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Compression of binary powder mixtures and solubility parameters of solids

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Summary

Compactibility and compressibility of binary powder mixtures A/B, is investigated in order to detect possible physical interactions. The compactibility P_{max} and compressibility γ of the powder mixtures are quantified on the basis of the deformation hardness values P (Brinell hardness) obtained from tablets which resulted after compression of the powder mixtures with compressional stress σ_c to form a compact of relative density ρ_r:

$$P(\text{mixture A/B}) = P_{max}(\text{mixture})[1 - \exp[-\gamma(\text{mixture})\sigma_c\rho_r]]$$

According to an additivity rule which was derived earlier, the interaction term P_{WW} can be quantified as follows:

$$\ln P_{max}(\text{mixture A/B}) = x \ln P_{max} + (1 - x)\ln P_{max_B} + x(1 - x) \ln P_{WW}$$

with x, (1 − x) = % weight/weight of component A, resp. B. Where adhesive forces A–B dominate over cohesive forces A–A, resp. B–B, $\ln P_{WW} > 0$, i.e. a positive interaction is present. The binary mixtures investigated, consisting of brittle and soft materials, show a negative interaction, i.e. cohesive forces dominate. As similar situations occur in non-ideal solutions, showing a positive or negative deviation from Raoult's law, it is possible to relate $\ln P_{WW}$ to the activity coefficient $\ln \gamma_2$ of a solute 2 forming a non-ideal solution with solvent 1. The results of this paper show that the binary mixtures investigated behave as 'regular solid solutions'. Knowing the interaction term P_{WW} and the solubility parameter δ_A, it is possible to estimate

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solubility parameter δ_B. Consequently, the concept of solid solutions should be reviewed: is it possible to produce by the compression of suitable binary powder systems perfect, ideal, regular or non-ideal 'solid solutions'?

Introduction

The biopharmaceutical and physicochemical performance of a dosage form can be related to the sum of the interactions between the different constituents (excipients, active substance). In the case of a tablet, most of the quality parameters, such as tensile strength, friability, disintegration time and dissolution, are often highly interrelated. In this paper our investigations are limited to the compression behaviour of binary powder mixtures, i.e. compactibility and compressibility, in order to quantify possible physical interactions. Compactibility and compressibility are determined according to the following equation (Leuenberger, 1980, 1982):

$$P = P_{max}\left[1 - \exp(-\gamma\sigma_c\rho_r)\right] \tag{1}$$

with P = deformation hardness of the tablet (Brinell hardness, Leuenberger, 1982); P_{max} = max. deformation hardness at compression stress $\sigma_c \to \infty$; ρ_r = relative density; γ = compression susceptibility.

It was possible to show that P_{max} is related to the crystal hardness of the substance compressed (Jetzer, 1982; Jetzer et al., 1983a). The parameter P_{max} is a valuable expression for the compactibility of a powder system. Press susceptibility γ is directly correlated to the compressibility of the powder bed (Leuenberger and Jetzer, 1984).

Eqn. 1 is valid for pure substances as well as binary mixtures (A + B) (Leuenberger, 1982; Jetzer et al., 1983b). Thus special additivity rules for parameters P_{max} and γ can be derived (Leuenberger, 1982; Leuenberger and Rohera, 1985). Depending on the initial conditions imposed, the following equations can be applied.

(a) Exact additivity rule (Leuenberger 1982):

$$\ln P_{max}(\text{mixture}) = x \ln P_{max_A} + (1 - x)\ln P_{max_B} + \ln \frac{\gamma_A^x \cdot \gamma_B^{1-x}}{x\gamma_A + (1 - x)\gamma_B} \tag{2}$$

$$\gamma(\text{mixture}) = x\gamma_A + (1 - x)\gamma_B \tag{3}$$

with P_{max}, P_{max_A}, P_{max_B} = compactibility parameter of the mixture and pure substances A, B; γ, γ_A, γ_B = compression susceptibility of the mixture and substances A, B; x, 1 − x = % (weight/weight) of the substances A, B.

