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Invited review

The use of solubility parameters in pharmaceutical dosage form design

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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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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:

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

where V_T is the total volume, ΔE_V is the energy of vapourisation, V_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:

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

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 (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):

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

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 (δ) of a material is linked to its heat of vapourisation (ΔH_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

Table 2 (continued)

Material	Sol. param. ($MPa^{0.5}$)	Polarity	Method	Reference
Hydroxyethylcellulose	25.5–19.8	0.8—0.81	Calculated	Choi et al., 1994
Hydroxyethylcellulose	31.0–29.2	0.70–0.43	Molecular modelling	Choi et al., 1994
Hydroxypropylcellulose	22.1–20.8	0.76–0.72	Calculated	Choi et al., 1994
Hydroxypropylcellulose	23.7–22.1	0.71–0.58	Molecular modelling	Choi et al., 1994
Hydroxypropylcellulose	25.5–22.1	0.71–0.48	—	Roberts and Thomas, 1978; Choi et al., 1994
Hydroxypropylmethylcellulose	22.8–30.6	0.60–0.66	Solubility, calculated	Rowe, 1988b; 1989a,b; Archer, 1992
HPMCP	26.4–17.2	—	Calculated	Sakellariou et al., 1986
Iron oxide (red)	28.0	0.45	—	Hansen, 1967b
Isopropanol	23.0	—	—	Vaughan, 1985
Lactic acid	30.2	—	Calculated	Vaughan, 1985
Lactose (anhydrous)	33.2	0.74	Calculated	Ticehurst, 1994
Lactose (anhydrous)	36.0–39.9	0.74–0.82	Inverse gas chromatography	Huu-Phuoc et al., 1987; Ticehurst, 1994; Maeda et al., 1992, 1995
Lactose (monohydrate)	36.3	0.75	Inverse gas chromatography	Nakai et al., 1989
Lauric acid	17.3	—	Calculated	Vaughan, 1985
Lauryl alcohol	19.4	—	Calculated	Vaughan, 1985
Magnesium stearate	18.2	0.26	—	Little, 1966; Rowe, 1988c,d; 1989a
Methanol	29.3–29.7	0.74	—	Grulke, 1975; Vaughan, 1985
Methyl cellulose	21.3	0.56	—	Rowe, 1988a; 1989a,b
Methylene chloride	19.5	—	—	Vaughan, 1985
Methyl paraben	24.5	—	Calculated	Vaughan, 1985
Mineral oil	14.5	—	—	Vaughan, 1985
n-octanol	17.8–21.3	0.34–0.37	—	Grulke, 1975; Bustamante et al., 1993b
n-propanol	24.3	0.58	—	Grulke, 1975
N-methyl pyrrolidone	23.1	0.38	—	Grulke, 1975
Nylon 6,6	22.9–27.8	0.37	—	Tobolsky, 1960; Grulke, 1975
Oleic acid	15.8–16.1	0.18	—	Grulke, 1975; Vaughan, 1985
Palmitic acid	16.1	—	Calculated	Vaughan, 1985
Petrolatum	15.0	—	—	Vaughan, 1985
Polyethylene	17.6	0.00	—	Barton, 1983; Rowe, 1988a
Polyethylene oxide	34.7	—	—	Lee, 1968
Polyethylene glycol	18.0–26.1	—	Calculated	Vaughan, 1985; Sakellariou et al., 1986
Polyoxyethylated ethers	24.9–29.6	0.52–0.60	Calculated	Samaha and Naggar, 1988
Polyoxyethylated nonyl phenols	25.1–27.0	0.50–0.55	Calculated	Samaha and Naggar, 1988

Table 2 (continued)

Material	Sol. param. ($MPa^{0.5}$)	Polarity	Method	Reference
Polyoxyethylated octyl phenols	23.7–28.4	0.45–0.54	Calculated	Samaha and Naggar, 1988
Polytetrafluoro-ethylene	12.7	—	—	Tobolsky, 1960
Polyvinylacetate	25.6	0.33	—	Barton, 1983; Rowe, 1988a
Polyvinyl alcohol	19.9–34.4	—	Calculated	Sakellariou and Rowe, 1996
Polyvinyl chloride	21.4	0.28	–	Barton, 1983; Rowe, 1988a; 1989b
Polyvinyl pyrrolidone	21.2	0.47	Calculated	Rowe, 1988b
Propylene glycol	25.8–30.3	0.69	—	Grulke, 1975; Lewis and Enever, 1979; Vaughan, 1985
Sorbic acid	24.4	—	Calculated	Vaughan, 1985
Sorbitan laurate	8.61	—	Calculated	Vaughan, 1985
Soybean oil	17.2–18.2	—	—	King, 1995
Stearic acid	15.8–17.6	0.13	Calculated	Hansen, 1967b; Vaughan, 1985; Rowe, 1988c
Sucrose	32.8	—	Calculated	Roberts et al., 1994
t-butanol	21.0	—	—	Vaughan, 1985
Titanium dioxide	34.4	0.51	—	Hansen, 1967b
Triacetin	22.0	—	Calculated	Vaughan, 1985
Tweens	24.4–29.4	0.45–0.57	Calculated	Samaha and Naggar, 1988
Water	47.9	0.90–0.93	—	Lewis and Enever, 1979; Grulke, 1975; Bustamante et al., 1993b

allows characterisation of a material when there may not be sufficient available for experimental determinations. Rowe and co-workers (Rowe, 1988b, 1989b; Roberts et al., 1994) have used group contribution methods to determine the partial and total solubility parameters of a wide range of pharmaceutical drugs and excipients (Tables 1 and 2). This method has also been used to estimate the solubility parameters of biological systems such as the human skin (Groning and Braun, 1996). Solubility parameters can be estimated from molecular structure using molecular modeling and molecular dynamics calculations. The solubility parameters of several organic solvents and one common pharmaceutical polymer (hydroxypropyl cellulose) have been determined in this way and the results compare favourably with those determined experimentally (Choi et al., 1994; Suga and Takahama, 1996).

