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iGC SEA Case Study 603

Correlating drug-binder adhesive strengths measured using Inverse Gas Chromatography with tablet performance

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Drug-binder interactions have a significant impact on wet-granulation behaviour and product performance. Such interaction can be described by the work of adhesion between drug and binder. In this study, the work of adhesion is calculated from surface energy measurements carried out on the individual components by Inverse Gas Chromatography. The drugs Acetaminophen and Ibuprofen have been studied as well as the binders HPC, HPMC and PVP. HPC showed the strongest adhesion, followed by HPMC and PVP. This correlated well with the trends in tablet hardness and friability. The higher the work of adhesion the higher the tablet strength and the lower the friability.

Introduction

The primary particles of pharmaceutical materials often exhibit poor flow and compression behaviour. Granulation can be applied to improve these powder properties. In a wet-granulation polymeric excipients are usually added as binding agents for this purpose. Controlling the adhesive strength between binders and active drugs is paramount in developing successful pharmaceutical formulations. Poor drug-binder adhesion often leads to insufficient binder spreading and inferior granule and tablet mechanical properties. The goal of this study is to predict drug-binder interactions based on surface energy measurements of the individual formulation components and to correlate results with mechanical properties of the final product.

Theoretical Background

The prediction of drug-binder interactions is based on the determination of the surface energy. The surface energy, Υ is directly related to the work of adhesion, W_{adh} by the expression in Equation 1.

$$W_{adh} = 2(\gamma_1 * \gamma_2)^{1/2} \quad (1)$$

In this equation the numbers 1 and 2 stand for the individual components of the blend (drug and binder). The surface energy can be split into a dispersive contribution, Υ^d describing Lifshitz-van der Waals interactions and a specific component, Υ^{sp} reflecting Lewis acid-base interactions [1]. Good and van Oss suggested to replace the general expression for the specific contribution with an acid and base parameter (γ^+ and γ^-) [2].

$$W^A_{total} = 2(\gamma_1^d * \gamma_2^d)^{1/2} + 2((\gamma_1^+ * \gamma_2^-)^{1/2} + (\gamma_1^- * \gamma_2^+)^{1/2} \quad (2)$$

Equation 2 shows that if the individual contributions to the surface energy can be measured then the determination of the work of adhesion is possible. Rowe showed in previous studies that W_{adh} is a suitable parameter for the description of drug-binder interactions (adhesive strength) [3]. If components 1 and 2 are the same material then the work of cohesion, W_{coh} can be

obtained as well. The ratio of adhesion to cohesion gives additional information on the thermodynamic "compatibility" of drug and excipients.

Surface energy determinations are typically carried out by wetting techniques such as contact angle measurements. However, those have a limited sensitivity and are difficult to perform on powders [4]. For this reason Inverse Gas Chromatography (IGC SEA) has been used in this study.

IGC SEA is a well-established technique for quickly and accurately measuring the surface energetics for a wide range of solids [5].

Method

The following materials were used: HPLC grade solvents (Heptane, Octane, Nonane, Decane, Undecane, Toluene and Chloroform), marketed by Aldrich Chemicals, UK; Klucel® EF Pharm Hydroxypropylcellulose (HPC) NF, marketed by Aqualon Division, Hercules Incorporated, Willmington, DE; Methocel® E5 Premium Hypromellose (HPMC), Type 2910, USP, marketed by Dow Chemical Company, Midland, MI; Plasdone® K29/32 Povidone (PVP), USP, marketed by International Speciality Products, Wayne, NJ; Ibuprofen, USP, marketed by BASF Coparation, Mount Olive, NJ; Acetaminophen, USP, marketed by Rhodia Inc., Cranbury, NJ; Ac-Di-Sol® croscarmellose sodium, NF, marketed by FMC Cooparation, Philadelphia, PA; Cab-O-sil® amorphous fumed silica (colloid silicon dioxide) NF, marketed by Cabot Corparation, Tuscola, IL; Lactose, regular grind, NF, marketed by Foremost Frams USA, Rothschild, WI; Calcium sulfate, hydrous, NF, marketed by J.T. Barker, Philipsburg, NJ; Magnesium stearate, NF, marketed by the Compton Corparation, Middlebury, CT.