(b) Additivity rule taking into account a positive or negative interaction term ln P_{WW} (Leuenberger 1982):

$$\ln P_{max}(\text{mixture}) = x \ln P_{max_A} + (1 - x)\ln P_{max_B} + x(1 - x)\ln P_{WW} \tag{4}$$

Eqn. 4 can be derived as an exact equation using a statistical model approach

(Leuenberger and Rohera, 1985). The interaction term P_{WW} can be interpreted qualitatively as the ratio of adhesive to cohesive forces between unlike particles or molecules.

$$P_{WW} \sim \frac{\text{adhesive forces}}{\text{cohesive forces}} \sim \frac{\text{interactions between unlike particles}}{\text{interactions between like particles}} \tag{5}$$

The following expression is equivalent but uses scalars instead of the vectorial forces

$$P_{WW} \approx \frac{\text{adhesive energy per unit volume}}{\text{cohesive energy per unit volume}} \tag{6}$$

A negative interaction term $\ln P_{WW}$ indicates that cohesive forces A–A, B–B dominate over adhesive forces A–B, B–A.

Due to the fact that in non-linear regression analysis the estimation of parameters P_{max} and γ in Eqn. 1 are correlated, the following expression could be derived:

(c) Approximate additivity rules for the compactibility parameters P_{max} (Leuenberger and Rohera, 1985):

$$P_{max}(\text{mixture}) \cong \frac{1}{\dfrac{x}{P_{max_A}} + \dfrac{1-x}{P_{max_B}}} \tag{7}$$

Eqn. 7 corresponds to the harmonic mean of values P_{max_A}, P_{max_B}.

From the point of view of application, the differences in Eqns. 2, 4 and 7 are important. Eqns. 2 and 7 allow a straight-forward calculation of the value P_{max} for the mixture from the values of the pure substances A, B. In case of Eqn. 4, the interaction term $\ln P_{WW}$ is initially unknown and has to be determined beforehand. Its value may be positive or negative. Comparing Eqns. 2, 4 and 7, Eqns. 2 and 7 can only account for a negative interaction. The validity of Eqns. 1–4 and 7 was checked using the non-linear regression analysis programme 09835-15040, Hewlett Packard, Fort Collins, CO, U.S.A. Theory and experimental results coincided very well (Leuenberger and Rohera, 1985). On the basis of these results, the following theory can be presented.

Theory

The concept of solutions

Solutions (liquid-in-liquid, solid-in-liquid) are called ideal where the attractive forces between molecules of the solute and solvent are approximately identical (e.g. Hildebrand and Scott, 1964). In the case of non-ideal solutions there is an interaction between molecules of the solute and the solvent. This interaction can be quantified by the coefficient of activity γ_2 of substance 2 (solute), which is dissolved in solvent 1. The value of γ_2 is only equal to one in case of an ideal solution where Raoult's law is valid. In the case of non-ideal solutions, γ_2 may be > 1 (positive deviation from Raoult's law) or < 1 (negative deviation from Raoult's law). To quantify the extent of interaction, e.g. vapour pressure measurements can be taken.

A positive deviation from Raoult's law means that the cohesive forces between like molecules dominate over the adhesive forces between unlike molecules. Thus the thermodynamic activity of the molecules in this system is enhanced. Qualitatively the activity coefficient γ_2 can be described as the ratio cohesive forces/adhesive forces

$$\gamma_2 \sim \frac{\text{cohesive forces}}{\text{adhesive forces}} \sim \frac{\text{self-interaction (like molecules)}}{\text{interaction between unlike molecules}} \tag{8}$$

According to Eqn. 8, γ_2 is related indirectly to the interaction term P_{WW} (cf. Eqn. 5) in the case of a 'solid solution'

$$\ln P_{WW} \approx -\ln \gamma_2 \tag{9}$$

Regular solutions

Regular solutions can be treated as a special case of non-ideal solutions (Hildebrand et al., 1970). In a regular solution, the cohesive forces between like molecules dominate. Thus the adhesive energy, e_{12}, per unit molar volume is smaller than the mean cohesive energy $(e_1 + e_2)/2$ per unit molar volume and ideal solubility is reduced. In the case of regular solutions, interaction energy e_{12} is assumed to be the geometric mean of the respective cohesive energies e_1, e_2. This assumption is based on the dipole–dipole interaction energy for polar substances and the London dispersion interaction energy for non-polar substances. Along these lines Hildebrandt et al. developed the concept of solubility parameters δ_1, δ_2 which permit the calculation of the activity coefficient γ_2 of a regular solution.

$$\ln \gamma_2 = (\delta_1 - \delta_2)^2 \cdot \frac{V_2 \phi_1^2}{RT} \tag{10}$$

$\delta_1 = \sqrt{e_1}$ = solubility parameters of the solute 1; $\delta_2 = \sqrt{e_2}$ = solubility parameters of the solute 2; V_1, V_2 = molar volumes (solvent, solute).

$$\phi_1 = \frac{X_1 V_1}{X_1 V_1 + X_2 V_2} \tag{11}$$

X_1, X_2 = molar ratios; e_1, e_2 = cohesive energy per unit molar volume of solvent, resp. solute; R = gas constant; T = temperature.

