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Highly loaded interactive mixtures for dry powder inhalers: Prediction of the adhesion capacity using surface energy and solubility parameters

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In order to correlate drug adhesion properties of a highly loaded interactive mixture for the use in dry powder inhalers with the surface energy and to establish a link to the solubility parameter, surface free energy was detected for micronized substances (salbutamol sulfate, salbutamol base, theophylline and α-lactose monohydrate) using inverse gas chromatography (IGC). Interactive mixtures with coarse crystalline α-lactose monohydrate as a carrier were prepared at loading levels from 7.5 to 20% (w/w) and analyzed with respect to their adhesion capacity (C_A) using the air jet sieving method. Solubility parameters were taken from literature or calculated. As a result the C_A was independent of the drug load and correlated linearly with volume specific surface energy interaction (SEI_V) values of the adherents ($R^2 = 0.98498$). A link between SEI_V and the size normalized solubility parameter (δ_{tot}/d_{50}) was found. Consequently, plotting δ_{tot}/d_{50} versus C_A resulted also in a strong linear relationship ($R^2 = 0.99140$). Overall a powerful tool was established to judge and quantify adhesion properties of highly loaded interactive mixtures even for estimates in early preformulation at a time where just the molecular structure of the active ingredient is known.

1. Introduction

Interactive mixtures are used in dry powder inhalers (DPIs) to deliver small drug particles (1–10 μm) into the lung (Byron 1986). The system is generally consisting of a binary powder mixture delivered through an applicator and seems to be quite simple. However, the inhalable drug fraction is dependent on various factors like the right carrier (Tee et al. 2000; Bosquillon et al. 2001), particle size (Steckel and Müller 1997), morphology of the drug and carrier (Swaminathan and Kildsig 2000; Kawashima et al. 1998) as well as humidity (Bérard et al. 2002; Young et al. 2003). Despite reports on the influencing factors stated above, only few articles reduced the even larger number of factors to a few decisive ones, which would facilitate DPI development in the preformulation stage. A few decisive factors could even render an estimating model on the basis of computer simulation or listed data.

Preparing the powder mixture, the coarse carrier together with the micronized drug are forming an "interactive mixture" during the mixing process, representing a mixture where the micronized active ingredient (Egermann 1983; Schmidt and Benke 1985) is strongly adhered to the carrier due to interparticulate forces, like Lifshitz van der Waals, electrostatic and capillary forces. Consequently, the adhesion between carrier surface and drug particles and or drug particles among themselves next to the aerodynamic properties of the particles are determining the dispersion of the drug particles during the inhalation process. The Lifshitz van der Waals forces were found to have the greatest impact on adhesion (Rumpf 1974; Podczeck 1998), however, further energetic values were often suspected to be important but, refused to fit in a common model.

Podczek et al. (1996) for example investigated the adhesion strength as a function of the Hansen-solubility parameter; however, the prediction of the adhesion strength was only partially possible.

Sethuraman and Hickey (2002) introduced a predictor for the particle dispersion also on the basis of the solubility parameter or cohesive energy density. However, the model still lacks proof. Probably the best approach towards a prediction model was introduced by Cline and Dalby (2002), who correlated the *in vitro* inhalable fraction of a powder with the surface energy interaction (SEI) determined via inverse gas chromatography (IGC). This correlation included the combined influence of adhesion and aerodynamic flow properties for low dose (1% (w/w) drug per carrier) DPIs. However, for the optimization of the inhalable powder fraction the relation between adhesion and aerodynamic parameters is important. A decreasing particle size for example increases adhesion forces (Podczeck 1998; Stieß 1995) leading to reduced fine particle fractions during in vitro testing (Chew and Chan 1999; Chew et al. 2000), on the other hand particles above 10 μm are unlikely to be respired (Byron 1986).

In order to separate adhesion and aerodynamic factors the present study focuses on the adhesion properties of highly loaded interactive mixtures employing the air jet sieving

method (Schmidt and Benke 1985; Ida et al. 1999). An advantage of this method is the quantification of the fine particles remaining adhered onto the carrier after the jet sieving process instead of determining the dispersed particle fraction.
On the basis of the surface energy interaction SEI (Cline and Dalby 2002; van Oss 1994) this study aims to describe the main factors influencing the adhesion properties. Therefore the adhesion properties of various micronized drug powders on a crystalline α-lactose monohydrate carrier as a function of drug particle size, drug load (7.5–20%) and surface free energy, determined by inverse gas chromatography (IGC) were investigated. Additionally, a link between predictable or tabulated energetic parameters like the solubility parameter and the SEI values was developed by means of transformation.

