ELSEVIER

International Journal of Pharmaceutics 148 (1997) 1–21

international journal of pharmaceutics

Invited review

# The use of solubility parameters in pharmaceutical dosage form design

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Received 15 October 1996; received in revised form 21 November 1996; accepted 28 November 1996

**Abstract**

The use and potential of solubility parameters for pharmaceutical dosage form design are reviewed in this paper. Specific reference is given to the development of the approach, its previous usage and likely future applications. The advantages, assumptions and limitations of this type of approach are also described. © 1997 Elsevier Science B.V.

*Keywords:* Cohesive energy density; Solubility parameter; Interaction; Polarity; Formulation

## 1. Introduction

The rational design of pharmaceutical dosage forms results from a clear understanding of: (i) the chemical and physical properties of the dosage form components and (ii) their potential to interact with each other and the environments to which they are exposed. Such material properties and subsequent interactions can be readily estimated from a knowledge of the solubility parameters (or cohesive energy densities (CED)) of the formulation components.

## 2. Background

The cohesive energy of a material is the energy which holds that substance together. It is the amount of energy required to separate the constituent atoms or molecules of the material to an infinite distance, and hence it is a direct measure

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*PII* S0378-5173(96)04828-4

of the attraction that its atoms or molecules have for one another. Cohesive energy is the net effect of all the inter atomic/molecular interactions including Van der Waals interactions, covalent bonds, ionic bonds, hydrogen bonds, electrostatic interactions, induced dipole and permanent dipole interactions. An understanding of cohesive energies is important to the materials scientist because they can be used to explain or predict how substances will behave when they are subjected to external stresses, such as heat, light or mechanical forces. Cohesive energies are especially important to the pharmaceutical materials scientist because they determine many of the critical physico-chemical properties (e.g. solubility, melting point) of drugs and excipients. A thorough understanding of cohesive energies can increase our awareness of how pharmaceutical materials will behave when processed or when dosed into the human body.

The cohesive energy of a material can be quantified in a number of ways. The most common approach is to use the so-called solubility parameter ($\delta$) (Hildebrand and Scott, 1950; Hansen, 1969; Barton, 1983; 1985). Solubility parameter theory was developed by Hildebrand and co-workers (Hildebrand and Scott, 1950) based on regular solution theory. According to their approach when two materials are mixed together the heat of mixing ($\Delta H$) is given by:

$$\Delta H = V_T\{(\Delta E_{V1}/V_{m1})^{0.5} - (\Delta E_{V2}/V_{m2})^{0.5}\}^2 \cdot \phi_1 \cdot \phi_2 \quad (1)$$

where $V_T$ is the total volume, $\Delta E_V$ is the energy of vapourisation, $V_m$ the molar volume, $\phi$ is the volume fraction, and 1 and 2 refer to the solvent and solute components, respectively. The solubility parameter of each component is defined as the square root of its CED, measured as the energy of vapourisation per unit volume:

$$\delta = (CED)^{0.5} = (\Delta E_v/V_m)^{0.5} \quad (2)$$

When the solubility parameters of two materials are similar Eq. (1) predicts they will be mutually and athermally soluble. The units of the solubility parameter are $(J/m^3)^{0.5}$, $MPa^{0.5}$ or $(cal/cm^3)^{0.5}$, and one $(cal/cm^3)^{0.5}$ is equivalent to 2.0421 $MPa^{0.5}$ or $(J/m^3)^{0.5}$.

The concept of solubility parameters was originally developed for simple liquid mixtures and in order to extend the principles to consider more complex situations several approximations and assumptions are required. Typically gases are treated as hypothetical liquids whilst solids are treated as supercooled liquids. With these assumptions it is possible to apply solubility parameter theories to ideal gases, and to organic solids with a low level of crystallinity. Regular solution theory, upon which the concept of solubility parameters is based, also applies best to non-polar molecules which interact through weak dispersion forces. Several methods have been proposed to extend solubility parameter concepts to the more polar strongly interacting species which are typical of pharmaceutical materials. Various authors (Hansen, 1967a,b, 1969; Karger et al., 1978) have sub-divided the total solubility parameter ($\delta_t$) (also known as the Hildebrand solubility parameter) into components which express the contributions from the different types of interatomic/intermolecular forces (e.g. hydrogen bonds ($\delta_h$), dispersion forces ($\delta_d$), 'polar' interactions ($\delta_p$):

