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Application of Hansen solubility parameters for understanding and prediction of drug distribution in microspheres

Kerstin Vay[a,*], Stefan Scheler[a], Wolfgang Frieß[b]

[a] Sandoz GmbH, Sandoz Development Center Austria, Biochemiestrasse 10, A-6250 Kundl, Austria
[b] Department of Pharmacy, Pharmaceutical Technology and Biopharmaceutics, Ludwig-Maximilians-Universitaet Muenchen, D-81377 Munich, Germany

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ABSTRACT

In an emulsion solvent extraction/evaporation process for the preparation of microspheres the employed solvents have a tremendous influence on the characteristics of the resulting particles. Nevertheless the solvent selection is often based on empirical data rather than on calculated values. The purpose of this investigation was to use the concept of solubility parameters for interpretation and improved understanding of solvent effects in the process of microparticle preparation. Partial solubility parameters of 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on, which was used as a model drug, were determined experimentally using an extended Hansen regression model. Poly(lactide-co-glycolide) microparticles were prepared with an emulsion solvent removal process employing methylene chloride and its mixtures with benzyl alcohol and n-butanol. It could be shown, that the encapsulation efficiency was influenced by the change of the solvent composition during the extraction process. Furthermore the solvent selection had an essential influence on the morphological state of the drug and it could be shown and explained, that by a decrease of the dissolving power a completely amorphous product was obtained.

1. Introduction

The microencapsulation of a drug substance in a polymeric matrix offers the possibility of a controlled drug release with many clinical benefits like the drug targeting to a specific location or higher compliance of the patient because of a reduced dosing frequency. There are several methods to prepare microspheres from preformed polymers and the emulsion solvent extraction/evaporation process is one of the most frequently used techniques. In this preparation process, the properties of the utilized solvents are among the primary factors determining the characteristics of the resulting microspheres (Bodmeier and McGinity, 1987; O'Donell and McGinity, 1997; Cho et al., 2000; Moldenhauer and Nairn, 1992, 1994). Nearly every step of the particle formation process is affected by the solvents in a distinct way. In the first step where an organic solution of the polymer or, as in most cases, a solution of drug and polymer is formed the dissolving power of the solvent determines the upper concentration limit of the organic phase. If it is not intended to incorporate the drug as a suspension, both, drug substance and polymer should be well soluble in the organic solvent. In a second step an emulsion is formed from this solution and an aqueous phase. By feeding the emulsion into a stirred reactor containing an aqueous medium, the solvent is extracted into the external phase from where it can be evaporated in case of volatile solvents. During this process different diffusion processes take place like the transfer of the organic solvent out of and in return the non-solvent into the microspheres. This solvent exchange causes the transformation of the droplets into solid microspheres and is determined by the miscibility of the solvents and the aqueous medium. The drug, however, ideally should not be soluble in the aqueous medium otherwise it will be leached out of the particles resulting in a low encapsulation efficiency (Bodmeier and McGinity, 1988).

A variety of different solvent parameters like volatility and boiling point, reactivity or viscosity have to be considered in order to tailor the resulting microparticle properties. Another critical factor is the toxicological safety, as a certain amount of solvent residues remains in the product and thus restricts the range of suitable solvents. However one of the most important criterions on which a suitable solvent has to be chosen is an optimum balanced affinity to the other process compounds.

Often the solvent selection is based on empirical data rather than on calculated values. An initial estimate based on solubility calculations can help to optimize the results and to minimize experimental expenditure. An established tool to estimate the solubility behaviour of a substance is the concept of solubility parameters, originally defined by Hildebrand (Hildebrandt and Scott, 1964). He proposed the square root of the cohesive energy density as a

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[*] Corresponding author. Tel.: +43 5338 200 2835; fax: +43 5338 200460.
E-mail addresses: kerstin.vay@sandoz.com, kerstinvay@yahoo.de (K. Vay).