It is possible to determine partial and total solubility parameters by measuring the solubility/miscibility of a material in liquids with known cohesive energies (Reuteler-Faoro et al., 1988). The solubility parameter of the test substance is assumed to be the same as that of the liquid in which it most completely and athermally dissolves (Fig. 1). This method of determining solubility parameters is very popular because of its practical simplicity and its applicability to solids, liquids and gases. Archer (1992) has recently used this technique to determine the solubility parameters of some pharmaceutical film-coating polymers. For highly accurate measurements the approach can be combined with solution calorimetry (Rey-Mermet et al., 1989, 1991).

The cohesive energy of a material is directly proportional to its surface free energy (Gardon, 1977; Samaha and Naggar, 1990) and it can be shown that:

Table 3
Total solubility parameters of caffeine, theophylline and phenylbutazone obtained by various methods ($MPa^{0.5}$) (Rey-Mermet et al., 1991)

Method	Caffeine	Theophylline	Phenylbutazone
Calculated	25.6	28.8	23.9
Sublimation	27.1–28.1	34.4	—
Vapourisation	22.4	31.9	—
Inverse gas chromatography	26.6	28.7	28.1
Solubility	27.2–28.2	28.2–28.7	25.2
Partition	24.3	—	—
Calorimetry	29.9	24.0	26.6
Surface tension	26.0	29.1	—

$$\delta^2 = (\gamma / V_m^{1/3})^n \quad (6)$$

where γ is the surface free energy of a material and n is a constant related to the arrangement of atoms or molecules in space. Thus, it is possible to calculate solubility parameters directly from surface free energies and molar volumes (Koenhen and Smolders, 1975; Van Krevelen and Hoftyzer, 1976; Gardon, 1977; Roberts and Thomas, 1978). This method has been compared with other methods of determining solubility parameters for a wide range of pharmaceutical materials and found to correlate very well (Fig. 2) (Samaha and Naggar, 1990). As a consequence of this relationship it is possible to use any of the methods used to evaluate surface energetic properties to determine solubility parameters. These methods (e.g. contact angle analysis) and their application to pharmaceutical systems have been extensively described in the literature (Stamm et al., 1984; Buckton, 1990, 1992) and will not be described any further here.

The solubility parameters of pharmaceutical solids and liquids can also be determined using inverse gas chromatographic (IGC) experiments, from the retention times of gases of known cohesive energies. This method has been used for a wide range of pharmaceutical excipients and drugs (Tables 1–4) (Huu-Phuoc et al., 1986, 1987; Nakai et al., 1989; Egawa et al., 1992; Ticehurst, 1994; Ticehurst et al., 1994; King, 1995). The method gives precise and reproducible solubility parameters, but it is not a true equilibrium method and the results obtained may be affected by a heterogeneous distribution of active sites on the stationary phase. It has been argued that the necessary manipulation of the stationary phase and its prolonged exposure to the carrier gas(es) during the experiment may alter the measured cohesive energy density (e.g. by drying) (Ticehurst, 1994; Ticehurst et al., 1994). The occasional differences in results reported between this method and other simpler approaches (Tables 3 and 4) probably result from its greater sensitivity to surface heterogeneities compared to bulk cohesive energy determination methods.

The cohesive energy of a solid plays a major role in determining its fundamental mechanical properties and, thus, solubility parameters can be estimated from the results of mechanical property measurements (Roberts and Rowe, 1993; Roberts et al., 1994). Willbourn (1976) reported that the CED of various polymers is related to their Young's modulus, and Gardon has shown a simple relationship between the tensile strength of a range of inorganic materials and their solubility parameters (Gardon, 1977). Roberts and Rowe (1993) have shown the validity of this type of approach for pharmaceutical materials. These authors measured the Young's modulus and critical stress intensity factor of compressed specimens of microcrystalline cellulose in solvents of differing solubility parameters. They found that the partial solubility parameters calculated for the microcrystalline cellulose using this technique were very similar to those determined by methods such as inverse gas chromatography and contact angle analysis. More recently these authors have demonstrated correlations between the Young's

Table 4
Partial solubility parameters and fractional polarity of caffeine, theophylline and phenylbutazone obtained by various methods ($MPa^{0.5}$) (Rey-Mermet et al., 1991; Ticehurst, 1994)

Material	Method	δ_t	δ_d	δ_p	δ_h	X_p
Caffeine	IGC	26.7	17.0	11.7	17.0	0.59
	Solubility	26.6–28.7	20.1–20.6	7.2–13.9	10.5–18.6	0.43–0.48
	Partition	23.3	21.4	3.8	8.3	0.16
	Calorimetry	25.8	17.3	13.7	13.4	0.55
	Calculated	28.0	20.0	14.3	13.3	0.49
Theophylline	Solubility	29.8	23.8	13.4	11.9	0.36
	Calorimetry	24.4	16.8	11.3	13.7	0.53
	Calculated	27.4	19.4	14.2	13.2	0.50
Phenylbutazone	Solubility	23.9–27.3	16.9–24.5	9.2–13.0	7.6–10.7	0.19–0.50
	Calorimetry	24.0	17.5	12.5	10.7	0.47

modulus, tensile strength and critical stress intensity factors of a wide range of pharmaceutical materials and their solubility parameters (Roberts et al., 1996).