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (3)$$

This approach allows a more detailed characterisation of the system of interest. It also permits the calculation of the polarity of a material ($X_p$) (Zografi and Tam, 1976):

$$X_p = \delta_p^2/\delta_t^2 \quad (4)$$

This parameter provides insight into the balance of polar and non-polar forces operating between adjacent atoms/molecules and between material surfaces. An alternative 'extended solubility parameter' theory has been developed by Martin and co-workers (Adjei et al., 1980; Martin et al., 1980, 1981) in order to describe the solubility of crystalline solids in both polar and non-polar liquids. These authors used an interaction parameter to account for specific solute–solvent interactions. In the case of a perfectly regular solution this interaction parameter equals one. When there is attraction between the solute and solvent the parameter is greater than unity and when there is self association by either component

Table 1
Solubility parameters and fractional polarities of some drugs

| Material | Sol. param. ($MPa^{0.5}$) | Polarity | Method | Reference |
|---|---|---|---|---|
| Aspirin | 24.1–24.9 | 0.29 | Calculated | Samaha and Naggar, 1990; Roberts et al., 1991 |
| Barbital | 27.6 | — | Solubility | Khalil and Martin, 1967 |
| Benzocaine | 31.7 | — | Solubility | Most, 1972 |
| Benzoic acid | 23.5–24.3 | — | Solubility, calculated | Chertkoff and Martin, 1960; Samaha and Naggar, 1990 |
| Betamethasone | 24.5 | — | Calculated | Samaha and Naggar, 1988 |
| Caffeine (anhydrous) | 26.6 | 0.60 | Inverse gas chromotography | Huu-Phuoc et al., 1987; Rowe, 1989a |
| Caffeine (anhydrous) | 28.0 | 0.49 | Calculated | Ticehurst, 1994 |
| Caffeine (anhydrous) | 28.2 | — | Solubility | Adjei et al., 1980 |
| Caffeine (anhydrous) | 23.3–28.7 | 0.16–0.59 | Partition, solubility, inverse gas chromotography, calorimetry | Rey-Mermet et al., 1991 |
| Carbamezapine | 31.2–33.2 | 0.61–0.65 | Inverse gas chromatography | Ticehurst, 1994 |
| Carbamezapine | 22.4–22.6 | 0.23–0.25 | Calculated | Ticehurst, 1994 |
| Cephalexin (20.8% crystalline) | 37.4 | 0.72 | Inverse gas chromotography | Egawa et al., 1992 |
| Cephalexin (36.7% crystalline) | 38.0 | 0.72 | Inverse gas chromotography | Egawa et al., 1992 |
| Cephalexin (88.6% crystalline) | 27.0 | 0.60 | Inverse gas chromotography | Egawa et al., 1992 |
| Cephalexin (freeze dried) | 31.4 | 0.61 | Inverse gas chromotography | Egawa et al., 1992 |
| Cephalexin | 22.4 | 0.30 | Calculated | Ticehurst, 1994 |
| Ethinamate | 28.2 | — | Calculated | Samaha and Naggar, 1990 |
| Griseofulvin | 21.3 | — | Calculated | Samaha and Naggar, 1990 |
| Hydrocortisone | 25.3 | — | Calculated | Samaha and Naggar, 1990 |
| Hydrocortisone acetate | 23.7 | — | Calculated | Samaha and Naggar, 1990 |
| Ibuprofen | 20.4 | 0.14 | Calculated | Roberts et al., 1994 |
| Indomethacin | 25.2 | — | Calculated | Samaha and Naggar, 1990 |
| Norethindrone derivatives | 19.8–22.2 | — | Solubility | Lewis and Enever, 1979 |
| Paracetamol | 26.2 | 0.41 | Calculated | Ticehurst, 1994 |
| Phenacetin | 23.6 | — | Calculated | Samaha and Naggar, 1990 |
| Phenobarbital | 25.6 | 0.32 | Calculated | Rowe, 1989b |
| Phenylbutazone | 22.9–27.3 | 0.19–0.50 | Solubility, calorimetry | Samaha and Naggar, 1988; Rey-Mermet et al., 1991 |
| Propanolol hydrochloride | 24.4 | 0.22 | Calculated | Ticehurst, 1994 |
| Propanolol hydrochloride | 35.5 | 0.68 | Inverse gas chromatography | Ticehurst, 1994 |
| Salicylamide | 31.3 | — | Calculated | Roberts et al., 1994 |
| Salicylic acid | 22.1 | — | Solubility | Khalil and Martin, 1967 |
| Steroids | 17.2–25.3 | — | Calculated | Michaels et al., 1975; Samaha and Naggar, 1988 |