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numeric value to specify the solubility characteristics of a specific solvent:

$$\delta = \sqrt{\Delta H - \frac{RT}{V_m}} \qquad (1)$$

where ΔH is the heat of vaporization, R is the gas constant, T is the temperature and V_m is the molar volume. The cohesive energy density of a liquid is the energy of vaporization per volume unit. It reflects the degree of attractive forces holding the molecules together. This amount of energy is required to separate the atoms or molecules of the material from each other and is the effect of all interatomic/molecular interactions. Hansen subdivided the total Hildebrand value δ_t into three fractions: dispersive interactions (δ_d), polar interactions (δ_p) and hydrogen bonding (δ_h). These 3 parameters can be visualized as coordinates in a 3-dimensional diagram, which allows a good illustration of the miscibility or solubility of different materials. The smaller the distance between the coordinates of two substances is in this 3-dimensional space, the better is their mutual solubility.

In this study the principle of Hansen solubility parameters was applied to an emulsion-solvent evaporation process for the preparation of PLGA microspheres. Moldenhauer and Nairn used Hansen solubility parameters to choose alternative solvent systems for the production of microcapsules with similar properties and showed that particle characteristics and release rates could be correlated with the solubility parameters of solvent mixtures (Moldenhauer and Nairn, 1992). Bordes et al. applied them for the solvent substitution in a microencapsulation process with poly(ε-caprolactone). The objective of our work was to optimize the particle characteristics by modifying the solvent mixture of the dispersed phase. Starting with methylene chloride, which is often used in this process, binary mixtures of methylene chloride with benzyl alcohol and n-butanol were tested to analyze their influence on the morphology of the drug substance, the encapsulation efficiency and the drug release rate. Furthermore the solubility of the drug in the polymer matrix could be estimated.

Experimentally determined Hansen parameters of a huge number of solvents, drug substances and other chemicals are listed in the literature. However no values can be found so far for 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on. In this study we determined these parameters experimentally and compared them with those obtained by group contribution methods according to Hoftyzer/Van Krevelen and Hoy.

2. Materials and methods

2.1. Materials

3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on was obtained by Jubilant Organosys (Mysore, India) with an assay of 100.2% and 0.19% total impurities (main impurities: N-oxide-derivative and 9-OH-derivative); poly(D,L-lactide-co-glycolide) 75:25 (Resomer 755 S), Mw = 64,710 Da was purchased from Boehringer Ingelheim (Ingelheim, Germany). All solvents used were of analytical grade and were used as obtained.

2.2. Determination of the solubility of the API in PLGA by differential scanning calorimetry (DSC)

To determine the solubility of the drug substance in PLGA the enthalpy of fusion of pure PLGA, drug substance and three mixtures of PLGA with 30.9%, 49.3% and 81.8% of API were measured. Approximately 2 mg were weighed in a standard aluminium pan, sealed and heated from −20 to 250 °C with a heating rate of 50° per minute in a DSC (823e/500) from Mettler Toledo (Greifensee, Switzerland). The melting peak of the drug substance at 170 °C was integrated. The heat of fusion thus obtained was plotted against the drug concentration in the mixture as described in the literature (Panyam et al., 2004).

To examine if the decomposition occurs the pan with pure drug substance was heated for a second time up to 250 °C. The thermogram was unchanged compared to the first one indicating that the drug substance is stable in a range between −20 and 250 °C. PLGA is described in literature to undergo no decomposition in this temperature range (De and Robinson, 2004).

2.3. Determination of the morphological state of the drug by X-ray powder diffractometry

X-ray powder diffraction (XRPD) patterns were collected with an Unisantis XMD 300 X-ray powder diffractometer (Unisantis, Georgsmarienhütte, Germany) with a position sensitive detector in parallel beam optics using the following acquisition conditions: tube anode: Cu, 40 kV, 0.8 mA; 3–43° $\theta/2\theta$; simultaneous detection of regions of 10° per step with detector resolution 1024, counting time 300 s per step. Samples were measured at room temperature in a standard sample holder on a rotating sample spinner.

2.4. Determination of the solubility

The solubility of on the API was determined in 17 different solvents (Table 1) by adding a surplus of drug substance in a glass vial to 5 ml solvent. The vials were sealed and shaken at room temperature for 24 h to assure saturation. 2 ml of the saturated solution were filtered through a 1.0 μm Teflon filter and the solvent was evaporated at RT. After dissolving the residue in 0.1 N HCl, the concentration of the drug substance was determined by HPLC with a DAD detector at 235 nm and analyzed with chromeleon^{TM} 6.7 (Dionex, Sunnyvale, CA, USA). A XTerra RP 18 (20 mm × 3.5 mm) column was used at a flow rate 1 ml/min and an injected volume 10 μl. The mobile phase consisted of a phosphate buffer (pH 8.5) and acetonitrile at a ratio of 75:25 (v/v). The precision of this method was determined to 0.37%.