Solubility parameters of pharmaceutical polymers can be estimated from the upper limiting intrinsic viscosities of their solutions in solvents of varying quality, or from their Flory–Huggins polymer–solvent interaction parameters (Cowie, 1965; Roberts and Thomas, 1978; LaPack et al., 1994; Paik and Writer, 1995). Kent and Rowe (1978) used intrinsic viscosity measurements to determine the solubility parameter of ethylcellulose utilised in pharmaceutical film coatings and achieved results which were identical to several other methods (Fig. 3). Flory–Huggins polymer–solvent interactions parameters can be determined from measurements of solvent sorption, solution vapour pressure, osmotic pressure or light scattering measurements. Thus, this method has great potential for determining the solubility parameters of pharmaceutical polymers.

The solubility parameters of pharmaceutical materials can be estimated from a range of other fundamental material properties (e.g. refractive index (Koenhen and Smolders, 1975; James et al., 1976; Vaughan, 1985), coefficients of thermal expansion (Van Krevelen and Hoftyzer, 1976; Vaughan, 1985)). Such methods are not routinely used and they have an unknown degree of uncertainty associated with their results (Van Krevelen and Hoftyzer, 1976). For more details the reader is referred to the book by Van Krevelen and Hoftyzer (1976)

4. Use of solubility parameters in pharmaceutical dosage form design

A knowledge of the cohesive energy density of a material is invaluable in determining how it will behave when exposed to different external conditions (e.g. during processing, under physiological conditions). As a consequence of this solubility parameters have found widespread application in all aspects of pharmaceutical dosage form design. It is possible to divide the reported applications of solubility parameters into three main groups. These are: (i) prediction of unknown material properties; (ii) assessment of processing effects on material properties; and (iii) the prediction of interactions and incompatibilities between materials.

4.1. Prediction of unknown material properties

Many fundamental material properties are linked to the cohesive energy holding the atoms or molecules of that material together. It is thus possible to estimate unknown material properties from a knowledge of their solubility parameters. For example, the thermal properties of materials are connected to their interatomic/molecular cohesive forces, and fundamental relationships be-

Table 5
Partial solubility parameters of ibuprofen calculated using group contribution parameters ($MPa^{0.5}$) (Roberts et al., 1994)

Group	Frequency	Partial molar volume ($cm^3.mol^{-1}$)	${}^zF_d$ ($J^{0.5}.cm^{1.5}.mol^{-1}$)	${}^zF_p^2$ ($J\ cm^3\ mol^{-2}$)	${}^zU_h$ ($J\ mol^{-1}$)
C_6H_4 (aromatic ring)	1	52.4	1270	12 100	0
CH	2	−2.0	2 × 80	0	0
CH_2	1	16.1	270	0	0
CH_3	3	100.5	3 × 420	0	0
COOH	1	20.8	530	176 400	10 000
Total		187.8	3490	188 500	10 000
$\delta t = (\delta_d^2+\delta_p^2+\delta_h^2)^{0.5} = 20.36$		$X_p = (\delta_p^2+\delta_h^2)/\delta_t^2 = 0.14$	$\delta_d = 3490/185.2 = 18.84\ MPa^{0.5}$	$\delta_p = (1\,885\,000)^{0.5}/185.2 = 2.34\ MPa^{0.5}$	$\delta_h = (10\,000/185.2)^{0.5} = 7.35\ MPa^{0.5}$

Molecular weight = 206.3 $g.mol^{-1}$, true density = 1.11 $g\ cm^3$, total molar volume = 185.2 $cm^3\ mol^{-1}$.

tween the melting point and glass transition temperature of pharmaceutical solids and their solubility parameters have been reported (Tobolsky, 1960; Lee, 1968; Michaels et al., 1975). Paruta et al. (1962) have also demonstrated that the dielectric constant of pharmaceutical solvents can be related to their total solubility parameter (Fig. 4). The mechanical properties of solids are likewise related to their interatomic/intermolecular forces. Willbourn (1976) showed that the Young's modulus of various polymers is related to their CED in a linear fashion, and Gardon (1977) showed a similar relationship between the tensile strength of inorganic materials and their solubility parameters. Roberts et al. (1991, 1994, 1996) and York (1992) have recently demonstrated that similar relationships exist for a wide range of drugs and excipients (Figs. 5 and 6). Yamamoto and Furukawa (1995) have used cohesive energy densities in their model to predict the shear yield stress of a series of amorphous polymers. With the recent

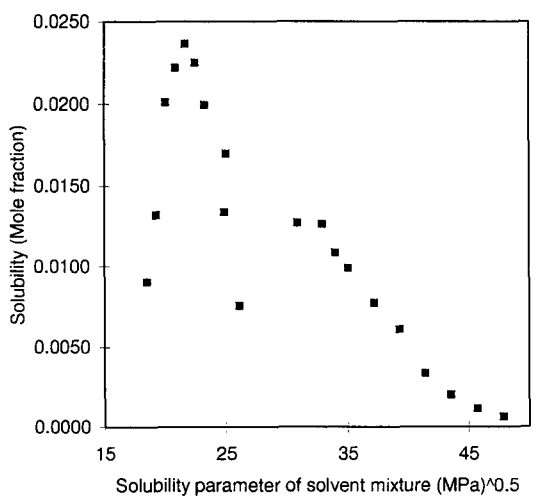

Fig. 1. Solubility of sulfanilamide as a function of solvent solubility parameter for ethanol–water mixtures and ethanol–ethyl acetate mixtures (data from Bustamante et al., 1994).

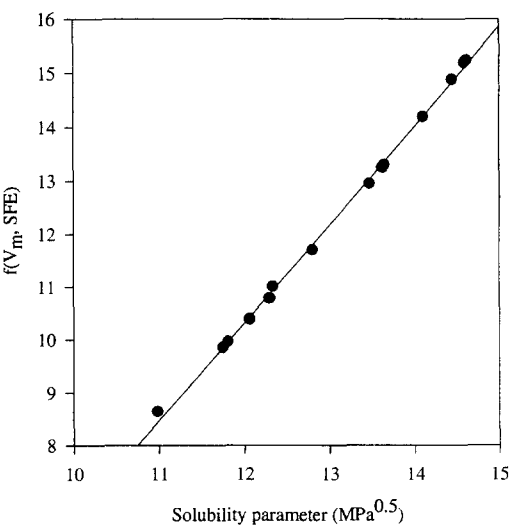

Fig. 2. Correlation between the surface free energies and solubility parameters of some pharmaceutical solids (data from Samaha and Naggar, 1990).

