the surface energy is obtained indirectly via the specific free energy and different acid-base theories, obtained by injecting a range of polar probe molecules.

By applying an appropriate concept, the acid-base numbers can be calculated from the specific free energies. The study of acid-base properties by IGC SEA has the additional benefit that changes in the orientation of surface groups can be studied. Those changes are not necessarily related to variations in composition. For this reason spectroscopic methods are less appropriate for the study of these effects [5].

A common approach for acid-base calculations used in IGC SEA is the van Oss concept [6], which provides acid and base numbers in the same units as the dispersive surface energy.

$$\Delta Gsp = N_A * a_m * 2 * ((\gamma_L^+ * \gamma_S^-)^{1/2} + (\gamma_L^- * \gamma_S^+)^{1/2}) \quad (1)$$

In Equation 1 γ_S^+ and γ_S^- are the electron acceptor (acid) and electron donor (base) parameters of the surface and γ_L^+ and γ_L^- are the electron acceptor and donor parameters of the probe molecule. Unfortunately, in its original form, this equation can only be used for relative comparison due to inaccurate starting parameters leading to an overestimation of the basicity [7]. To correct this and decrease probe sensitivity, the input parameters have been rescaled for a more reliable determination of acid/base values according to Della Volpe [7]. With this rescaling, the van Oss concept is useful for the determination of the specific surface energy. The specific surface energy can be obtained from the γ_L^+ and γ_L^- numbers according to Equation 2:

$$\gamma_S^{SP} = 2 \cdot \sqrt{\gamma_S^+ \cdot \gamma_S^-} \quad (2)$$

From the dispersive (γ^D), specific (γ^{SP}), and total ($\gamma^T = \gamma^D + \gamma^{SP}$) surface energy values obtained from the individual components it is possible to predict blend performance based on the spreading coefficient [8]. Equation 3 gives the spreading coefficient ($\lambda_{1/2}$) for Sample 1 (i.e. drug) over Sample 2 (i.e. excipient).

$$\lambda_{1\ 2} = 4\ \frac{\gamma_1^D \gamma_2^D}{\gamma_1^D + \gamma_2^D} + \frac{\gamma_1^{SP} \gamma_2^{SP}}{\gamma_1^{SP} + \gamma_2^{SP}} - \frac{\gamma_1^T}{2} \quad (3)$$

A positive value for $\lambda_{1/2}$ indicates that material 1 is thermodynamically favoured to spread over material 2 and the higher $\lambda_{1/2}$ value the stronger the interaction between the two materials and the greater the likelihood that the samples will mix. The spreading coefficient theory was originally developed for systems where at least one component is a liquid. In this study, the approach is being expanded to investigate solid-solid interactions.

Method

Materials

Acetaminophen was used as a model drug. Mannitol (Partek M100), microcrystalline cellulose (MCC; Avicel PH 102), and Prosolv (Prosolv 90) were used as model excipients. The Acetaminophen powder was sieved using a 270 mesh screen, and the sieved portion was used resulting in particle size less than 53 µm. Excipient powders were sieved using a 200 mesh screen and the retained portion was used, resulting in a particle size greater than 74 µm.

Surface Energy Measurements

IGC SEA was used to measure the surface energy values of the Acetaminophen and excipients, independently. Samples were sieved as mentioned above prior to surface energy analysis. All surface energy measurements were performed at 30 °C, 10 sccm flow rate, and 0.03 P/Po injection concentration. The spreading coefficient (Equation 3) was used to predict blend behaviour from the individual component surface energy values. For the IGC SEA experiments the samples were packed into silanised glass columns (30 cm long, 4 mm ID). Prior to measurement the

sample was pre-treated at the measurement temperature for 2 hours in situ to remove any surface vapour contaminants. IGC SEA measurements were performed using the SMS-IGC SEA 2000 system (Surface Measurement Systems, UK). The probe molecules were injected into the helium stream via a loop with 250 µl volume at a concentration of 0.03 p/p0 to obtain infinite dilution conditions where only vapour-adsorption interactions are measured. The dead-time was determined by a methane injection. A Flame Ionization Detector (FID) was used to determine retention times.

Mixture Characteristics

Blends were prepared by mixing at the appropriate weight ratio in a V-blender for 30 minutes. Five samples from each blend were collected for content uniformity. The content uniformity was expressed by relative standard deviation (%RSD). For loss upon tapping, the blends were placed on top of a 200 mesh sieve screen sized such that only the API may pass through and tapping energy was applied by Rotap. After 1 minute of tapping, the retained fraction was sampled and analyzed for API load. All samples were analyzed by HPLC using an Agilent 1100 with in-line degasser, quaternary pump, autosampler, and single-wavelength detector. Quantification was performed per USP acetaminophen assay.