3. Results and discussion

3.1. Determination of the solubility parameters

3.1.1. Experimental determination

Since experimentally derived Hansen solubility parameters of 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on could not be found in literature they were determined by own measurements. The total and the partial solubility parameters of a substance can be calculated from its solubility values in a series of different solvents with known cohesive energies (Reuteler-Faoro et al., 1988). The method is based on the rule that the more similar the parameters of two substances are, the better is their miscibility or the solubility of one substance in the other. If the parameters match exactly the solubility becomes ideal which means that the activity coefficient γ_2 which is the ratio of the ideal mole fraction solubility X_2^i and the experimental mole fraction solubility X_2 equals 1. In terms of total solubility parameters this condition is expressed by Eq. (2)

$$\ln \gamma_2 = \ln \frac{X_2^i}{X_2} = (\delta_1 - \delta_2)\frac{V_2 \phi_1^2}{RT} \qquad (2)$$

Table 1
Solubility parameters, molar volume and solubility for the API in different solvents.

Solvent	δ_d [MPa$^{1/2}$]	δ_p [MPa$^{1/2}$]	δ_h [MPa$^{1/2}$]	Molar volume V_1 [ml mol^{-1}]	API Concentration [mg/ml]
2-Propanol	15.8	6.1	16.4	76.8	5.67
Acetone	15.5	10.4	7.0	74.0	8.89
Acetonitrile	15.3	18	6.1	52.6	4.35
Benzyl alcohol	18.4	6.3	13.7	103.6	277.13
Chloroform	17.8	3.1	5.7	80.7	392.52
Diethylamine	14.9	2.3	6.1	103.2	3.21
DMSO	18.4	16.4	10.2	71.3	8.68
Ethanol	15.8	8.8	19.4	58.5	19.47
Ethylacetate	15.8	5.3	7.2	98.5	8.82
Hexanol	15.8	4.3	13.5	124.6	13.63
Methyl acetate	15.5	7.2	7.6	79.7	10.19
Methylene chloride	18.2	6.3	6.1	63.9	85.11
n-Butyl acetate	15.8	3.7	6.3	132.5	6.28
n-Hexane	14.9	0	0	131.6	0.07
Pyridine	19.0	8.8	5.9	80.9	110.37
Tetrahydrofuran	16.8	5.7	8.0	81.7	50.79
Toluene	18.0	1.4	2.0	106.8	27.88

where R is the gas constant, T is the temperature at which the experiment is performed (K) and ϕ_1 is the volume fraction of the solvent. ϕ_1 can be expressed as follows:

$$\phi_1 = \frac{V_1(1-X_2)}{V_1(1-X_2)+V_2X_2} \qquad (3)$$

with V_1 and V_2 as the molar volumes of the solvent and the solutes, respectively. In all variables the subscript 1 refers to the solvent and the subscript 2 to the solute. On the basis of Eq. (2) Martin (Martin et al., 1981) and Beerbower (Beerbower et al., 1984) developed an extended regression model involving Hansen partial solubility parameters.

$$\frac{\ln(X_2^i/X_2)}{V_2\phi_1^2/(RT)} = D_0 + D_1(\delta_{1d}-\delta_{2d})^2 + D_2(\delta_{1p}-\delta_{2p})^2 + D_3(\delta_{1h}-\delta_{2h})^2 \qquad (4)$$

where $\delta_{1d}, \delta_{1p}, \delta_{1h}, \delta_{2d}, \delta_{2p}, \delta_{2h}$ are the partial solubility parameters of the solvent and the solute, respectively. D_0 to D_3 are constants. Eq. (4) can be converted into the regression Eq. (5).