In the case of a 1 : 1 (w/w) solution, Eqn. 10 can be simplified as follows:

$$\ln \gamma_2 = \frac{(\delta_1 - \delta_2)^2}{RT} \cdot \frac{V_2 \rho_2^2}{(\rho_1 + \rho_2)^2} \tag{12}$$

with ρ_1, ρ_2 = true density of solvent resp. solute.

It must be noted that the indices in Eqn. 12 cannot be exchanged, as we assume that substance 2 is dissolved in solvent 1. This concept is not readily applicable for binary powder mixtures which are compressed to form a kind of 'solid solution'. We may possibly assume that substance B is 'dissolved' in substance A in a case where the outer phase of the tablet is formed with substance A. Thus substance B has to be 'coated' completely by substance A during the compression process. Instead of the expression 'dissolved' in substance A, the term 'dispersed' should be used. For a sufficient 'dispersion' the starting materials need to be fine and the particles of substance A, B should be of similar size (see Table 1a). Investigating all possible ratios of the binary powder mixture, a phase inversion has to be postulated. It was possible to show experimentally that the soft component is squeezed out under pressure and that it encapsulates the brittle component (caffeine) completely (Rohera et al., 1985). Thus substance B, which may initially form the inner phase, will change to the outer phase when the amount of substance B in binary mixture A + B is increased. System B dispersed in A changes to a system A dispersed in B. To take this fact into account, Eqn. 12 had to be slightly modified to obtain a symmetrical expression.

$$\ln \gamma_2 \approx \frac{(\delta_1 - \delta_2)^2}{RT} \frac{\sqrt{V_1 V_2}\,\rho_1 \rho_2}{(\rho_1 + \rho_2)^2} \qquad (13)$$

The second term corresponds to the geometric mean values. Comparing Eqns. 2, 4, 9 and 13 the following expressions can be derived for the case of 1 : 1 (w/w) mixtures: $x = 1 - x = 0.5$

$$0.25 \ln P_{WW} \cong \ln \frac{2 \cdot \sqrt{\gamma_A \gamma_B}}{\gamma_A + \gamma_B} \qquad (14)$$

or

$$P_{WW} \cong \frac{16 \gamma_A^2 \gamma_B^2}{(\gamma_A + \gamma_B)^4} \qquad (15)$$

Assuming an indirect correlation between P_{max_A} and γ_A (Leuenberger and Rohera, 1985), one obtains

$$P_{WW} \cong \frac{16 P_{max_A}^2 \cdot P_{max_B}^2}{(P_{max_A} + P_{max_B})^4} \qquad (16)$$

$$\ln P_{WW} \cong -(\delta_A - \delta_B)^2 \cdot \frac{\sqrt{V_A V_B}}{RT} \cdot \frac{4 \rho_A \rho_B}{(\rho_A + \rho_B)^2} \qquad (17)$$

with δ_A, δ_B = solubility parameters of the solid substances A, B; V_A, V_B = molar volumes of the substances A, B; ρ_A, ρ_B = true densities of the substances A, B.

Eqns. 15 and 16 allow an estimate of the interaction term P_{WW} from the compression behaviour of the pure substances A, B. In Eqn. 17, interaction term

P_{WW} is related to solubility parameter δ_A, δ_B of the pure substances A, B. Thus if we know P_{WW} and δ_A, then δ_B can be estimated and vice versa.