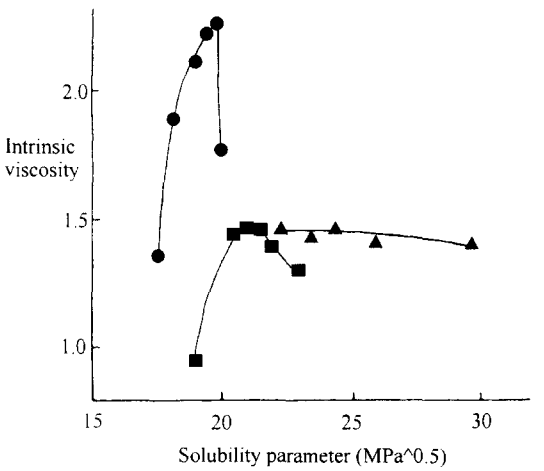

Fig. 3. The viscosity of ethyl cellulose in three classes of solvents as a function of their solubility parameter (data from Kent and Rowe, 1978).

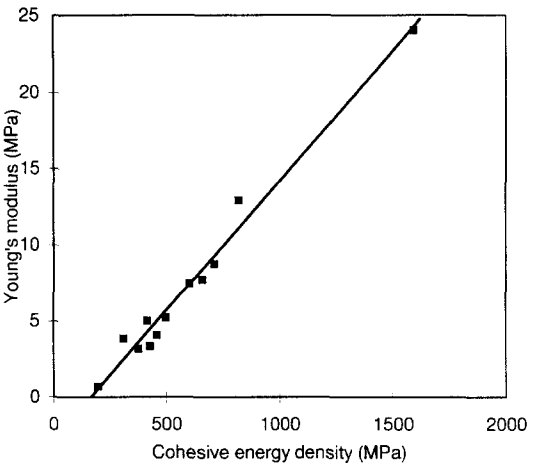

Fig. 5. Correlation between the Young's modulus and cohesive energy density (CED) of a series of drugs and excipients (data from Roberts et al., 1991).

development of reliable models for predicting macroscopic material properties from molecular structure information it may soon be possible to use solubility parameters to predict many more fundamental material properties.

The solubility parameters of well characterised materials can often be used to calculate those of less well studied but structurally similar compounds. For example, the partial solubility parameters of pure cellulose have been determined by extrapolating those of cellulose acetate with varying degrees of substitution (Bochek and Petropavlovsky, 1993) (Fig. 7). In a similar way the solubility parameters of several alcohols have been calculated from those of a related homologous series of alcohols (Paruta et al., 1962; Carre and Vial, 1994) (Fig. 8). Samaha and Naggar (1988) used a correlative approach to study the surface active properties of a series of nonionic surfactants and showed that critical micelle concentration (CMC) varied in a systematic way

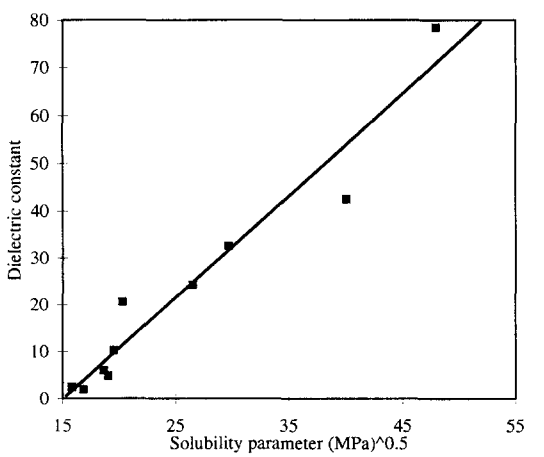

Fig. 4. Correlation between the dielectric constants and solubility parameters of some common pharmaceutical solvents (data from Table 3).

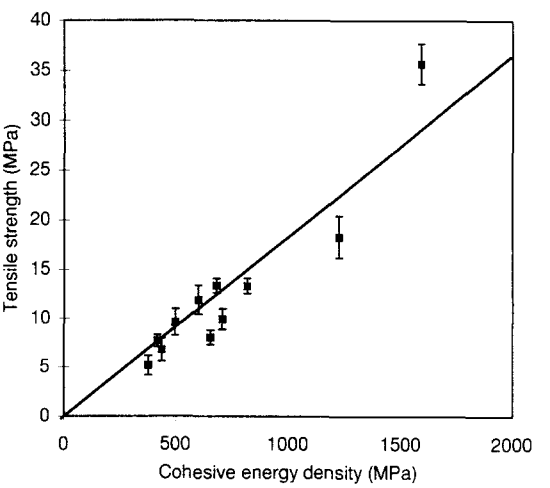

Fig. 6. Correlation between the tensile strength and cohesive energy density (CED) of a series of drugs and excipients (data from Roberts et al., 1996).