Results

Mixing Results

Relative goodness-of-blend was tested using both the loss on tapping (blend stability) and the content uniformity of the initial blend (quality of initial blend). Greater weight was placed on loss on tapping, as experience has shown that at times a blend with good content uniformity (low %RSD) can be prepared, but can then segregate when energy is applied. Results show that acetaminophen-mannitol and acetaminophen-Prosolv showed no loss upon tapping, while acetaminophen-MCC showed significant loss upon tapping ($p < 0.001$). Thus, acetaminophen-MCC is ranked as the worst performing blend. To differentiate the acetaminophen-mannitol and acetaminophen-Prosolv results the content uniformity values were used: the %RSD was 3.7% for acetaminophen-mannitol compared to 5.4% for acetaminophen-Prosolv, placing acetaminophen-mannitol higher in a rank-order comparison. Thus the final rank order based on loss on tapping and content uniformity is acetaminophen-mannitol > acetaminophen-Prosolv > acetaminophen-MCC. The content uniformity (%RSD) and loss on tapping results (p values for significant loss) are shown in Table 1 for the different mixtures.

Table 1. Mechanical mixing behaviour for the different acetaminophen-excipient blends.

Mixture	Content Uniformity (% RSD)	Loss on Tapping (p value for significant loss)
Acetaminophen-Mannitol	3.72	p = 0.13
Acetaminophen-Prosolv	5.40	p = 0.11
Acetaminophen-MCC	2.18	p < 0.001

Spreading Coefficients

The dispersive and specific surface energy values for acetaminophen and the different excipients are displayed in Figure 1. Mannitol has the highest surface energy, followed by Prosolv and MCC. Therefore, the Mannitol surface is the most active and is expected to have the highest affinity for the acetaminophen particle.

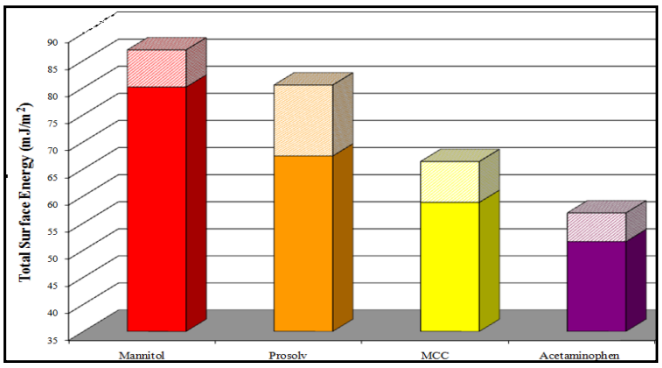

Figure 1. Dispersive (solid) and specific (shaded) surface energies for the acetaminophen and excipient samples.

As mentioned previously, the acetaminophen particles were sieved to be smaller (less than 53 µm) than the excipient particles (greater than 74 microns). Therefore, the spreading coefficients were calculated using Equation 3, with the acetaminophen spreading over the excipient. The calculated spreading coefficients are displayed in Figure 2. The spreading coefficients were as follows: 23.7, 18.2, and 8.6 mJ/m^2 for the acetaminophen-mannitol, acetaminophen-Prosolv, and acetaminophen-MCC mixtures, respectively. Higher spreading coefficients indicate the acetaminophen is more likely to stick to the larger excipient particles. The spreading coefficients obtained from the individual component surface energy values show the same trends as the physical mixtures. Therefore, the mixing performance as predicted by the surface energy values correlates directly with the blend properties measured by mechanical testing.

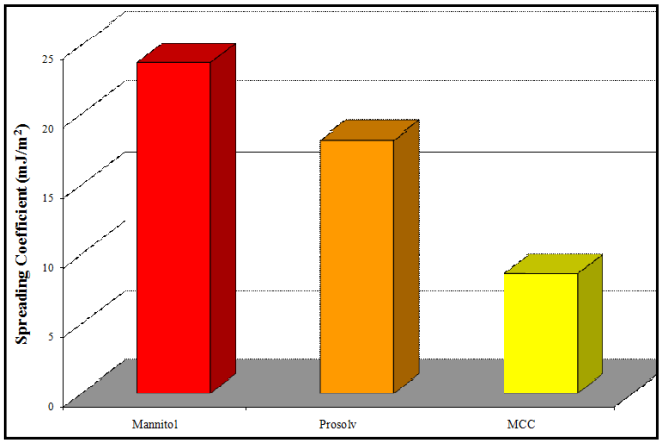

Figure 2. Spreading coefficients for the different acetaminophen-excipient blends.

Conclusion

Both mechanical (content uniformity and loss on tapping) and thermodynamic (spreading coefficient) mixing parameters indicated the following trend of excipients when blended with acetaminophen: mannitol > Prosolv > MCC. Therefore spreading coefficients obtained through the individual components' surface energy values could be used to predict ultimate blend performance. This methodology could be applied to any solid-solid or solid-liquid system where accurate surface energy (solids) or surface tension (liquid) values can be determined.

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