$$\frac{\ln(X_2^i/X_2)}{V_2\phi_1^2/(RT)} = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \qquad (5)$$

with

$$C_0 = D_0 + D_1\delta_{2d}^2 + D_2\delta_{2p}^2 + D_3\delta_{2h}^2 \qquad (6)$$

$$C_1 = D_1 \qquad (7)$$

$$C_2 = -2D_1\delta_{2d}^2 \qquad (8)$$

$$C_3 = D_2 \qquad (9)$$

$$C_4 = -2D_2\delta_{2p}^2 \qquad (10)$$

$$C_5 = D_3 \qquad (11)$$

$$C_6 = -2D_3\delta_{2h}^2 \qquad (12)$$

The constant coefficients C_0–C_6 are obtained by regressing the left hand term against the partial parameters of the solvents. Bustamante et al. (1993) simplified the model by proving that the partial solubility parameters can also be obtained by regressing only the logarithm of the experimental mole fraction solubility X_2 against the partial solubility parameters of the solvents.

$$\ln X_2 = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \qquad (13)$$

From Eqs. (6)–(12) the partial solubility parameters δ_{2d}, δ_{2p}, and δ_{2h} are calculated as

$$\delta_{2d} = -\left(\frac{C_2}{2C_1}\right) \qquad (14)$$

$$\delta_{2p} = -\left(\frac{C_4}{2C_3}\right) \qquad (15)$$

$$\delta_{2h} = -\left(\frac{C_6}{2C_5}\right) \qquad (16)$$

As they represent the function's maximum they can be also obtained from the zero points of the partial derivatives $\partial \ln X_2/\partial\delta_{1(d,p,h)}$.

17 different solvents were employed for this study. Their Hansen solubility parameters, molar volumes and the experimentally determined saturation concentration of 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on in each solvent are listed in Table 1. The following partial solubility parameters of the drug substance were calculated from these data: δ_{2d} = 18.7 MPa$^{1/2}$, δ_{2p} = 5.4 MPa$^{1/2}$, and δ_{2h} = 11.6 MPa$^{1/2}$.

3.1.2. *Estimation of the solubility parameters by group contribution methods*

As the solubility of a material is largely determined by its chemical nature, the solubility parameters can also be calculated from its molecular structure. In this work two different approaches were chosen, on the one hand the calculation of the solubility parameters according to the group contribution method from Hoftyzer and Van Krevelen and on the other hand according to Hoy (Van Krevelen, 2009) (Table 2).

3.1.2.1. Method of Hoftyzer and Van Krevelen. According to Hoftyzer and Van Krevelen the partial solubility parameters can be calculated using the following equations:

$$\delta_d = \frac{\sum F_{di}}{V} \qquad (17)$$

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} \qquad (18)$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} \qquad (19)$$

where F_{di} and F_{pi} are the group contributions to the dispersion and the polar component (F_d and F_p) of the molar attraction constant, respectively. E_{hi} is the hydrogen bonding energy per

Table 2
Comparison of the different parameters contributing to the calculated results of the applied methods.

Hoftyzer and Van Krevelen			Hoy			Experimental determination[a]	
Parameter; derived from		Formula	Parameter; derived from		Formula	Parameter; derived from	
V	Calculated from density		V	Group contribution tables		V	Literature
F_{di}	Group contribution tables	$\delta_d = \frac{\sum F_{di}}{V}$	F_{ti}	Group contribution tables	$\delta_d = \sqrt{\delta_t^2 \delta_p^2 \delta_h^2}$	c_{sn}	Experimentally determined
F_{pi}	Group contribution tables	$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V}$	F_{pi}	Group contribution tables	$\delta_p = \delta_t \left(\frac{(1/\alpha) F_p}{F_t + B} \right)$		
E_{hi}	Group contribution tables	$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}}$	ΔT_i	Group contribution tables	$\delta_h = \sqrt{\delta_t \left(\frac{\alpha - 1}{\alpha} \right)}$		

[a] Since the simplified model according to Bustamante et al. (1993) was used only the saturation solubility (c_s) and the molar volume are contributing to the calculation.

structural group in J mol^{-1} and V the molar volume of the solvent in ml mol^{-1}. The Hansen partial solubility parameters were calculated as $\delta_d = 20.8$ MPa$^{1/2}$, $\delta_p = 6.1$ MPa$^{1/2}$, and $\delta_h = 9.2$ MPa$^{1/2}$.

3.1.2.2. Method of Hoy. The procedure of Hoy differs in many respects from the method mentioned before. It is based on a molar attraction function (F_t), a polar component (F_p), the molar volume of the solute molecule (V), the Lyderson correction for non-ideality (Δ_T) and auxiliary equations (Van Krevelen, 2009). The values obtained by this method are $\delta_d = 18.0$ MPa$^{1/2}$, $\delta_p = 12.1$ MPa$^{1/2}$, and $\delta_h = 5.1$ MPa$^{1/2}$.