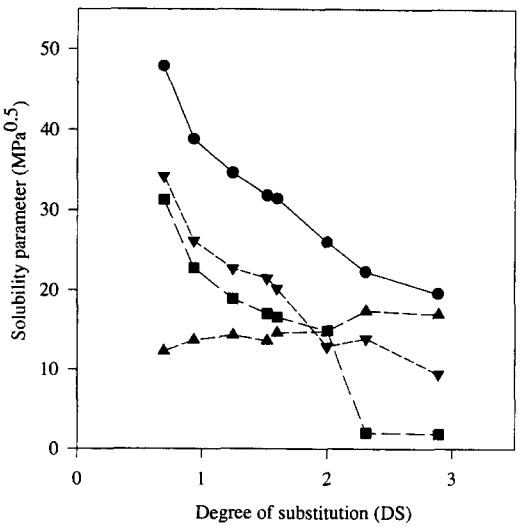

Fig. 7. Partial solubility parameters for cellulose acetates of varying degrees of substitution (DS) ■ = δ_p, Δ = δ_d, ▽ = δ_h, ● = δ_t (data from Bochek and Petropavlovsky, 1993).

with the partial solubility parameters. It was argued that the CMC of structurally related homologs could be predicted from the observed relationship with reasonable accuracy. Such approaches have great potential for determining the properties of a new chemical entity prior to synthesis, and in predicting structure–activity relationships (SAR).

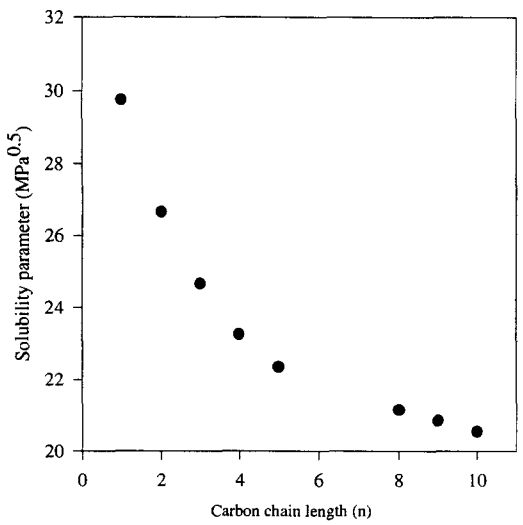

Fig. 8. Solubility parameters for alcohols of varying carbon chain lengths (n) (data from Carre and Vial, 1994).

The solubility parameter of a theoretical molecular mixture can also be predicted from those of the mixture components by assuming that simple rules of mixing apply to the system under consideration (Chertkoff and Martin, 1960; James and Roberts, 1968; Sunwoo and Eisen, 1971; Yalkowsky et al., 1972; Breon et al., 1980; Samaha and Naggar, 1990; Bochek and Petropavlovsky, 1993; Rasmussen and Walmstrom, 1994). This approach has been used in the selection of optimal solvents for chromatographic separations and several other pharmaceutical operations (e.g. solvent coating processes) (Bakalyar et al., 1977; Karger et al., 1978; Buchmann and Kesselring, 1981). Predictions for simple binary mixtures of like solvents are usually most accurate with deviations seen as the properties of the components become more dissimilar or as the number of components increases.

4.2. Assessment of the effects of material processing

It is possible to assess the effects that processing has upon a pharmaceutical material by determining its solubility parameters before and after the processing operation. For such experiments it is necessary to be able to measure solubility parameters with high accuracy and reproducibility and most authors have used inverse gas chromatographic (IGC) techniques for their analyses. Nakai et al. (1989) and Egawa et al. (1992) demonstrated significant differences in total and partial solubility parameters of cefalexin powder following milling or lyophilisation. As the crystallinity of the drug was reduced by processing each of the solubility parameters increased indicating that the energy of the cohesive interactions between molecules had increased. Such behaviour is consistent with the proposed 'activating' effect of these pharmaceutical processes (Hansford et al., 1980; Buckton et al., 1988). Ticehurst (Ticehurst, 1994; Ticehurst et al., 1994) studied the effect of comminution on the solubility parameters of several pharmaceutical powders (including aspirin, carbamezapine, lactose, propanolol, and salbutamol) using IGC. This author determined that the solubility parameters of aspirin and carbamezapine were not significantly affected by

Table 6
Predicted strength of some substrate-binder interactions (Rowe, 1988b, 1989b)

Substrate	Strength of substrate cohesive interaction (MPa)	Relative strength of substrate-binder adhesive interaction	
		Polyvinylpyrrolidone	Hydroxypropyl methylcellulose
Caffeine (anhydrous)	176.9	0.67	0.84
Cellulose (microcrystalline)	386.1	0.22	0.33
Lactose (anhydrous)	398.0	0.21	0.31
Theophylline (anhydrous)	204.5	0.59	0.74
Testosterone proprionate	94.0	1.07	1.12

milling whereas those of lactose, propanolol and salbutamol were. As in the previous studies high energy mechanical treatment increased the cohesive energy of these materials as measured by IGC. Maeda et al. (1992) and Maeda et al. (1995) have studied the effects of heat treatment on the cohesive energy of samples of anhydrous lactose by IGC. They found that higher pre-treatment temperatures resulted in an increased cohesive energy and polarity of the material consistent with a thermal activation effect. Only these few studies of the effects of material processing on cohesive energies have been reported to date because of the high degree of experimental care that is usually required. However, the increasing demand for a better understanding of the physical properties of drugs, and the enhanced sensitivity of modern IGC methods should mean that such reports will be common in the future (Williams, 1991).

4.3. Prediction of material interactions and compatibilities

Perhaps the most common use of solubility parameters in the decelopment of a pharmaceutical dosage form is in predicting how materials will interact when combined in multi-component formulations. Hildebrand's original theory was developed with such an application in mind and it is particularly well suited for predicting such situations. By using the partial solubility parameter approaches developed by Hansen and other workers (Hansen, 1967a,b, 1969; Karger et al., 1978) it is possible to go beyond simple predictions of solubility or miscibility and to define the exact type and strength of the forces which control 'compatibility'. Adhesive and cohesive interactions at surfaces can be predicted from the solubility parameters of the formulation components by using geometric or harmonic mean methods to estimate the strength of the interfacial interaction forces (Table 6). In addition spreading (λ) and interaction (ϕ) parameters can be calculated from the solubility parameters of the individual raw materials (Gardon, 1977; Rowe, 1988a,b,c, 1989a,b, 1992, Barra et al., 1996).