Table 1 (continued)

| Material | Sol. param. ($MPa^{0.5}$) | Polarity | Method | Reference |
|---|---|---|---|---|
| Sulphonamides | 20–28 | — | Solubility | Samaha and Naggar, 1988; Bustamante et al., 1993a |
| Testosterone proprionate | 19.4 | 0.41 | Solubility | James et al., 1976; Rowe, 1989a |
| Theophylline (anhydrous) | 28.5 | — | Solubility | Martin et al., 1980 |
| Theophylline (anhydrous) | 28.6 | 0.45 | Inverse gas chromotography | Huu-Phuoc et al., 1987; Rowe, 1989a |
| Theophylline (anhydrous) | 29.8,24.4 | 0.36, 0.53 | Solubility, calorimetry | Rey-Mermet et al., 1991 |
| Theophylline (anhydrous) | 27.4 | 0.50 | Calculated | Ticehurst, 1994 |
| Tolbutamide | 22.0 | — | Calculated | Samaha and Naggar, 1988 |

then the parameter is less than one. This approach can be used to describe almost any solute–solvent system but it has very limited predictive capabilities.

There have been many detailed reviews of the development of solubility parameters over the past 40 years and the reader is referred to these for further background information (Hansen, 1969; Barton, 1983, 1985). In the remainder of this paper the use of solubility parameters specifically for the design of pharmaceutical dosage forms is described. The methods suitable for determining the solubility parameters of pharmaceutical materials are first reviewed, then examples of the properties and interactions that can be predicted from solubility parameters are given. Finally the advantages and limitations of using a solubility parameter approach for pharmaceutical dosage form design are outlined.

## 3. Determination of solubility parameters of pharmaceutical materials

Of all the direct and indirect methods available for determining solubility parameters many are suitable for use with pharmaceutical materials (Tables 1 and 2). Different methods give slightly different results (Barton, 1983; Rey-Mermet et al., 1991) and the best methods to choose are those which most closely represent the in-use situation of the material(s) under consideration. The level of variation seen between different methods is illustrated for three typical pharmaceutical materials in Tables 3 and 4. Variations in both the total solubility parameter and the fractional polarity of pharmaceutical materials are common.

By definition the solubility parameter ($\delta$) of a material is linked to its heat of vapourisation ($\Delta H_v$):

$$\delta = (\mathrm{CED})^{0.5} = (\Delta E_v / V_m)^{0.5} = ((\Delta H_v - RT)/V_m)^{0.5} \quad (5)$$

For materials which are stable above their boiling points the heat of vapourisation can be directly determined. However, this method only provides the total solubility parameter, and it is often unsuitable for drugs and excipients because of thermal instabilities. The heat of vapourisation of pharmaceutical liquids can be indirectly determined from their vapour pressure using the Clausius–Clapeyron equation (Sunwoo and Eisen, 1971) or from their boiling points using an empirical equation (Vaughan, 1985; Lin, 1992).