Surface Energy Measurements

Surface energies were measured for model drugs (acetaminophen and ibuprofen) and common binding agents: hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC). The surface energy values were used to calculate the adhesive strengths for the various drug-binder combinations, which were subsequently compared with tablet strength data. All surface energy measurements were carried out on an SMS-iGC SEA 2000 (Surface Measurement Systems Ltd., London, UK) instrument. The materials were packed into glass columns (0.3 cm ID, 30 cm in length). Measurements were performed with Heptane, Octane, Nonane, Decane and Undecane for the determination of the dispersive contribution of the surface energy. Specific surface energies were determined using Toluene and Chloroform. Prior to the measurements a pre-treatment was carried out for 2 hours at 303 K to establish equilibrium with the samples and the carrier gas. After the pre-treatment procedure, pulse injections were performed by a 0.25 ml gas loop at 303 K and under infinite dilution conditions.

Granulation and Tabletting

Dry blends (approximately 1.5 kg) of the actives and fillers were granulated with binder solution in a 12 quart Hobart low shear mixer. The first dry blend comprised ibuprofen and lactose (83.3% and 9.9% of the final formula respectively). For the second model formulation a blend of acetaminophen, calcium sulfate and lactose (83.3% and 5.1% and 5.1% of the final formula respectively) was wet-granulated. The binder solutions were prepared so that the binder concentration in the final granulation was 4%. Binder solutions (500 cps or less) were added via a peristaltic pump over a 3 minute period. The granulations were dried to 0.5% moisture and milled through a 0.065" Fitzmill (Fitzpatrick, Elmhurst, IL) screen. Colloidal silicon dioxide, 0.25% and croscarmellose sodium, 2% were hand-screened (20 mesh) and blended with the granulation for 5 minutes in a V-blender (Peeterson-Kelly, Stroudsburg, PA). This was followed by addition of 0.5% magnesium stearate through a 20 mesh screen and further mixing for

2 minutes. Tablets (600 mg) were compressed at a force of 25 kN and a speed of 37 rpm on a instrumented Manesty Betapress using 7/16“ standard concave tooling. Crushing strength (average of 10 tablets in diametral compression) was measured using a Schleuniger 6D hardness tester (Pharmathron, Germany). Friability (10 tablets, 250 rotations, Vander Kamp fibrilator) and tablet weight uniformity were also recorded.

Results

The dispersive and specific surface energy values were measured on the drugs and binding agents as shown in Figure 1.

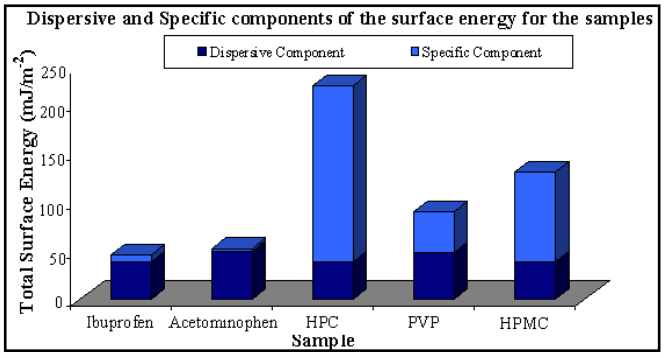

Figure 1. Dispersive and specific components of the surface energy obtained from IGC SEA experiments at infinite dilution. The dispersive contribution was measured by a series of alkanes (heptane to undecane). The specific contribution was obtained from measurements with toluene and chloroform.