4.3.1. Solid–solid interactions

In the production of solid pharmaceutical dosage forms a great many solid–solid contacts are formed, for example, during the initial stages of powder blending. In all powder blends the efficiency and quality of mixing is strongly influenced by the cohesive and adhesive properties of the mixture components. Rowe (1988c,d, 1989a) has demonstrated for mixtures containing functional excipients such as colourants, lubricants or glidants the homogeneity of the formulation can be 'optimised' by using solubility parameters to dictate the choice of the auxiliary components in the mixture. For example, it was noted that for a hydrophilic tabletting excipient such as microcrystalline cellulose there is a rank order of interaction with tabletting lubricants (magnesium

stearate > stearic acid > polytetrafluoroethylene). The ideal adhesive strength between components and their interaction parameter, ϕ, can be calculated, the most likely material interactions predicted, and the best lubricant then selected. Often one component can have a tendency to coat the surface of another because of favourable adhesive interactions and an ordered mixture can be created which resists segregation. This can be advantageous if uniformity of mixing is important (e.g. for even colouration), but may be disadvantageous if a surface coating reduces wetting or inter-particle bond formation (e.g. with a hydrophobic lubricant). In formulations where colloidal silica and magnesium stearate are combined, for example, the strong interaction between these components may alter the lubricating properties of the magnesium stearate (Rowe, 1988c,d). Multi-component interactions can also be predicted and the results used to assess whether problems are likely to occur in multi-component powder blends, such as those intended for use in direct–compression tablet formulations. Bonding between powder particles during compression is closely related to the solid state interactions between the formulation components and it has been shown that calculation of interactions between materials from solubility parameters can be useful in optimising the mechanical properties of pharmaceutical compacts (Luangtana-Anan and Fell, 1990). Solid-state compatibility studies may also be simplified by consideration of the cohesive energies of the materials being used and their likely interactions. Selective sorption at surfaces may occur and this can potentiate physical or chemical instabilities in the formulation and possibly cause processing problems later on (Podczek et al., 1996).

The choice of plasticiser for use in polymer film coatings can be optimised with a knowledge of the solubility parameters of the coating components. Rowe and co-workers (Rowe, 1982, 1986; Rowe et al., 1984; Sakellariou and Rowe, 1996) and Salmen and Back (1977) showed that a compatible plasticiser with maximal plasticising efficiency can be selected quite rapidly using such an approach. This allows a coating formulation to be designed which possesses the desired mechanical properties, whilst resisting phase separation upon drying and storage. The best plasticiser is usually that with the best 'solvent properties', or the most similar solubility parameter. The adhesion of such a film coat to the tablet surface can be concurrently optimised during this design process (Rowe, 1988a), as can any other adhesive process (Table 6) (Gardon, 1977). The optimal choice of additives such as plasticisers, pigments, opacifiers, and extenders can be made using a similar approach. This should enable coatings to be produced which have minimal internal stresses which can cause film cracking, bridging of intagliations, surface crazing, and edge splitting. Cosmetic differences between batches and poor processing control and reproducibility may also result from sub-optimal selection of the coating components.

The design of bio-compatible polymers which adhere efficiently to biological membranes has benefited from approaches for predicting polymer–membrane adhesion (Kaelble and Moacanin, 1977; Lehr et al., 1993). Membrane compatibility with drugs for controlled release applications has also been rationally improved by several groups of workers by relating the solubility parameters of the drug and the membranes to the release characteristics of the dosage form (Khalil and Martin, 1967; Lhoest, 1972; Most, 1972; Michaels et al., 1975). Sakellariou and Rowe (1996) have used solubility parameters to characterise and predict material properties and interactions in polymer blends used as matrices for controlled drug delivery. An understanding of the phase behaviour and mechanical properties of such systems is essential for the rational and reliable design of extended release dosage forms. The polymer blend properties can be optimized by the correct choice of polymers, plasticisers, extenders and solvents based on interactions predicted from solubility parameters.

4.3.2. Solid–liquid interactions

Solid–liquid interactions of all types can be predicted with a high degree of accuracy by considering the influences of cohesive energy densities and this is probably where the application of solubility parameter concepts to pharmaceutical systems has been most widespread to date. When

a solid and a liquid come into contact the first process which must occur is wetting. Mitsui et al. (1972) studied the wetting of powders (such as titanium dioxide and iron oxide) by a variety of solvents and reported that the solubility parameter of both the powder and the liquid were very important in determining the extent of wetting. Wetting is a key parameter in the selection of polymer solutions for use as binders in pharmaceutical wet granulation or film coating processes, and solubility parameters have been used in this selection process (Kent and Rowe, 1978; Johnson and Zografi, 1986; Rowe, 1988a,b,c,d, 1989a,b, 1992). In order to achieve the best binder distribution in a wet granulation process, or to maximise polymer film coating performance, wetting of the substrate should be spontaneous and adhesion to the granule or tablet surface should be maximal (Table 6). Analysis of the properties of dried granules and coated tablets has shown that this approach to selecting a wet-granulation binder or a film coating agent is both accurate and reliable. Rowe (1992) noted that there is a parabolic relationship between the spreading tendency of polymer solutions and the polar partial solubility parameter of the substrate. This means that each solid substrate will have a different 'optimal' binder/film former depending upon the polar cohesive energy make-up of its surface. Micro-encapsulation performance has likewise been optimised by careful identification of desirable solid–liquid (polymer–solvent) interactions within solid dosage formulations (Moldenhauer and Nairn, 1994). Moldenhauer and Nairn (1994) used two dimensional solubility parameter maps (Fig. 10) in an attempt to identify the optimum solvent system for their ethylcellulose based microsphere system. The use of a 'wetting interaction approach' for designing conventional and advanced pharmaceutical dosage forms has great value and it has even been incorporated into expert systems for formulation design (Rowe, 1993; Rowe and Upjohn, 1993).