Materials and Methods

Caffeine anhydrous (Knoll, Ludwigshafen, Lot No. 09280) was chosen as a model substance. Caffeine is rather a brittle substance but parameters P_{max} and γ can be

TABLE 1a

PHYSICAL CHARACTERISTICS OF THE POWDER MATERIAL

Substance	Poured density (g/cm^3)	Tapped density (g/cm^3)	Particle size analysis (RRS-B distr.)		Loss in drying % (w/w)
			n	d (μm)	
Caffeine	0.331	0.476	2.43	34.0	0.1
Magnesium stearate	0.184	0.347	2.46	32.3	2.5
Polyethylene glycol 4000	0.516	0.725	2.82	45.7	0.4
Sodium lauryl sulphate	0.192	0.269	3.11	39.8	0.5
Sodium stearate	0.250	0.431	2.68	34.9	1.5

TABLE 1b

PHYSICAL CHARACTERISTICS OF STARTING MATERIALS

	True density (g/cm^3)	Molecular weight	Solubility parameter (Barton, 1983) (MPa$^{1/2}$)
Caffeine anh.	1.458	194.2	(see Table 1c)
Magnesium stearate	1.048	591.27	–
Polyethylene glycol 4000	1.213	~3700	19.4
Sodium lauryl sulphate	1.258	288.38	29.0
Sodium stearate	1.089	306.47	19.0

TABLE 1c

EXPERIMENTAL VALUES δ_A FOR CAFFEINE KNOWN FROM LITERATURE

δ_A [MPa$^{1/2}$]	References
23.7 *	Huu-Phuoc (1984); Lerk et al. (1976)
24.5	Martin et al. (1981)
26.6	Huu-Phuoc (1984)
28.2	Martin et al. (1981)

* Calculated by Huu-Phuoc on the basis of surface free energy reported by Lerk et al. (1976) (see also Barton, 1983, p. 429, Eqn. 12).

easily determined (Rohera, 1984). To prepare binary powder mixtures, consisting of brittle and soft material, caffeine was added to the following excipients:
Magnesium stearate (Chemische Fabrik, Schweizerhalle)
Polyethylene glycol 4000 (Huls Chemie AG, Zurich, Lot 17M)
Sodium lauryl sulphate (Siegfried, Zofingen, Lot 029691)
Sodium stearate (Siegfried, Zofingen, Lot 999076).

TABLE 2a

EXPERIMENTAL CONDITIONS OBSERVED IN THE PREPARATION OF TABLETS

Moisture content of starting materials	Equilibrated with laboratory air at relative humidity 50% ± 10%
Tablet weight	400 mg
Tablet form	round, flat-faced
Diameter of die	11 mm
No. of tablets at each compression	6–8
Compression rate	0.5 cm/min
Decompression rate	0.5 cm/min
Ejection rate	5 cm/min
Pressure transducer	Instron load cell (type GRM) at lower punch
Dwell time at max. compression stress	Duration of pressure constant at < 0.1 s (via electronic switching)

TABLE 2b

P_{max} AND γ VALUES OF SINGLE SUBSTANCES

Substance	P_{max} [MPa]	95% confidence intervals	$\gamma \times 10^2$ $[MPa]^{-1}$	95% confidence intervals
Caffeine (anh.)				
(Indentation load 3.92 N)	133	129–137	0.72	0.68–0.77
(Indentation load 9.81 N)	180	168–192	0.67	0.58–0.76
Magnesium stearate *	21.6	20.6–22.7	4.75	4.09–5.42
Polyethylene glycol 4000	36.2	35.8–36.7	4.22	4.01–4.42
Sodium lauryl sulphate	9.79	9.59–10.00	14.9	13.5–16.2
Sodium stearate	36.7	35.9–37.6	4.7	4.26–5.14

* Indentation load: 3.92 N; for other substances: 9.81 N.

TABLE 2c

INTERACTION TERM P_{WW} ACCORDING TO EQN. 4

Mixtures: Caffeine with	P_{WW}	95% confidence intervals
Magnesium stearate	0.25	0.19–0.31
Polyethylene glycol 4000	0.43	0.34–0.53
Sodium lauryl sulphate	0.11	0.06–0.16
Sodium stearate	0.16	0.12–0.20

Soft excipients were chosen to show either hydrophobic or hydrophilic properties. In practice, these excipients are used in small concentrations as lubricants or hydrophilization agents. In higher concentrations, polyethylene glycol 4000 is used in practice as a solid solution vehicle. The physical characteristics of the starting materials are compiled in Tables 1a and 1b. The tablets were compressed on an Universal Testing Instrument (model TT-DM, Instron, High Wycombe, U.K.) in order to keep the experimental conditions as constant as possible (see Table 2a). The individual powders and their binary mixtures were compressed at a number of pressures, selected on the basis of their compression behaviour. Thus tablets were