2. Investigations and results

2.1. Theory

2.1.1. Conversion of values

In order to normalize the surface specific values (mJ/m^2) obtained from IGC all energetic values:

γ^D = dispersive component of the surface free energy,
K^A = acidic component of the surface free energy and
K^B = basic component of the surface free energy,

were expressed as mJ/g by multiplication of the mJ/m^2 values with the specific surface area (SSA) (Cline and Dalby 2002). However, the main force responsible for adhesion is seen as the Lifshitz van der Waals force (F_{LvdW}) (Podczeck 1998):

$$F_{LvdW} = \frac{\hbar\varpi \cdot d}{32 \cdot \pi \cdot b^2} \quad (1)$$

Were $\hbar\varpi$ is the Lifshitz-van der Waals constant (8×10^{-19} J), d the diameter of the sphere and b the distance of separation between the contiguous bodies. The ratio between F_{LvdW} and the gravitational force (F_g) should hence, be proportional to the adhesion capacity (C_A) (Stieß 1995). This assumption might be better reflected by a further conversion of the mass specific surface energy values (mJ/g) into geometry or volume specific values (mJ/cm^3). This conversion was performed by multiplication of the mass specific surface energy values with the true density of the fine component. These volume specific values display the advantage to be independent of the active ingredients true density. If indeed the Lifshitz van der Waals force is the decisive force responsible for adhesion, the volume specific surface energy values should lead to a better correlation between surface energy interaction (SEI) and adhesion capacity (C_A) than mass specific values.

2.1.2. Calculation of surface energy interaction (SEI)

SEI calculations for interactive mixtures with low drug load (1% w/w) can be performed according to the van Oss equation for the interfacial tension of two liquids (Cline and Dalby 2002; van Oss 1994):

$$SEI_{1,2} = 2\sqrt{\gamma_1^D\gamma_2^D} + 2\sqrt{K_1^AK_2^B} + 2\sqrt{K_2^AK_1^B} \quad (2)$$

$SEI_{1,2}$ = surface energy interaction between fine drug particles (1) and coarse carrier (2).
However, the higher the drug load of the mixture the lower the SEI fraction between carrier and drug compared to the SEI fraction between drug particles among themselves on the overall SEI of the mixture. Thus, the SEI of highly loaded interactive mixtures was calculated as the SEI between the particles of the active ingredient:

$$SEI_{1,1} = 2\gamma_1^D + 4\sqrt{K_1^AK_1^B} \quad (3)$$

$SEI_{1,1}$ = surface energy interaction between fine drug particles (1).
Dependent on the units of γ^D, K^A and K^B the SEI is either expressed as:

SEI_S = surface specific SEI (mJ/m^2),
SEI_m = mass specific SEI (mJ/g),
SEI_V = volume specific SEI (mJ/cm^3).

2.1.3. Solubility parameter

Like the SEI the Hansen solubility parameter (δ_{tot}) (Hansen 1969) reflects dispersion (δ_d) and polar (δ_p) components but, additionally hydrogen bonding components (δ_h):

$$\delta_{tot} = \sqrt{\delta_d^2 + \delta_p^2 + \delta_h^2} \quad (4)$$

The unit is hence, $(J/cm^3)^{0.5}$. However, these values are derived on the basis of molecular volumes and do not reflect particle size, surface or volume. So if the solubility parameter correlates to the SEI and C_A, a size normalization should be essential. According to the surface free energy values this normalization could be performed by multiplication of δ_{tot}^2 with SSA or even more simply by dividing δ_{tot} by the mean particle size (d_{50}). All solubility parameters used in this study were taken from the literature or in case of salbutamol base calculated employing the SPWin software developed by Breitkreutz (1998).