Once wetting has occurred in a solid–liquid system a number of other processes can take place. The solid may be: (i) suspended; (ii) swell; or (iii) dissolve in the liquid. Suspension stability has been considered by Young and Buckton (1990) in a surface energetic interaction investigation of the properties of some barbiturate suspensions. The most stable suspensions were those where it was predicted that the suspending medium would spontaneously wet and spread over the surface of the drug particles. An identical outcome would also have been attained if the solubility parameters of the materials had been used to determine the most likely solid–liquid interactions. The swelling of polymer matrices for controlled release dosage forms can be readily investigated using conventional solubility parameter approaches (Barton, 1983). Maximum swelling is expected when the solubility parameter of the solvent and the polymer are similar (Thode and Guide, 1959; Bajpai, 1996). Dissolution of the solid is often desirable and the selection of an optimal solvent system can be facilitated through a knowledge of both the solid and liquid solubility parameters. Cosolvent systems for use in lyophilized or ophthalmic preparations can be designed in this way. For highly polar systems it may be necessary to match both the polarity and the total cohesive energy of the components under consideration. Ensuring complete dissolution of a drug powder during formulation is often critical and there are many reports of the influence of the solubility parameter of the drug substrate (Fig. 1). The range of materials that has been studied includes caffeine (Adjei et al., 1980; Martin et al., 1981), sulphonamides (Mauger et al., 1972; Bustamante et al., 1993a,b, 1994), benzoic acid and its derivatives (Chertkoff and Martin, 1960; Restaino and Martin, 1964), testosterone esters (James and Roberts, 1968; James et al., 1976), norethindrone derivatives (Lewis and Enever, 1979), theophylline and theobromine (Martin et al., 1980, 1981), and alkyl-*p*-aminobenzoates (Yalkowsky et al., 1972). In a compressed tablet preparation the rate of dissolution of the drug is very important. A correlation between the rate of dissolution and the solubility parameters of cefalexin powders has recently been reported by Egawa et al. (1992).

Once a solution has been formed many of its fundamental properties are determined by the interactions between the dissolved solute and the solvent atoms/molecules. The viscosity of polymer solutions is critical in many pharmaceutical sys-

tems (e.g. ophthalmic preparations, topical formulations) and this can be markedly affected by the type and magnitude of the polymer–solvent interactions. Maximal solution stability and viscosity will occur at the point at which the solubility parameters of solute and solvent are identical, and either polymer or solvent can be selected based on the known cohesive energy of the other component (Kent and Rowe, 1978). Partitioning of a drug between phases in a mixed solvent system can also be predicted from the solubility parameters of the drug and solvents. This approach can be used to predict partitioning behaviour *in vivo* or *in vitro* and thus has applications as diverse as estimating bioavailability of a drug (Khalil et al., 1976), predicting permeation behaviour across a membrane (Khalil and Martin, 1967; Michaels et al., 1975; LaPack et al., 1994) (Fig. 9) or determining the optimal solvents for a chromatographic assay (Bakalyar et al., 1977; Karger et al., 1978; Buchmann and Kesselring, 1981; Gonzalez and Asuero, 1993; Sun et al., 1994). Groning and Braun (1996) recently reported that partial solubility parameters were very valuable in determining the transdermal transport properties of steroids, analgesics and other common drugs. They used a theoretical

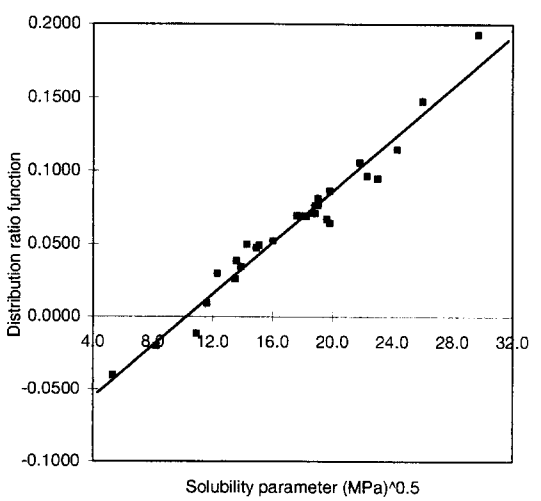

Fig. 9. Correlation between the distribution ratio functions and solubility parameters of some liquids and gases permeating a silicone elastomer membrane (data from LaPack et al., 1994).

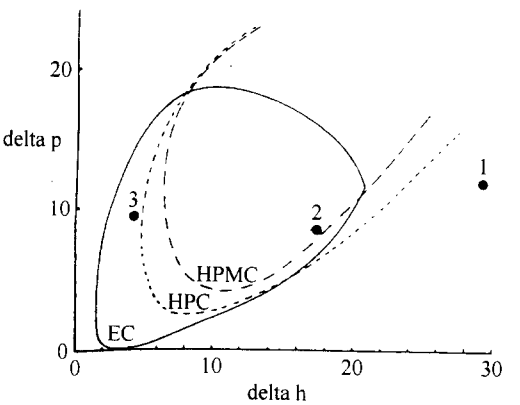

Fig. 10. Solubility parameter map for ethylcellulose, hydroxypropyl methylcellulose and hydroxypropyl cellulose showing the positions of the plasticisers glycerol (1), hexaethylene glycol (2) and diethylphthalate (3) (data from Rowe, 1986).

approach to predict a rank order of transdermal permeation and showed that their predictions were consistant with previous experimental data.

