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The importance of surface energetics of powders for drug delivery and the establishment of inverse gas chromatography

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Abstract

Powders are complex systems with more than one value for surface energy. The presence of different faces, defects, physical forms and impurities will alter the surface properties. There are few good ways to measure powder surface energies, with vapour sorption, especially inverse gas chromatography (IGC) being a logical choice. The significance of surface energy is reviewed briefly, as is the difference between contact angle and IGC data. The utility of IGC for studies of batch to batch variability and some issues relating to finding a suitable number to describe a complex range of surface energies are discussed. The utility of IGC in studies of the amorphous state is shown, where there is value in being able to monitor molecular mobility thresholds, glass transition, collapse and crystallisation, as well as relaxation and its impact on surface energy. The conclusion is that the complexity of powders means that scientists should not expect simple correlations between measurements and performance, but that correlations are likely to be there if the correct data are recorded in the most appropriate way.

Keywords: Inverse gas chromatography; Surface energy; Contact angle; Glass transition; Amorphous forms; Batch variability

Contents

1. Background

All processes occur by an initial surface contact, thus surface interactions can be expected to relate to the ease of production (for example, mixing, granulation, tabletting etc), the stability (given that solid state chemical interactions and reactions will be through surface contact [1]) and the ultimate biological fate (e.g. dissolution rate of solid dosage forms or the distribution of particles in the blood stream) (see Buckton 1995 [2] for a full range of examples). Hence the study of surface properties of powders can be expected to provide data that will at worst explain batch to batch variability, and at best provide control for approaches such as process analytical technology.

As the pharmaceutical industry develops its materials science capabilities and moves to gain improved understanding of how materials properties impact on the performance of active pharmaceutical ingredients (APIs) and excipients, it is logical

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that surface science of powders will be a factor to consider and thus vital to understand how surface properties may best be measured for powders.

The measurement of the surface tension of pure clean liquids is simple using readily available methodology (such as a Wilhelmy plate and a micro balance). The study of solutions becomes more difficult, due to the dynamic effects as molecules diffuse and potentially adsorb at the air/liquid interface. Indeed it is the dynamic effects that are of practical importance for many solution systems, as they are used in such a way rather than as an equilibrated surface (for example film coating solutions [3]). For smooth flat solid surfaces, for example polymers, the measurement of surface properties is also not too demanding, as small drops of liquid can be applied to the surface and contact angles measured. However, for drug delivery we generally start with an API and excipients that are in powder form. As will be discussed in greater detail below, powders are complex, it is reasonable to assume that each face of a crystal, each edge and defect, will have different surface properties due to the different proportions of various functional groups that are present. Amorphous materials, or crystals with some amorphous content, will relax with changes in surface energy as a function of time. Hence it is folly to seek the surface energy of a powder, as simply there can never be a single surface energy. The surface scientist Israelachvili once wrote "There are neither simple liquids nor solids, but rather a myriad of dissolved solute molecules, small molecular aggregates, or macroscopic particles interacting in liquid and vapour. It is the forces in such systems that ultimately determine the behaviour and properties of everyday things: soils, milk and cheese, paints and ink, adhesives and lubricants, many technological processes, detergents, micelles, biological molecules and membranes and we ourselves" [4]. Our natural tendency is to simplify complex behaviour such that it is described by a single number. We have to accept that if we search for a single number to describe powder surface energy then at best it will be a mean value, and at worst meaningless. This should be remembered as any method for powder surface energy is considered, used or even rejected.

For decades researchers have tried to find ways of assessing the surface energy of powders and it has always presented problems. A number of contact angle methods have been explored, including the rate of liquid penetration through powder beds, measurement of contact angles formed by drops on compressed powder surfaces, or Wilhelmy plate methods on compressed plates or on powder adhered to a glass cover slip. All of these methods have significant limitations for powders and have been reviewed previously [2].

The fact that contact angle methods for powders have limitations is not open to question, but despite these limitations they have often proved successful in providing correlations of surface energy values to product performance. Rowe used surface energy data derived from contact angle measurements on powders to predict interactions between binders and substrates in wet granulation [5] and then to correlate such interactions with granule and tablet properties [6]. Similar use of contact angle derived surface energy terms has been shown to correlate to the properties of aqueous [7] and non-aqueous suspensions [8] and even mucoadhesion [9,10]. This demonstrates that the many approximations and problems encountered with contact angle methodology for powders provide a real cause for concern, but that the mean values that are obtained are still of meaning when correlated to functionality. However the concerns over the methodologies have resulted in the growth of the use of vapour probes to assess surface energy for powders.

Fundamentally there is no difference in assessing surface energy via a vapour interaction or a liquid interaction with the solid. With vapour probes it is the affinity for different vapours with a solid surface that is used to assess the solid surface properties. The complexity comes from the fact that powder surfaces are not homogeneous, hence the multitude of different binding sites can be expected to give rise to different surface energy values. The fact that there are many surface energies to be determined gives rise to the chance to study the surface with great detail and understanding, but equally may present problems if the measured energy is not the one that dominates the process of interest.

Powder vapour interactions can be studied either gravimetrically, calorimetrically or chromatographically. Calorimetric studies involve adsorption of vapours to surfaces and measuring the enthalpy change directly. This does provide surface energy terms and as a full adsorption isotherm can be studied there will be a range of values available to map the energetics of the powder surface. This is the least developed of the methods and will not be discussed further here. Gravimetric studies are now routine, and since the arrival of automated temperature and humidity (vapour pressure) controlled microbalance systems, these provide accurate data. Whilst it is not always appreciated that adsorption isotherms relate to the surface energy profile of the powder, this is the case and it provides a sensitive method for comparison of different batches of powders. If organic vapours are used it is possible, but practically often difficult due to low mass changes, to calculate surface energy terms from gravimetric data. Chromatographic approaches are the ones that have been seen an increase in use and the application and limitations of this approach will be reviewed here.

2. Inverse phase gas chromatography

Inverse gas chromatography (IGC) is becoming well known in the pharmaceutical sector, although publications have only started in this field in the early 1990s ([11] for example), the technique was already well established in other disciplines and the subject of a number of books (for example [12–14]). Over the last decade the numbers of pharmaceutical publications have been increasing so that it is now possible to consider the application of this method.

2.1. Basic IGC theory

The concept of IGC is a simple one and that is to take a standard GC experiment and invert the known and unknown, such that the unknown is the column packed with the powder to test, and the known is the vapour (in fact vapours) that is (are) injected. In order to calculate surface energies it is most usual to plot $RT\ln V_n$ as a function of $a(\gamma_L^D)^{1/2}$, where R is the gas constant,