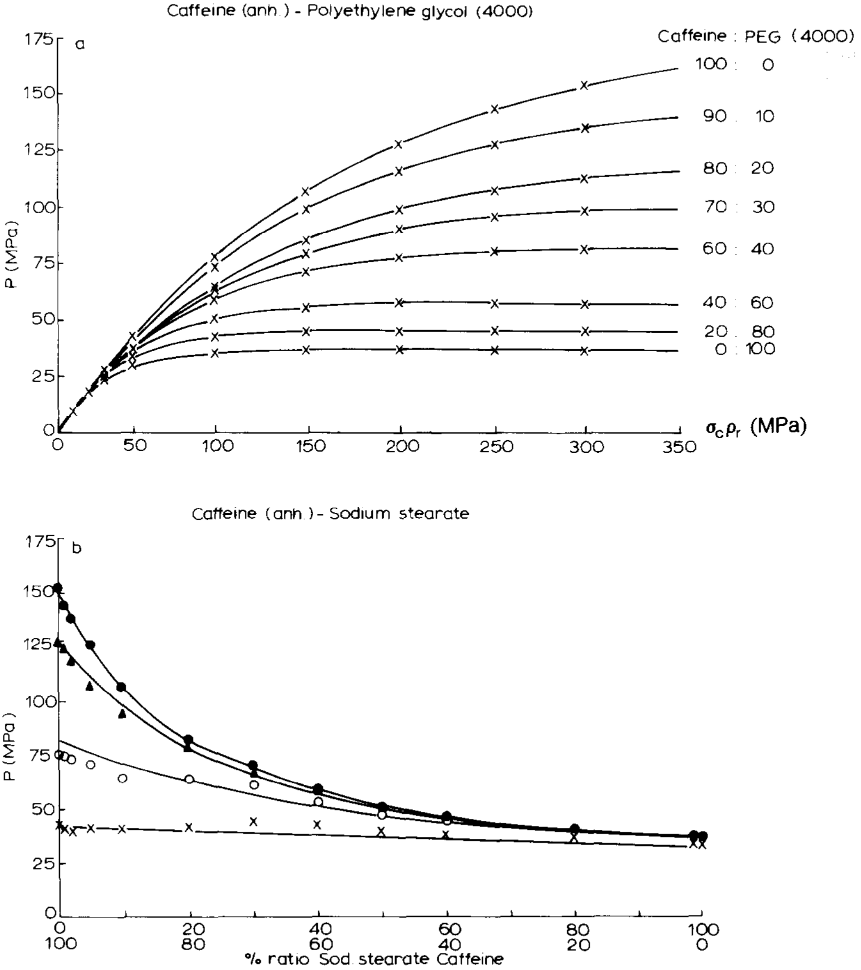


Fig. 1. a: plot of deformation hardness (P) against the product of compression stress (σ_c) and relative density (ρ_r) for various composition ratios (w/w). b: changes in deformation hardness (P) with composition ratio (w/w) and compression stress (σ_c). ———, fitting curve derived from basic Eqn. 1 using the additivity rules Eqns. 2 and 3. Compression stress (MPa): ×, 51.6; ○, 103; ▲, 206; ●, 310.

compressed at six or more of the following pressures: 5.16 MPa, 10.3 MPa, 15.5 MPa, 20.7 MPa, 25.8 MPa, 31.0 MPa, 41.3 MPa, 51.6 MPa, 77.4 MPa, 103 MPa, 129 MPa, 155 MPa, 206 MPa, 258 MPa, 310 MPa. To quantify deformation hardness of the tablets, a semi-static Brinell hardness test was used (Leuenberger, 1982). The compression behaviour of binary mixtures is listed in Tables 2b, 2c. Two typical, but different, plots are shown in Fig. 1a for binary mixture caffeine (anh.)–polyethylene glycol (4000) and Fig. 1b for binary mixture caffeine (anh.)–sodium stearate. Details about experimental procedures used to prepare and test the compacts, including the evaluation of parameters, are described in previous publications (Leuenberger, 1982; Jetzer and Leuenberger, 1984; Rohera, 1984). Concerning the hardness test (Brinell), it is important to know that compressibility parameter γ is not sensitive to the change in indentation load (Rohera, 1984). The calculated P_{max} values depend, however, on the indentation load. It is therefore necessary to take this property into account and apply the corresponding P_{max} values in calculations, e.g. Eqn. 16.