4.3.3. Liquid–liquid interactions

Liquid–liquid interactions and their manifestations are perhaps the simplest of all interactions to measure so solubility parameters have not been used very often to calculate and predict the properties of pharmaceutical liquid mixtures. This is despite the fact that the solubility parameter approach usually shows a very high degree of accuracy when applied to such systems (Barton, 1983, 1985). Samaha and Naggar (1988) have reported using solubility parameters to determine the critical micelle concentration (CMC) of a series of liquid surfactants dispersed in water. The interaction between the surfactant molecules and the water molecules varied according to the calculated solubility parameter of the surfactant, and the authors were able to predict the solubilising properties of the surfactant–water mixtures. A similar approach could be of great help when first designing a liquid pharmaceutical formulation 'on paper'. For example, for predicting the compatibility of liquids used in topical formulations (e.g. oils, alcohols) (Lhoest, 1972), or for designing a solvent system for a drug with unusual solubility properties (Martin et al., 1980).

4.3.4. Solid–gas interactions:

The affinity of vapours for solid surfaces has been widely studied and can be clearly related to the cohesive energies of the system components (Mitsui et al., 1972). Solid–vapour interactions are of interest to the pharmaceutical scientist for two main reasons. Firstly, many pharmaceutical products interact strongly with water vapour in the atmosphere and this can lead to dramatic changes in their physical properties and in their chemical stability (Ahlneck and Zografi, 1990). Secondly, the loss or gain of volatile agents (e.g. flavourings) from a formulation can lead to problems during manufacture, storage or transport of pharmaceutical products. Both these problems require that the product be packaged to resist the transport of the vapour component(s) either in or out of the product. Few pharmaceutical studies of such problems have made use of solubility parameters to determine the strength of the solid–vapour interactions, however, there are many examples which can be taken from the food science or packaging literature. For example, the uptake of water in to various cellulose samples and its effects on the physical properties of the cellulose were modeled by Salmen and Back (1977) using solubility parameters and the predicted behaviour was found to be very consistent with measured performance. Likewise a solubility parameter approach proved to be very useful in determining optimal package configurations in a recent study of the loss of synthetic volatile flavours through polymeric packaging materials (Paik and Writer, 1995).

5. Assumptions, limitations and restrictions

The use of solubility parameters in the design of pharmaceutical dosage forms requires several key assumptions and has some specific limitations and restrictions. It should be remembered that solubility parameter theory only accounts for the direct contact energies between components and does not take into account the effects of entropy, or the free volume of amorphous solids (Rey-Mermet et al., 1991; Rudolf et al., 1995). It should also be remembered that solubility parameter theory is based on the assumptions of regular solution theory and deviations from such behaviour (e.g. changes in volume on mixing) must be accounted for. Problems often occur with aqueous systems, which are highly hydrogen bonded, and with charged ionic species (e.g. salt forms). Solids and gases are also approximated as liquids in the extended solubility parameter approaches and some deviation from ideal behaviour should be expected with these materials.

There are likely to be some errors associated with determining the solubility parameters of solids, liquids and gases by both direct and indirect methods. In particular organic solids, which are common pharmaceutical materials, can be troublesome. Wherever possible more than one method should be used to determine the solubility parameter of a material and predictions of material properties or interactions should ideally be used in conjunction with other supporting methods of analysis. The experimental conditions should also be very carefully defined because solubility parameters can change with temperature (Grulke, 1975; Lin, 1992; King, 1995; Rudolf et al., 1995), pressure (Barton, 1983; Rudolf et al., 1995) and molecular weight for polymers (Rudolf et al., 1995).

Fundamental material properties (e.g. melting point) are usually well correlated with solubility parameters but the exact relationship is not always identical to that predicted from theory and may be slightly different for different classes of materials (e.g. polymers, metals). In this situation it is necessary to know something of the behaviour of other similar materials before quantitative predictions can be made. The use of solubility parameters for quantifying process induced changes is limited by the accuracy, precision and reproducibility with which the properties of materials can be measured before, during and after processing. The most accurate application of solubility parameters to pharmaceutical systems is undoubtedly in determining interactions between components of mixed systems (formulations). This situation has been extensively studied and it is commonly observed that any non-idealities introduced by the effects of strong polar interactions often cancel each other out. Hence the

predicted behaviour in this situation is usually at least in semi-quantitative agreement with that observed. Systems which allow intimate mixing (e.g. wetting liquids, fine powders) usually behave as predicted irrespective of the type of phase(s) present. The surface and interfacial properties of such systems are often accurately predicted from their bulk cohesive energetic properties and vice versa. Immiscibility or incompatibility may be the result of the other physical properties of the materials being considered (e.g. particle size) rather than interactions which can be predicted from their cohesive energy densities. The use of solubility parameter theory to predict interactions is usually described for two component mixtures, however, given that mixtures of miscible materials show intermediate solubility parameters it should be possible to use multi-dimensional solubility parameter maps to determine the compatibility of multi-component mixtures.

6. Conclusions

The cohesive energy of drugs and excipients is important in determining many of their key physicochemical properties and their interaction potential. This cohesive energy can be readily quantified using solubility parameters and thus the physical properties of drugs and excipients and their potential interactions can be easily assessed. Determination of the solubility parameters of pharmaceutical materials is possible by a wide range of both experimental and theoretical techniques. The information obtained can be used with several simple and well tested approaches to determine parameters as diverse as Young's modulus, aqueous solubility, membrane transport rates, and film coating performance. These approaches can often reduce the need for time consuming and expensive pre-formulation screening, and are ideally suited for use in formulation expert systems (Rowe, 1993; Rowe and Upjohn, 1993) and for determining structure–activity relationships (SAR). An awareness of the widespread availability of solubility parameters for pharmaceutical materials and their potential use in designing optimal dosage forms is likely to be of great value to the formulation scientist.

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