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Invited review

The use of solubility parameters in pharmaceutical dosage form design

Bruno C. Hancock ^{a,*}, Peter York ^b, Raymond C. Rowe ^c

 ^a Merck Frosst Canada Incorporated, Pharmaceutical R&D Department, 16711 Transcanada Highway, Kirkland, Quebec H9H 3L1, Canada
 ^b School of Pharmacy, University of Bradford, Bradford, UK

^c Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK

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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.

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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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^{*} Corresponding author. Tel.: +1 514 4283342; fax: +1 514 4282677; e-mail: bruno_hancock@merck.com

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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 (δ) (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 (ΔH) is given by:

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

where $V_{\rm T}$ is the total volume, $\Delta E_{\rm v}$ is the energy of vapourisation, $V_{\rm m}$ the molar volume, ϕ 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:

$$\delta = (CED)^{0.5} = (\Delta E_{\rm v}/V_{\rm m})^{0.5} \tag{2}$$

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 $(J/m^3)^{0.5}$.

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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 (δ_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 (δ_h), dispersion forces (δ_d), 'polar' interactions (δ_p) :

$$\delta_{\rm t}^2 = \delta_{\rm d}^2 + \delta_{\rm p}^2 + \delta_{\rm h}^2 \tag{3}$$

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):

$$X_{\rm p} = \delta_{\rm p}^2 / \delta_{\rm t}^2 \tag{4}$$

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

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Table 1 Solubility parameters and fractional polarities of some drugs

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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	1	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, 1989;	
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% crys- talline)	37.4	0.72	Inverse gas chromotography	Egawa et al., 1992	
Cephalexin (36.7% crys- talline)	38.0	0.72	Inverse gas chromotography	Egawa et al., 1992	
Cephalexin (88.6% crys- talline)	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	
lbuprofen	20.4	0.14	Calculated	Roberts et al., 1994	
Indomethacin	25.2		Calculated	Samaha and Naggar, 1990	
Norethindrone derivatives	19.8-22.2	1775-1 Ve 1275	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	
henylbutazone	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 Steroids	22.1 17.2–25.3	()	Solubility Calculated	Khalil and Martin, 1967 Michaels et al., 1975; Samaha and Naggar, 1988	

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Table 1	(continued)	
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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

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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 (δ) of a material is linked to its heat of vapourisation ($\Delta H_{\rm v}$):

$$\delta = (\text{CED})^{0.5} = (\varDelta E_{\rm v}/V_{\rm m})^{0.5} = ((\varDelta H_{\rm v} - RT)/V_{\rm m})^{0.5}$$
(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 ma	terials

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	2 <u></u>	Viscosity	Cowie, 1965
Benzoic acid	23.5		_	Vaughan, 1985
Benzyl alcohol	25.1		Calculated	Vaughan, 1985
BHA	25.3	2	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,	Bochek and Petropavlovsky, 1993
			swelling	
Cellulose (microcrys- talline)	30.2	0.73	Calculated, modulus	Roberts and Rowe, 1993
Cellulose (microcrys-	39.3	0.76	Inverse gas chromatogra-	Huu-Phuoc et al., 1987
talline)	10 4 45 0	0.05 0.00	phy	
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	0.12	Calculated	Vaughan, 1985
Cyclohexane	16.8	0.00	Calculated	Grulke, 1975
D and C Red No. 22	22.8	—	-	Vaughan, 1985
(Eosin)	10.0 20.2	0.22		
Dibutyl	19.0-20.2	0.23		Grulke, 1975; Vaughan, 1985;
phthalate	20.5	0.24		Rasmussen and Walmstrom, 1994
Diethyl phthalate	20.5	0.26		Kent and Rowe, 1978; Grulke, 1975
Dimethicone	12.1	E internet in the second se		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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