Only δ_d is within the same range as the experimental value and as calculated according to the Hoftyzer/Van Krevelen method whereas δ_p is significantly higher and δ_h significantly lower. Tracing back the calculation procedure reveals that δ_h is strongly dependent on the molar volume which is calculated in case of Hoy's method also from group contributions. The resulting computed value of 360 cm^3 mol^{-1} is much higher than the molar volume of 296.8 cm^3 mol^{-1} found in literature database (Scifinder, 2010) which is identical with the value calculated from the molecular structure (Fig. 1) by the software ACD/ChemSketch Freeware (version 10.00, Advanced Chemistry Development, Inc., Toronto, ON, Canada, www.acdlabs.com, 2006). If the cohesion parameters are recalculated with the lower molar volume the values obtained are $\delta_d = 19.8$ MPa$^{1/2}$, $\delta_p = 13.3$ MPa$^{1/2}$, and $\delta_h = 12.6$ MPa$^{1/2}$, with δ_h matching better the experimental value. However δ_p is still higher than determined with the other methods. This fact supports the finding that the Hoy procedure does not appear to fully separate the polar and hydrogen bonding energies (Koleske, 1995).

Another set of values was published by Dwan'Isa et al. who computed the cohesion parameters using the software Molecular Modeling Pro (Dwan'Isa et al., 2005). These values ($\delta_d = 21.4$ MPa$^{1/2}$, $\delta_p = 6.9$ MPa$^{1/2}$, and $\delta_h = 9.5$ MPa$^{1/2}$) are very close to those obtained with the Hoftyzer/Van Krevelen method and are most likely calculated by the same algorithm.

On the whole, the experimentally determined values are within a similar range as those calculated by group contribution procedures (with the exception of δ_p according to Hoy) (Table 3). Nevertheless they are considered more reliable than those derived from molecular structure elements on the basis of empirical rules. Especially the calculated values for δ_d are extremely high and contrary to the measured solubility in less lipophilic solvents. Thus, for further considerations, only the experimental results were used.

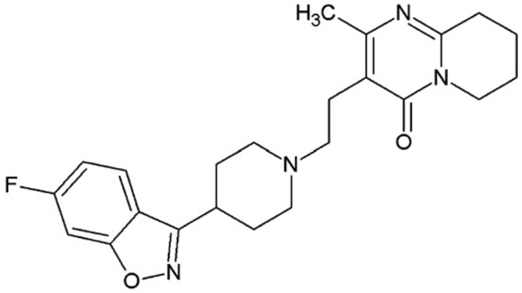

Fig. 1. Molecular structure of 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on.

Table 3
Experimentally obtained and calculated partial solubility parameters.

	δ_d [MPa$^{1/2}$]	δ_p [MPa$^{1/2}$]	δ_h [MPa$^{1/2}$]
Experimental results	18.7	5.4	11.6
Calculated values (Hoftyzer, Van Krevelen)	20.8	6.1	9.2
Calculated values (Hoy)	19.8	13.3	12.9
Value derived from literature[a]	21.4	6.9	9.5

[a] Dwan'Isa et al. (2005).

3.2. Estimation of the solubility of the drug substance in different solvents and in PLGA

Partial solubility parameters are often represented in a three-dimensional grid, the so-called Hansen space. The mutual miscibility of two substances or the solubility of one substance within the other can be estimated from their relative coordinate positions, i.e. the Euclidean distance between both coordinate points. The smaller the distance in the diagram, the better is the mutual solubility between the two substances. Fig. 2 shows the

