



Surface heterogeneity: Information from inverse gas chromatography and application to model pharmaceutical substances



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ABSTRACT

The general theory of electrokinetic phenomena strictly applies to ideal and rigid surfaces or particles. However, many interfaces are non-ideal with respect to both the surface smoothness and surface homogeneity. Detailed knowledge and understanding of the interface structure is often required for proper analysis of electrokinetic measurements. In this study, we investigate the option of studying surface heterogeneity using powder polycrystalline active pharmaceutical ingredients (APIs) as our model systems. We characterized these by a combination of physicochemical techniques, i.e. inverse gas chromatography surface energy analysis, SEM, thermal analysis and powder rheology, to assess the surface interface structure, topology, roughness, chemical heterogeneity and cooperative macroscopic behaviour. The latter characteristics are reflected in the three dimensional packing, which, in turn, affects the porosity and rigidity of the obtained powder bed. Such information is also of paramount interest for realizing proper fluid transport and dispersing or tableting API substances in the pharmaceutical industry. Notably, the 3D packing is affected not only by geometrical characteristics of the powders but also by the polarity and surface charge distribution. These characteristics can be correlated with surface energy data by means of surface energy profiles and surface energy distribution plots.

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1. Introduction

The general theory of electrokinetic phenomena strictly applies to ideal smooth, molecularly flat rigid surfaces or particles. However, many interfaces are non-ideal with respect to both surface smoothness and surface homogeneity. Moreover, two types of surfaces, i.e. hard and soft interfaces, can be distinguished. Hard surfaces are characterized by a sharp change of density at the boundary between the particle and surrounding medium, whereas soft surfaces are characterized by a gradual change in densities across the phase boundary. Thus, detailed knowledge and understanding of the interface structure in both the horizontal and vertical directions is vital for proper analysis of electrokinetic measurements data [1^{**}]. The properties of surfaces and interfaces have traditionally been characterized by the surface or interfacial tension and surface free energy [2–4]. However, the interfacial tension methods can only measure average surface characteristics over the contact area of the liquid at the tested interface. Hence, these techniques are not

sufficiently precise for heterogeneous surface analysis, where surface energy heterogeneity characterization is vital. Surface chemical interactions with a solid surface involve long- and short-range intermolecular forces, known as London dispersive and acid–base interactions, respectively [5^{**}]. The dispersive interactions are acting up to ~10 nm scale distance, stem from London dispersion forces. In contrast, acid–base interactions are specific short-range directional chemical interactions. They involve charge redistribution and sharing, as exemplified by the formation of weak chemical bonds. Hydrogen bonds are an example of acid–base interactions [6].

Surface heterogeneity can be divided into two types: structural and energetic [7]. A typical consequence of structural heterogeneity is a material pore size distribution. In contrast, energetic heterogeneity is demonstrated by a distribution of surface sites of different energetic levels. Such a heterogeneity profile can be represented by an energy distribution function. Generally, the energy distribution function can be determined from either the pressure or temperature dependence of adsorption. The temperature method has been successfully applied for the characterization of heterogeneity profiles of highly energetic surfaces, such as those with strong acid–base interactions between surfaces and probe molecules or with high adsorption potentials due to micro porosity [8^{**}]. In contrast, the pressure dependence

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method is more appropriate for the characterization of less energetic surfaces as these are particularly sensitive to small differences between energy levels. These can be studied by means of inverse gas chromatography methods.

2. iGC based surface energy analysis

Inverse gas chromatography (iGC) was introduced in the early 1940s by Martin and Synge. The background of the technique and its instrumentation is well described in a recent review article by Mohammadi-Jam and Waters [9^{**}]. One of the most interesting and commonly used applications of iGC is the measurement of surface free energies. The phenomenological parameters obtained from the method are the retention time and retention volume, which refer to the required time and carrier gas volume, respectively, to generate a peak as a result of interactions between the probe molecule and the stationary phase.

Non-covalent and non-electrostatic intermolecular forces, collectively called Lifshitz-van der Waals interactions (LW), can be divided into three groups according to their origin. The first group was defined by Keesom and includes the interactions operating between two molecules (1 and 2) with permanent dipoles. The energy of interaction between molecules is dependent on the thermal energy $k_B T$, as shown in the following equation:

$$V_{12}^{Keesom} = -\frac{2\mu_1^2\mu_2^2}{3(4\pi\epsilon_0)^2 k_B T r^6} = -\frac{C_{12}^P}{r^6} \quad (1)$$

where V is the potential energy, μ_1 and μ_2 are the dipole moments of molecules 1 and 2, respectively, ϵ_0 is the dielectric permittivity, k_B is the Boltzmann constant, T is the absolute temperature and r is the distance between the interacting molecules. The second type of LW interaction comprises induced interactions between molecules with a permanent dipole and neighbouring neutral molecules, referred to as Debye interactions. The potential energy of these forces between different molecules may be given as follows:

$$V_{12}^{Debye} = -\frac{\alpha_1\mu_2^2 + \alpha_2\mu_1^2}{(4\pi\epsilon_0)^2 r^6} = -\frac{C_{12}^I}{r^6} \quad (2)$$

where α denotes the polarizability of the molecules. In this case, the potential energy is independent of temperature because the induced dipole follows the motion of the permanent dipole independent of the thermal motion.