2.2. Results

For all mixtures the adhesion of micronized drug onto the carrier increased linearly with increasing the drug load (7.5–20%) without reaching any saturation plateau (Fig. 1). In other words, the percentage of the adhered material after the sieving process is constant and independent of the initial drug load. Hence, the slope of the linear regression of the adhesion profiles gave a mean value for the adhesion capacity (C_A) (Table 1).
Size, specific surface area (SSA) and true density data are shown in Table 2. The SSA magnitude of the different powders followed the same order independent of the measuring method applied (gas adsorption (BET) or particle size analysis (PSA)) and was approximately inverse proportional to the square of the mean particle size (d_{50}^2). The only exception was SorboLac 400 which displayed a higher SSA at a higher d_{50} value.
IGC measurement data are displayed in Table 3. For the three salbutamol sulfate powders A, B and C the dispersive free energy (γ^D) and the basic part of the free energy (K^B) decreased with increasing particle size or decreasing SSA, respectively. The acidic part of the free energy (K^A) kept

Table 1: Linear regression function of adhesion profiles of various micronized drugs with Inhalac 120 as a carrier

	slope or $C_{A\,det.}$	y-intercept	R^2
Salbutamol base	0.5539	−0.4853	0.9842
Salbutamol sulphate A	0.7956	−0.1245	0.9960
Salbutamol sulphate B	0.7786	−0.6482	0.9986
Salbutamol sulphate C	0.3392	−0.6294	0.9969
Theophylline	0.2521	0.1969	0.9749
SorboLac 400	0.3003	−1.0209	0.9846

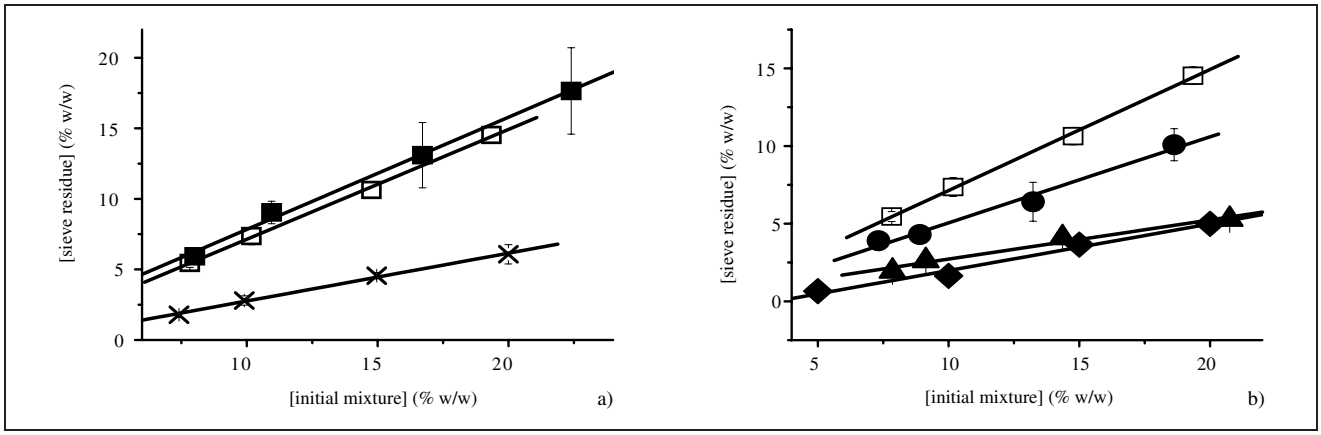

Fig. 1: Determined adhesion profiles as ratio of the drug concentration in the sieve residue ([sieve residue]) and the initial mixture ([initial mixture]): a) For salbutamol sulphate at various particle sizes: □: A ($d_{50} = 1.95$ µm), □: B ($d_{50} = 2.00$ µm), ×: C ($d_{50} = 6.08$ µm). b) For different drug types: □: salbutamol sulphate B ($d_{50} = 2.00$ µm), ●: salbutamol base ($d_{50} = 1.99$ µm), ▲: theophylline ($d_{50} = 10.22$ µm), ◆: Sorbo Lac 400 ($d_{50} = 10.51$ µm). Error bars represent the 95% confidence interval (n = 4)