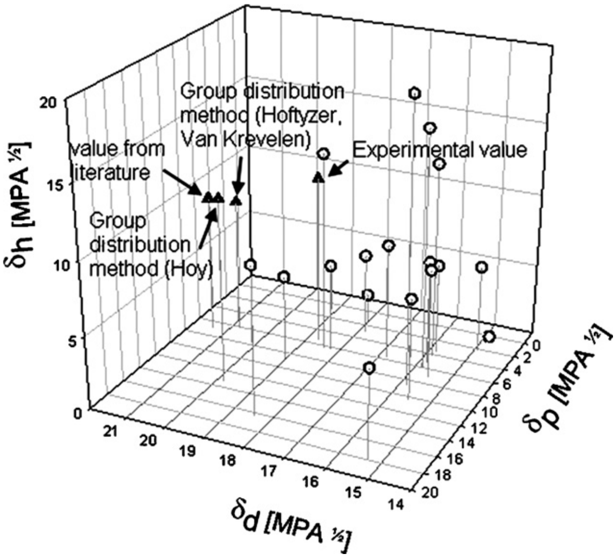

Fig. 2. Position of on the drug substance (calculated and experimentally determined) and the tested solvents (Table 1) in a three dimensional diagram.

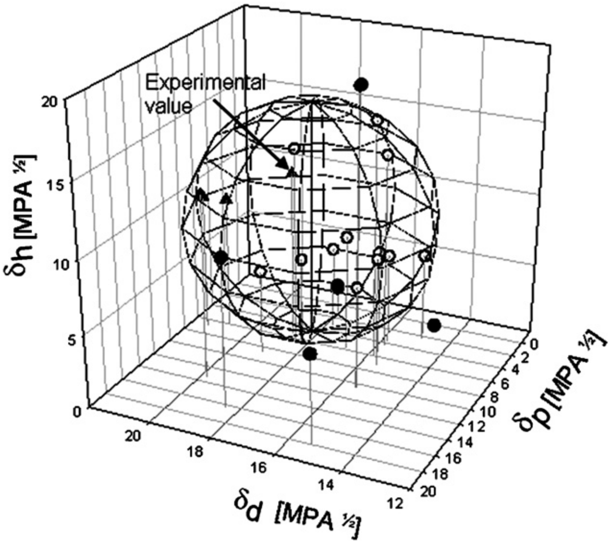

Fig. 3. Solubility sphere of PLGA (75:25) and the position of the solvents (●, outside the sphere; ○, inside the sphere) and on the drug substance (▲) in the δ_d–δ_p–δ_h-diagram.

coordinate positions of the solvents listed in Table 1 and the coordinate points of the API calculated by different methods.

In such diagrams solvents and low molecular molecules are commonly depicted as single coordinate points whereas polymers are drawn as volume structures, mostly spheres. They enclose the diagram range in which solvents with good solving or swelling properties for the polymer are located.

Schenderlein et al. used two different experimental methods and a group contribution approach to determine the center point and the interaction radius of the solubility sphere of PLGA (75:25) (Schenderlein et al., 2004). The following values are reported, differing especially with respect to δ_p: Swelling experiments ($\delta_d = 17.4\,\mathrm{MPa}^{1/2}$, $\delta_p = 8.3\,\mathrm{MPa}^{1/2}$, $\delta_h = 9.9\,\mathrm{MPa}^{1/2}$), turbidity titration ($\delta_d = 15.8\,\mathrm{MPa}^{1/2}$, $\delta_p = 3.5\,\mathrm{MPa}^{1/2}$, $\delta_h = 9.1\,\mathrm{MPa}^{1/2}$) and group contribution method ($\delta_d = 16.1\,\mathrm{MPa}^{1/2}$, $\delta_p = 9.7\,\mathrm{MPa}^{1/2}$, $\delta_h = 11.7\,\mathrm{MPa}^{1/2}$). The interaction radius which was only determined by polymer swelling amounts to $7.8\,\mathrm{MPa}^{1/2}$. As the experimental determination is considered to be more accurate than predictions from the molecular structure and the data obtained from swelling measurements are the most comprehensive as they provide also an interaction radius of the sphere, only these values were used for further calculations (Fig. 3).

The coordinate position of a substance with respect to a polymer solubility sphere is characterized by the ratio of the coordinates' distance to the center of the sphere and the sphere's interaction radius. This ratio is called the Relative Energy Difference (RED) (Hansen, 2000). A RED less than 1.0 indicates a high affinity or solubility (coordinate position within the sphere), a RED higher than 1.0 lower affinities to the polymer (coordinate position outside the sphere) (Fig. 4).