The overall numbers are relatively high. This is due to the infinite dilution conditions of the experiment. In this regime the higher energy sites on the surface interact strongly with the probe molecule. However, since these sites are the most energetic ones they should make the biggest contribution to the overall interaction.

From these values, the work of adhesion was calculated for each drug-binder pair. For both drugs, the calculated adhesion strengths with the three binding agents followed the trend of HPC > HPMC > PVP as can be seen in Table 1. The drug-drug works of cohesion are also listed in Table 1.

Table 1. *Work of adhesion and cohesion (drug-drug) as determined from surface energy measurements.*

Drug	Wcoh (mJ/m^2) Drug-Drug	Wadh (mJ/m^2) HPC	Wadh (mJ/m^2) HPMC	Wadh (mJ/m^2) PVP
Ibuprofen	89.17	143.68	124.88	118.17
Acetaminophen	103.28	141.03	121.13	119.72

The results for tablet hardness and friability measurements are shown in Table 2 and 3.

Table 2. *Average (n=10) crushing forces (kP) for tablets compressed at 25kN.*

Drug	HPC	HPMC	PVP
Ibuprofen	17.3	16.2	15.3
Acetaminophen	14.8	10.7	4.8

Table 3. *Average (n=10) friability (%) for tablets compressed at 25kN.*

Drug	HPC	HPMC	PVP
Ibuprofen	1.1	1.1	1.4
Acetaminophen	0.7	15.9	34.3

As seen in Tables 2 and 3, the HPC formulations have the highest tablet strength (crushing force) and the lowest friability, indicating a direct correlation between work of adhesion and tablet strength and an inverse relationship with the friability. In a more accurate approach the work of adhesion to cohesion (drug-drug) ratio is considered in relation to the mechanical strength. This is shown in Figure 2.

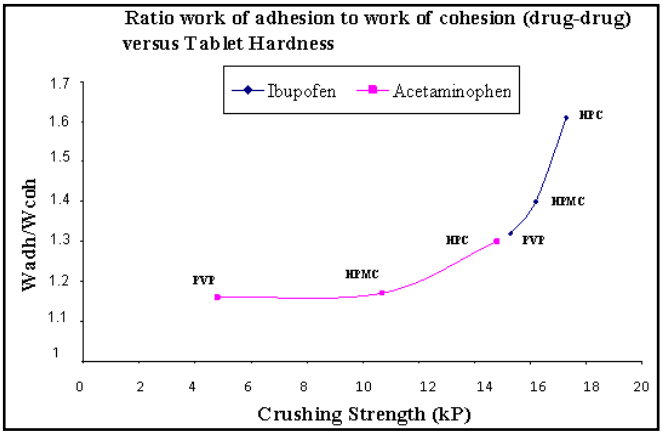

Figure 2. *Correlation of work of adhesion/cohesion ratio with tablet strength.*

Similar trends are observed: the higher the W_{adh} / W_{coh} ratio the higher the tablet hardness and the lower the friability. Therefore, higher work of adhesion values (in relation to work of cohesion) lead to stronger tablets. The W_{adh} / W_{coh} ratio is clearly a good measure for the tendency of particles from different materials to interact at their interfaces in comparison to their tendency of sticking together with a particle from the same material. In case of a wet-granulation this is important since a certain drug-binder interaction is required to cause spreading of binder over the drug and therefore to obtain uniform granules. If the drug-binder interaction is too low there is no spreading and it will not be possible to carry out a successful granulation consequently, regardless of the granulation conditions.

Conclusion

IGC SEA surface energy measurements can be used to predict adhesion strengths for different drug-binder systems. The higher the work of adhesion values in relation to the work of cohesion the stronger the tablets. This correlation shows that a "thermodynamic compatibility" between drug and binder is required in order to obtain uniform granules. Although other factors and components in the formulation can also affect this relationship the study shows the potential of this concept for the prediction of drug-excipient interactions in general and for a wet-granulation in particular.

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