almost constant. At similar particle size and SSA salbutamol base had lower γ^D and K^B compared to the sulfate salt (salbutamol sulfate B). γ^D and K^B values for theophylline and SorboLac 400 were similar to the finer powders although, theophylline and SorboLac 400 were much larger in size, while their K^A values were the highest detected.
However, none of the values stated above correlated to the C_A values. In contrary SEI_S (mJ/m^2) values which were converted into mass specific SEI_m (mJ/g) values (Table 3) correlated with C_A in the least square linear regression resulting in an $R^2 = 0.96001$ for the SEI_m values converted using the SSA detected via BET and $R^2 = 0.97947$ for the SEI_m values based on the SSA from the particle size analysis (Fig. 2). However, SEI_m values from powders of similar true density (salbutamol sulfate, theophylline and SorboLac 400) fitted better to the regression line than the SEI_m value of salbutamol base, which displayed the lowest true density of all powders examined. Implementation of a further normalization into volume specific SEI_V (mJ/cm^3) values (Table 3) could, hence, further improve the precision of the correlation resulting in an $R^2 = 0.96963$ (BET) and $R^2 = 0.98498$ (PSA) (Fig. 3).

Table 2: Powder properties (95% confidence interval in parentheses, n = 3)

	d_{50} (µm)	SSA_{PSA}[a] (m^2/g)	SSA_{BET}[b] (m^2/g)	true density (g/cm^3)	δ_{tot} $\left(\sqrt{\frac{J}{cm^3}}\right)$	δ_{tot}/d_{50}
Salbutamol sulphate A	1.84 (0.02)	3.347 (0.062)	7.291 (0.118)	1.356 (0.002)	46,4[a]	25,23 (0.30)
Salbutamol sulphate B	2.02 (0.02)	3.020 (0.128)	6.628 (0.016)	1.356 (0.002)	46,4[a]	23,15 (0.23)
Salbutamol sulphate C	6.08 (0.11)	1.450 (0.108)	1.807 (0.005)	1.356 (0.002)	46,4[c]	7,63 (0.14)
Salbutamol base	2.05 (0.01)	2.967 (0.006)	6.003 (0.044)	1.116 (0.004)	29[d]	14,17 (0.04)
Theophylline	10.23 (0.41)	0.740 (0.019)	0.894 (0.036)	1.512 (0.002)	25,33[e]	2,48 (0.10)
SorboLac 400	10.51 (0.12)	0.969 (0.013)	1.858 (0.110)	1.542 (0.002)	38,61[f]	3,84 (0.05)

Note: Values are mean and (95% confidence interval)
[a] specific surface area determined by particle size analysis (PSA); [b] specific surface area determined by gas adsorption (BET);
[c] Hirayama et al. (1995); [d] calculated with SPWin software according to Breitkreutz (1998); [e] Breitkreutz (1998); [f] Pena et al. (2000)

Table 3: IGC parameters for individual powders and surface (SEI_S), mass (SEI_m) or volume specific surface energy interaction (SEI_V) based on specific surface area (SSA) determined by BET[a] or PSA[b]

	γ^D (mJ/m^2)	K^A (mJ/m^2)	K^B (mJ/m^2)	SEI_S (mJ/m^2)	SEI_m (BET) (mJ/g)	SEI_m (PSA) (mJ/g)	SEI_V (BET) (mJ/cm^3)	SEI_V (PSA) (mJ/cm^3)
Salbutamol sulphate A	51.20 (1.18)	32.19 (2.45)	7.41 (0.23)	164.15 (4.72)	1196.76 (32.38)	497.37 (14.31)	1622.81 (46.31)	674.44 (20.40)
Salbutamol sulphate B	47.42 (0.20)	31.11 (0.27)	6.30 (0.68)	150.79 (3.19)	999.37 (21.15)	434.27 (9.19)	1355.15 (30.67)	588.87 (13.33)
Salbutamol sulphate C	35.27 (0.66)	33.71 (1.16)	3.51 (0.02)	114.01 (1.24)	206.02 (2.24)	158.48 (1.73)	279.36 (3.45)	214.90 (2.66)
Salbutamol base	41.91 (0.14)	30.96 (3.06)	5.43 (0.37)	135.67 (4.16)	814.40 (24.95)	381.22 (11.68)	908.87 (31.10)	425.44 (14.56)
Theophylline	35.91 (0.44)	45.20 (2.62)	6.82 (0.71)	123.64 (4.58)	110.53 (4.10)	95.20 (3.53)	170.44 (6.54)	146.80 (5.63)
Sorbo Lac 400	44.25 (0.76)	38.68 (3.07)	3.73 (0.19)	153.42 (0.54)	284.91 (1.00)	148.67 (0.52)	430.78 (2.08)	224.79 (1.08)