Results and Discussion

Estimation of the physical interaction P_{WW} during the compression of binary powder mixtures

The derivation of Eqns. 15 and 16 is possible because Eqns. 2, 4 and 7 fit very well the P_{max} values of the individual mixtures (see Fig. 2a–d) determined on the basis of Eqn. 1. According to Eqns. 15 and 16 the interaction term P_{WW} can be estimated from compression susceptibility parameters γ_A, γ_B, from compactibility parameters P_{max_A}, P_{max_B}, resp., of the pure substances (see Table 3).

In the case of the mixtures, caffeine/magnesium stearate and caffeine/sodium stearate, the experimental results correspond well to the calculated results P_{WW} (15), attained with Eqn. 15. The results of the other mixtures show a satisfactory rank order correlation between the experimental and theoretically estimated results. It should be noted that the calculation of P_{WW} (15) and P_{WW} (16), resp., is very sensitive to small variations of γ_A, γ_B and P_{max_A}, P_{max_B}, resp.

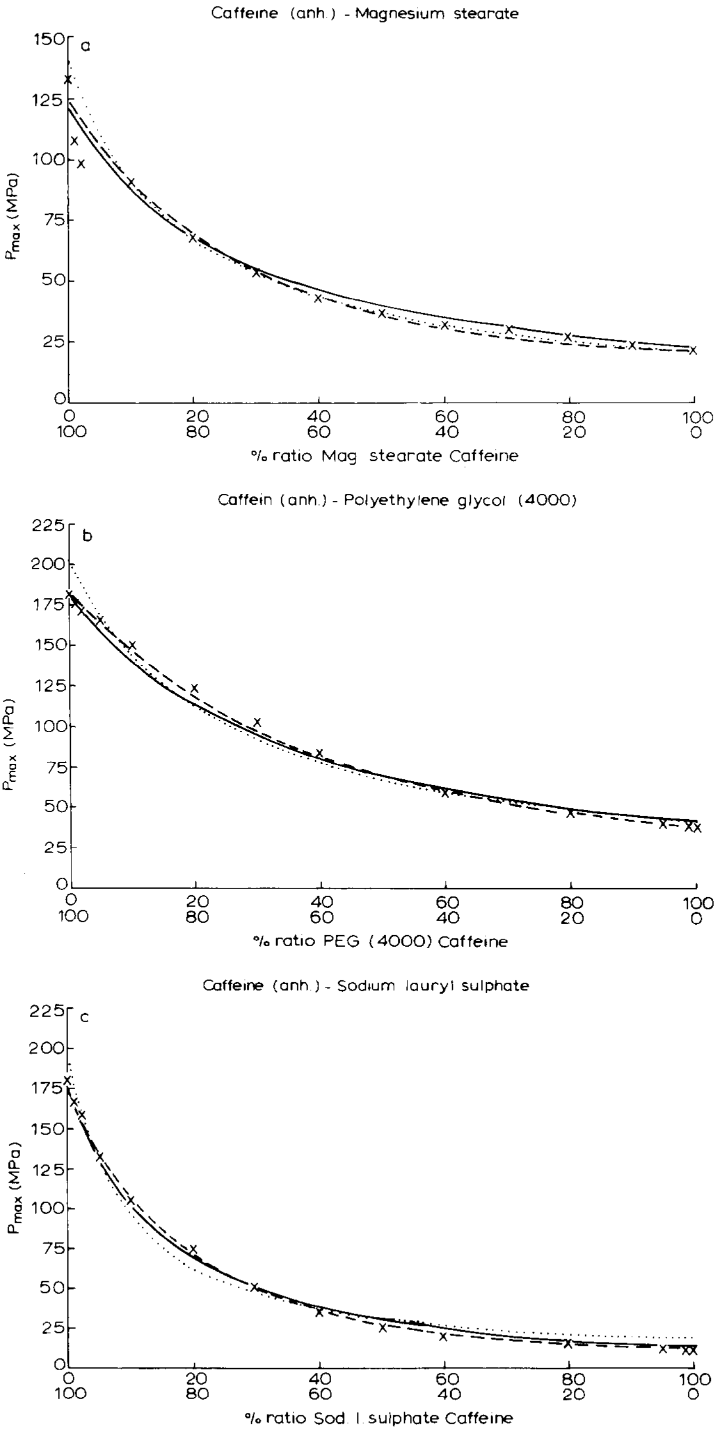
Estimation of solubility parameters

The solubility parameters of PEG 4000, sodium lauryl sulphate, sodium stearate and caffeine, are known from literature (Barton, 1983). Thus the solubility parame-