The last type of LW interactions, named after London, originate from random fluctuations in the polarization of molecules, generating temporary dipoles that influence each other. Although these forces are the weakest compared to the previous types, they are the most significant because they appear in all kinds of molecules, not only those containing polar molecules. Moreover, they are more or less of additive nature. The so-called dispersive interaction energy between unlike molecules may be described using the following formula:

$$V_{12}^{London} = -\frac{3\alpha_1\alpha_2}{2(4\pi\epsilon_0)^2 r^6} \frac{I_1 I_2}{I_1 + I_2} = -\frac{C_{12}^L}{r^6} \quad (3)$$

where $I = h\nu$ is the ionization energy (h stands for Planck's constant and ν for the frequency of fluctuation). The constants C_{12}^P , C_{12}^I , C_{12}^L in Eqs. (1)–(3) characterize the polar, induced and London interactions, respectively, between molecules 1 and 2. These three types of interaction can be combined into a single term because they are all inversely proportional to the sixth power of the distance between interacting molecules. The total LW interaction energy is then given by the sum of these components. Other forces influencing the magnitude of surface chemistry are Lewis acid–base interactions, which are generated between an electron acceptor (acid) and electron donor (base). They occur in compounds containing hydrogen bonds, i.e. strong secondary

bonds between atoms of hydrogen and a highly electronegative element, such as F, O, N and Cl, or other compounds interacting with Lewis acids and bases [2].

The surface Gibbs energies can be defined by the sum of dispersive and acid–base components of the surface energies. Here, acid–base (acceptor–donor) contributions include all components that are of non-dispersive nature. One of the most commonly applied methods for determining the dispersive component of surface energy was proposed by Schultz et al. [10,11^{**}]. They calculated the dispersive (London) component of the surface Gibbs energy (γ_{SD}) from retention parameters obtained with liquid n -alkane probes at infinite dilution, for which no acid–base interactions are present and Henry's Law is obeyed [12,13]. Under infinite dilution conditions it can be assumed that there are no interactions between adsorbate molecules. Consequently, a symmetrical Gaussian peak is expected in the iGC chromatogram. After injection into the column, it takes time for the probe molecule to interact with the stationary phase, termed the dead-time, t_0 . This parameter is often determined by passing an inert gas through the examined stationary phase. The solute exits from the column after a gross retention time, t_R . To obtain the net retention time (V_N), the dead-time must be deducted from the gross retention time. Hence, the net retention volume of the probe is given by Eq. (4) [14^{**}]:

$$V_N = j F_c (t_R - t_0) \quad (4)$$

where j and F_c are the James–Martin compressibility correction factor and the flow rate of the carrier gas in the column, respectively. The factor F_c corrects the effect of the pressure drop and packing density variation of the stationary phase on the retention time. In some experiments, the specific retention volume is used instead of the net retention volume to eliminate the effect of temperature and the quantity of the stationary phase, as described in Eq. (5) [14^{**}]:

$$V_g^0 = \left(\frac{V_N}{m_s}\right) \left(\frac{273.15}{T}\right) \quad (5)$$

where V_g^0 denotes the specific retention volume at 0 °C and m_s is the mass of the sample. Hence, by combining Eqs. (4) and (5), the specific retention volume can be expressed as follows [14^{**}]:

$$V_g^0 = \left(\frac{j}{m_s}\right) F_c (t_R - t_0) \frac{273.15}{T} \quad (6)$$

Interactions that occur between an adsorbate and adsorbent are either dispersive or specific. Dispersive and specific components of surface Gibbs energy can be calculated from thermodynamic equations. The standard Gibbs free energy change is related to the net retention volume, V_N , as follows [13,14^{**}]:

$$\Delta G_{ad}^0 = \Delta G_{de}^0 = RT \ln V_N + C \quad (7)$$

where ΔG_{ad}^0 and ΔG_{de}^0 are the standard molar Gibbs free energy changes of adsorption and desorption, respectively, R and T are the gas constant and absolute temperature (K), respectively, and the constant C is indicative of the reference states. The free energy of adsorption (ΔG_{ad}^0) can be calculated by the sum of the dispersive (ΔG_{ad}^D) and specific (acid–base, ΔG_{ad}^{SP}) components of the free energy of adsorption [15]:

$$\Delta G_{ad}^0 = \Delta G_{ad}^D + \Delta G_{ad}^{SP} \quad (8)$$

The assumption is that these two contributions are additive. When n -alkanes are used as probes, there are no specific interactions with the stationary phase, and hence $\Delta G_{ad}^0 = \Delta G_{ad}^D$ and their value depends on the number of carbon atoms in the alkane molecule [12]. The free energy of adsorption is defined as:

$$\Delta G_{ad}^0 = N_A a W_{adh} \quad (9)$$

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