Note: Values are mean and (95% confidence interval)
[a] Gas adsorption according to Bruner, Emmet and Teller; [b] Particle size analysis

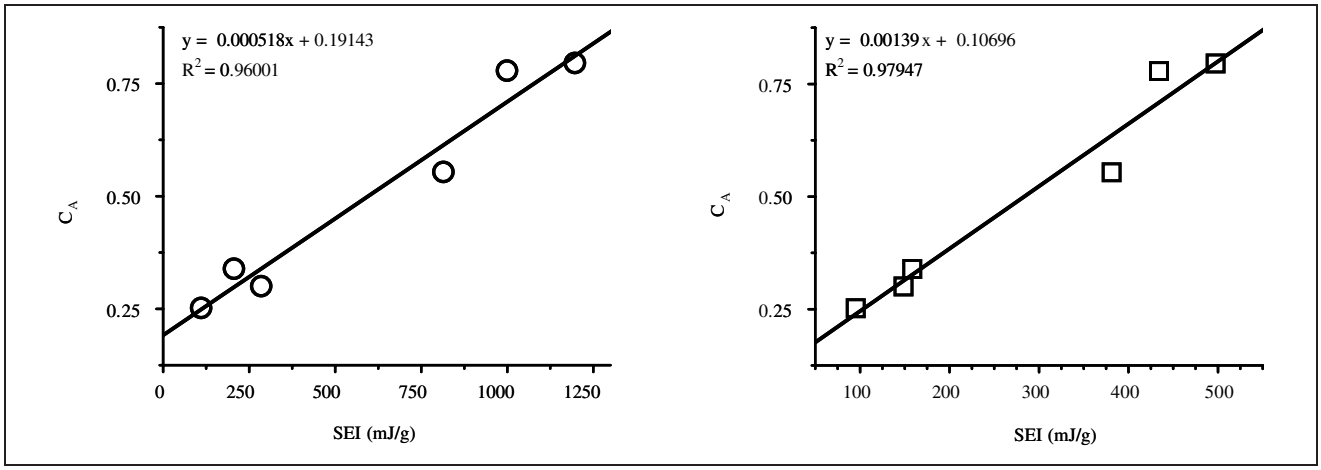

Fig. 2: Correlation of C_A versus mass specific SEI_m (mJ/g) calculated on the basis of SSA from ○ BET or □ PSA

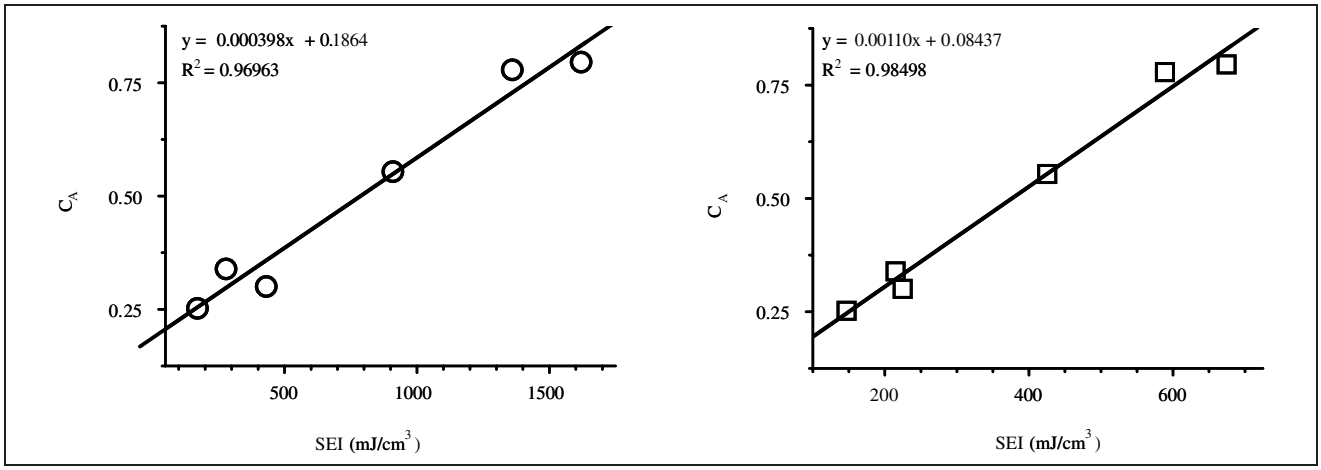

Fig. 3: Correlation of C_A versus volume specific SEI_V (mJ/cm^3) calculated on the basis of SSA from ○ BET or □ PSA