TABLE 3

EXPERIMENTAL AND CALCULATED VALUES OF P_{WW}

Binary mixtures	P_{WW}(exp.)	P_{WW}(15)	P_{WW}(16)
Caffeine/magnesium stearate	0.25	0.24	0.23
Caffeine/PEG 4000	0.48	0.22	0.31
Caffeine/sodium lauryl sulphate	0.11	0.03	0.04
Caffeine/sodium stearate	0.16	0.19	0.32


Caffeine (anh.) - Magnesium stearate

Caffein (anh.) - Polyethylene glycol (4000)

Caffeine (anh.) - Sodium lauryl sulphate

Fig. 2a–c.

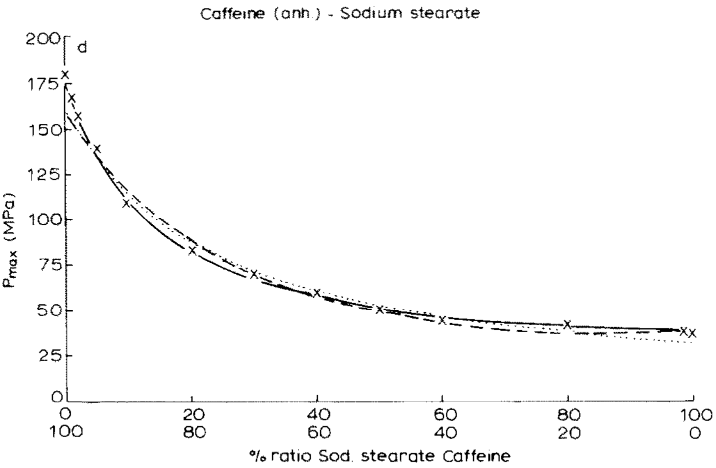


Fig. 2. a–d: P_{max} values (×) determined according to Eqn. 1 for the individual binary mixtures and graphical representation of the Eqns. 2 ———; 4 — — —; and 7 ······.

ter δ_A of caffeine is determined according to Eqn. 17 for the set of mixtures with PEG 4000, sodium lauryl sulphate and sodium stearate. This value was determined for comparison with the experimental values known from literature (see Table 1c) and to determine the unknown solubility parameter of magnesium stearate. Results were compiled in Table 4. It is interesting to note that solubility parameter δ_A calculated for caffeine does not depend very much on the matrix substance chosen for the binary mixture. Therefore for the determination of the unknown solubility parameter δ_B for magnesium stearate, the mean value δ_A^* was chosen. The values δ_A attained for caffeine are rather close to lower values compiled in Table 1c. Martin et al. (1981) found two different values for caffeine, which he attributed to the different solvent systems, in which caffeine was dissolved. Taking into account that Eqn. 17 was derived as an approximate expression, the agreement between experimental results and the calculated results is quite satisfactory. Consequently, it may be interesting to review the concept of solid solutions: is it possible to produce by the

TABLE 4

ESTIMATION OF THE SOLUBILITY PARAMETERS δ_A^* FOR CAFFEINE (ANH.) AND δ_B^* FOR MAGNESIUM STEARATE

Mixtures A/B	P_{WW}	ln P_{WW}^*[$MPa^{1/2}$]	δ_A[$MPa^{1/2}$]	δ_B[$MPa^{1/2}$]
Caffeine/PEG 4000	0.43	−0.844	21.2	19.4
Caffeine/sodium lauryl sulphate	0.11	−2.21	23.5	29.0
Caffeine/sodium stearate	0.16	−1.83	23.9	19.0
Caffeine (anh.)		mean value $\delta_A^* =$	22.9	
Caffeine/magnesium stearate	0.25	−1.39	22.9	$\delta_B^* = 19.3$

compression of suitable binary powder systems perfect, ideal, regular on non-ideal 'solid solutions'?

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