Several group contribution methods have been developed for calculating solubility parameters (Van Krevelen and Hoftyzer, 1976). This approach requires a knowledge of the chemical structure of the material, and this is normally available for pharmaceutical substances (Table 5). Such an approach is especially useful at the start of the pharmaceutical development process as it

Table 2
Solubility parameters and fractional polarities of some pharmaceutical solvents, excipients and packaging materials

| Material | Sol. param. ($MPa^{0.5}$) | Polarity | Method | Reference |
|---|---|---|---|---|
| Acetic acid | 21.3–21.5 | 0.55 | — | Vaughan, 1985; Bochek and Petropavlovsky, 1993 |
| Acetone | 19.8–20.3 | 0.41 | — | Grulke, 1975; Vaughan, 1985; Suga and Takahama, 1996 |
| Acetonitrile | 23.9–24.3 | 0.61 | — | Grulke, 1975; Vaughan, 1985 |
| Amylose | 24.5 | — | Calculated | Cowie, 1965 |
| Amylose | 25.3 | — | Viscosity | Cowie, 1965 |
| Benzoic acid | 23.5 | — | — | Vaughan, 1985 |
| Benzyl alcohol | 25.1 | — | Calculated | Vaughan, 1985 |
| BHA | 25.3 | — | Calculated | Vaughan, 1985 |
| Butylparaben | 21.6 | — | — | Vaughan, 1985 |
| Carbon black | 27.8 | 0.42 | — | Hansen, 1967b |
| Castor oil | 18.2–18.4 | — | — | Vaughan, 1985; King, 1995 |
| Cellulose | 25.7 | 0.76 | — | Grulke, 1975 |
| Cellulose | 36.2 | 0.69 | Calculated | Bochek and Petropavlovsky, 1993 |
| Cellulose | 56.2 | 0.96 | Viscosity, swelling | Bochek and Petropavlovsky, 1993 |
| Cellulose (microcrystalline) | 30.2 | 0.73 | Calculated, modulus | Roberts and Rowe, 1993 |
| Cellulose (microcrystalline) | 39.3 | 0.76 | Inverse gas chromatography | Huu-Phuoc et al., 1987 |
| Cellulose acetate | 19.6–47.9 | 0.25–0.93 | Viscosity, solubility | Archer, 1992; Bochek and Petropavlovsky, 1993 |
| Cellulose acetate phthalate | 21.7–27.2 | — | Calculated | Sakellariou et al., 1986 |
| Cetyl alcohol | 18.3 | — | Calculated | Vaughan, 1985 |
| Chloroform | 19.0 | 0.12 | — | Grulke, 1975 |
| Cholesterol | 19.5 | — | Calculated | Vaughan, 1985 |
| Cyclohexane | 16.8 | 0.00 | — | Grulke, 1975 |
| D and C Red No. 22 (Eosin) | 22.8 | — | — | Vaughan, 1985 |
| Dibutyl phthalate | 19.0–20.2 | 0.23 | — | Grulke, 1975; Vaughan, 1985; Rasmussen and Walmstrom, 1994 |
| Diethyl phthalate | 20.5 | 0.26 | — | Kent and Rowe, 1978; Grulke, 1975 |
| Dimethicone | 12.1 | — | — | Vaughan, 1985 |
| Dimethyl phthalate | 21.9–22.1 | 0.29 | — | Grulke, 1975; Kent and Rowe, 1978 |
| Dioctyl phthalate | 18.2 | 0.17 | — | Grulke, 1975; Vaughan, 1985 |
| Dimethyl-sulfoxide | 24.6–27.4 | 0.52 | — | Grulke, 1975; Vaughan, 1985 |
| Ethanol | 25.6–26.5 | 0.64 | — | Vaughan, 1985; Bochek and Petropavlovsky, 1993 |
| Ethyl acetate | 18.6–18.8 | 0.25 | — | Grulke, 1975; Vaughan, 1985 |
| Ethylcellulose | 20.6 | 0.34 | Viscosity, solubility | Kent and Rowe, 1978; Archer, 1992 |
| Ethylene glycol | 29.6 | — | — | Vaughan, 1985 |
| Freon 12 | 11.3 | — | — | Grulke, 1975 |
| Gelatin | 24.5 | — | Swelling | Bajpai, 1996 |
| Glycerol | 33.2–47.1 | 0.77–0.86 | — | Grulke, 1975; Lewis and Enever, 1979; Vaughan, 1985; Bustamante et al., 1993b |

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