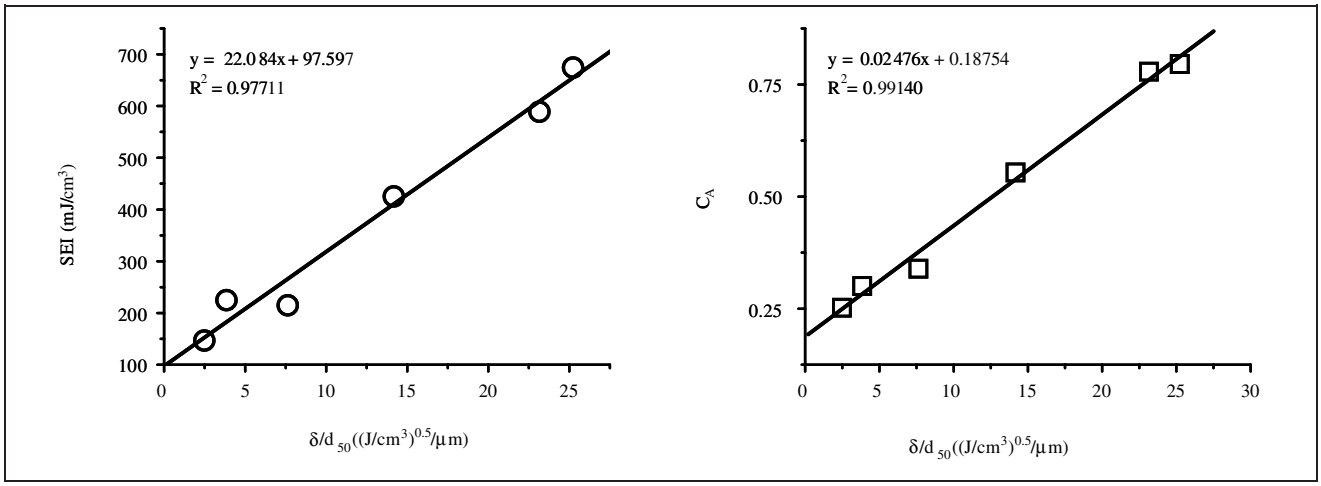

Fig. 4: ○: SEI_V in mJ/cm^3 vs. size normalized solubility parameter, □: Adhesion capacity vs. size normalized solubility parameter

These volume specific SEI_V values were also linearly correlating ($R^2 = 0.97711$) with the size normalized solubility parameters (δ_{tot}/d_{50}, Table 2) which is depicted in Fig. 4. Consequently, there was also a linear correlation between δ_{tot}/d_{50} and C_A resulting in an $R^2 = 0.99140$ (Fig. 4).

3. Discussion

Having a close look onto the adhesion phenomena of highly loaded interactive mixtures, one can divide the overall adhesion into two main parts; a) the adhesion of fine drug particles onto the carrier and b) the adhesion of fine particles among each other, also known as powder cohesion. The first should be energetically preferred due to a more or less sphere to plate contact of drug particle onto the carrier, which results in a Lifshitz van der Waals force double as high as for the likely sphere to sphere contact of case b) (Rumpf 1974; Stieß 1995). That is also the reason why no pure drug agglomerates could be seen on SEM pictures of the mixtures (data not shown), since

in the beginning of the adhesion a carrier-drug-contact is preferred and then further growth of the larger bodies by drug to drug adhesion was favored over the formation of pure drug agglomerates. Since the adhesion profiles were all linear for the entire range of applied drug concentrations (7.5–20% w/w), the energetic influence of the carrier was negligible, since otherwise a change in the slope of the adhesion profiles would have been occurred. Thus, the measured C_A were only dependent on the fine component of the mixtures. The error of this assumption is reflected by the y-intercept of the regression function of C_A, which was in between −1 and +0.2% (w/w) (Table 1) resulting from the different energies of the carrier to drug contact at low drug load. Besides the linearity, Fig. 1a and Table 2 depict that the finest grade of salbutamol sulfate (A) had the highest, the coarsest grade (C) the lowest C_A. This confirmed the size effect resulting from the ratio of Lifshitz van der Waals force to gravitational force (F_{LvdW}/F_g) of the adhered particles (Stieß 1995). While F_g is increasing by d^3 F_{LvdW} is just increasing by d^2 hence, the larger the particles the less their adhesion attraction, or in other words, their C_A. However, the SEI_S (mJ/m^2) of the three salbutamol sulfate powders also decreased with increasing particle size or decreasing SSA, mainly due to a decreasing γ^D. So even for one chemical substance the surface free energy was clearly size or SSA dependent. This is the reason the normalization of the surface specific SEI_S (mJ/m^2) values with SSA into mass specific SEI_m (mJ/g) rendered Cline and Dalby (2002) a good correlation between the fine powder fraction from *in vitro* testing of dry powder inhalers and the mass specific SEI_m (mJ/g). By assimilating the SEI calculation to the case of highly loaded interactive mixtures (Eq. 2), neglecting the carrier influence for the reason stated above, the correlation of C_A with SEI_m values yielded in good fitting results for all substances and sizes tested. A slightly better regression coefficient resulted when correlating SEI_m calculated on the basis of SSA_{PSA} ($R^2 = 0.97947$) compared to those calculated with SSA_{BET} ($R^2 = 0.96001$). This might be related to a greater influence of the size or volume of the particle compared to the BET surface including all superficial pores. The approach of a final normalization of SEI to the volume (mJ/cm^3) in order to relate volume and mass with respect to F_g, further improved the correlation between C_A and SEI_V (mJ/cm^3) to $R^2 = 0.98498$ (on the basis of SSA_{PSA}).

The good results of the linear relationship between the size normalized energetic value SEI_V (mJ/cm^3) and the C_A encouraged a comparison of SEI_V with a size normalized solubility parameter. The reason for the somehow unorthodox unit $(J/cm^3)^{0.5}/\mu m$ was due to the origin of the solubility parameter derived on the basis of molar volumes, which needed an additional normalization to the size of the solid particle. This empirical approach enables the extrapolation of molecular properties to surface and particle properties in a much simpler way than for example, proposed by Sethuraman and Hickey (2002) who introduced a dispersion value calculated on the basis of the solubility parameter. Of course the normalization with the d_{50} size parameter was just appropriate for the monomodal size distribution which was characteristic for all powders investigated (data not shown), however, for those it proved to be a suitable size representative.

In conclusion the SEI proved to be a suitable measure to judge and quantify adhesion properties of highly loaded interactive mixtures. Size and energy influences were thereby best reflected when volume specific SEI_V calculated on the basis of SSA_{PSA} was employed. The necessity of size or SSA normalization, respectively, even facilitated the use of the well known solubility parameter as a predictor for adhesion properties. The approach of using a size normalized solubility factor (δ_{tot}) correlated linearly with SEI_V and C_A thus, estimates of C_A can be performed even for systems if only the drug's molecular structure and required particle size is known. In order to optimize the dispersed drug fraction an ideal system should probably display low C_A, SEI_V or δ_{tot}/d_{50} at the smallest particle size possible. In case of salbutamol this could be performed by switching from the sulfate salt to the base reducing the adhesion capacity by a third at constant particle size.

4. Experimental

4.1. Materials

Mixture components: Crystalline α-lactose monohydrate (Inhalac 120), kindly supplied by Meggle GmbH, Wasserburg, Germany, was used as carrier substance. The model substances salbutamol sulfate (A, B, C) were provided by Dr. Willmar Schwabe GmbH, Karlsruhe, Germany; salbutamol base by Welding GmbH & Co., Hamburg, Germany, theophylline by BASF AG, Ludwigshafen, Germany and micronized α-lactose monohydrate (Sorbolac 400) by Meggle GmbH, Wasserburg, Germany. All substances were used as received and stored in tightly closed and light-protected containers at room temperature.

IGC probes: Methane (Messer, Maribor, Slovenia), n-hexane, n-heptane (Kemika, Zagreb, Croatia), n-octane, n-nonane, (Riedel-de Haën, Seezen, Germany), n-decane (Sigma, Munich, Germany), tetrahydrofurane (THF) and chloroform (Kemika, Zagreb, Croatia) were used for IGC measurements. All liquids were of gas chromatography grade and were employed without further purification.

4.2. Methods

4.2.1. Preparation of the interactive mixtures

First, a carrier portion of 10 g was passed through a metallic sieve (d = 315 μm) onto a glass petri dish, then the micronized drug was sieved onto the carrier in proportions of 1.5, 2, 3 or 4 g. Finally, carrier substance was added up to the final weight of 20 g. The resulting mixtures were blended using a metallic spoon in order to reduce the electrostatic charge and continued by mixing in a Turbula mixer (T2C, W. A. Bachofen, Basel, Switzerland) for 30 min at 42 rpm, using a brown glass container at a filling level of 40% of its total volume. Mixing conditions were 20–21 °C at 50–55% RH.

4.2.2. Determination of the drug content

Drug content in a powder mixture was determined using a UV-spectrophotometer (550 S, Perkin Elmer, Überlingen, Germany) at 276 nm (salbutamol base, salbutamol sulfate) and 279 nm (theophylline). Dissolved in 0.1 N hydrochloric acid, salbutamol and salbutamol sulfate were calibrated in the range of 5–12 mg/100 ml and theophylline in the range of 0.2–3.4 mg/100 ml.

4.2.3. Adhesion profiles

The initial drug content of the mixtures was determined by dispersing 1 g of the mixture in 100.0 ml 0.1 N HCl. To remove the drug fraction, which was not or just weakly adhered to the carrier, 10 g of the interactive mixture were sieved using a 32 μm air jet sieve apparatus (Hosokawa Alpine, Augsburg, Germany) at a sieve pressure of 15 mbar for 10 min. The complete sieve residue was filled into a 250 ml volumetric flask, dissolved and filled up with 0.1 N HCl and diluted until the absorption was in the calibrated range. The adhesion capacity (C_A), calculated, as the proportion of drug content of the sieve residue in relation to the drug content of the initial mixture was determined four times for each mixture.

4.2.4. Particle size analysis (PSA)

The particle size analysis (volume-distribution) was performed by laser diffraction using the Mastersizer 2000 (Malvern Instruments, Herrenberg, Germany) employing the dry dispersing unit Scirocco 2000S. The powder feeding was carried out using the micro volume module to provide a constant obscuration in the range of 2 and 10%. All calculations were performed using the Mastersizer software 4.0 (Malvern Instruments, Herrenberg, Germany) according to the Mie theory.

4.2.5. True density

The True density was determined (n = 3) using a Beckman helium comparison pycnometer (Model 930, Beckman Instruments, Inc., Fullerton, USA). Calibration was performed employing steel balls of different diameters.

4.2.6. Specific surface area (SSA)

SSA was determined by two different methods:
a) According to Brunnauer, Emmett and Teller (SSA_{BET}) using a Coulter SA 3100 apparatus (Beckman Coulter GmbH, Krefeld, Germany). The outgas time was 120 min at 100 °C. All measurements were performed in triplicate.
b) From particle size analysis the specific surface area (SSA_{PSA}) was further calculated (n = 3) employing the Mastersizer software 4.0 (Malvern Instruments, Herrenberg, Germany) on the basis of the particle size distribution and the true density of the respective powder assuming spherical particles.

4.2.7. Inverse gas chromatography

Inverse gas chromatography was carried out using the Agilent Technologies 6890N chromatograph with flame ionization detector (FID), Agilent 7683 series injector and a gas tight Hamilton syringe. The carrier gas was helium (Messer, Maribor, Slovenia) at gas flow 10 ml/min. The injector was heated at 150 °C the detector at 250 °C. Glass columns with an inner diameter of 3 mm and 30 cm in length were filled with a mixture of the respective sample powder and Chromosorb W HP (Supelco, USA) in a mass ratio of 1 : 1 by vertical tapping. Prior to the measurements all columns were conditioned at 30 °C for 4 h at a helium flow of 10 ml/min. IGC measurements were performed at infinite dilution at an oven temperature of 30 °C. Only symmetric, Gaussian peaks were further analyzed in triplicate. N-alkanes were used as nonpolar probes and according to Cline and Dalby (2002) chloroform (acid) and tetrahydrofuran (basic) were used as polar probes. The free enthalpy of desorption from the polar probes (ΔG_{sp}) were converted from kJ/mol into mJ/m^2 for further processing by dividing ΔG_{sp} by the Avogadro's number and the cross-sectional area of the probe.

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