The distance between two coordinate points within the Hansen space $D_{(S-P)}$ is calculated by the following equation (Hansen, 2000):

$$D_{(S-P)} = [4(\delta_d s - \delta_d p)^2 + (\delta_p s - \delta_p p)^2 + (\delta_h s - \delta_h p)^2]^{1/2} \tag{20}$$

From the experimentally determined solubility parameters of the API and the center coordinates of the PLGA 75:25 solubility sphere taken from literature (swelling data from Schenderlein et al.) a distance of 5.05 and a RED of 0.61 was calculated, which implies that the drug substance lies inside the sphere and should be soluble in the polymer to a certain extent.

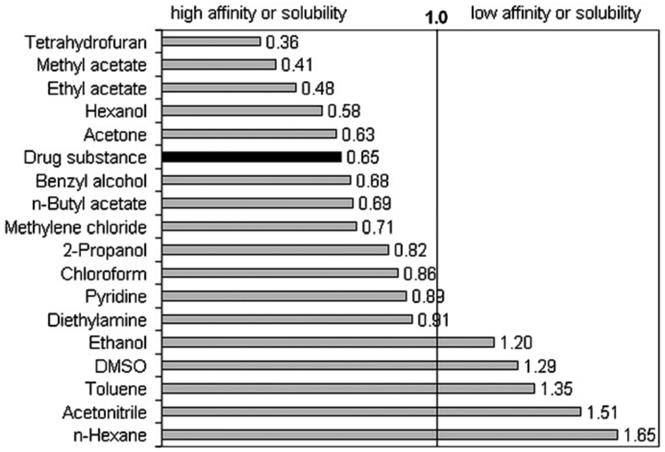

Fig. 4. Relative Energy Difference between PLGA (75:25) and the analyzed solvents and the API, respectively.

The true solubility within a polymer matrix, unbiased by depositions of unsolved crystalline or amorphous substance, is hardly accessible by direct chemical analysis. A mathematical approach was made by calculating the solubility in the polymer matrix based on the regression Eq. (13). After δ_{2d}, δ_{2p}, and δ_{2h} and the coefficients C_0–C_6 are calculated they can be inserted in Eq. (13) together with the polymer's δ_{1d}, δ_{1p}, and δ_{1h} to obtain X_2 as the solubility of on the drug substance in PLGA. The conversion of the mole fraction solubility into a w/w concentration was done on the basis of the average molecular weight of a repetitive monomer unit of PLGA (75:25) (68.6 g mol^{-1}). By this method X_2 was computed as 0.0235. This corresponds to 0.144 g API per g PLGA, which is a drug load of 12.6% (w/w) in the drug/PLGA mixture.

In order to demonstrate the plausibility of these results, a second approach was tried based on differential scanning calorimetry. Microparticles with different degree of drug load as well as physical API/PLGA mixtures (0%, 30.9%, 49.3%, 81.8% and 100%) were measured and the enthalpy of fusion was calculated from the melting peak of the drug. A linear correlation could be established between the enthalpy of fusion and the drug concentration in the mixtures. Also in case of the microparticles a linear correlation function was found with almost the same slope but enthalpies being between 14 and 21 J/g lower than those of the mixtures with a corresponding drug amount. This can be explained by the fact that the drug, which is dissolved in the polymer is not in a crystalline state and does not contribute to the enthalpy of fusion. The same applies to amorphous drug which is finely dispersed between the polymer chains and thus protected against recrystallization. From the offset between the correlation curves, we could calculate a fraction of 13–16% on the API dissolved in the polymer matrix. Taking into consideration that both, the theoretical approach as well as the DSC measurements are afflicted with a certain error, the results are within the same range.

3.3. Prediction of drug–polymer interactions during processing based on solubility parameters and effects on the properties of the resulting microspheres

For the microparticle preparation process three sets of solubility parameters (for the drug, the polymer and the solvent or solvent mixture) have to be considered. It is essential, that the drug substance and the polymer are soluble in the solvent of the dispersed phase. On the other hand the solvent should be soluble in the aqueous phase to some degree and extractable from the droplets to induce microparticle solidification. The solvent has to be chosen, to meet both criteria.

Table 4
Influence of the solvent mixture on encapsulation efficiency and drug release rate.

	Ratio (w/w)	Ratio (v/v)	Encapsulation efficiency [%]	Drug released after 25 d [%]
Methylene chloride			83.6	40.2
Methylene chloride:benzyl alcohol	90:10	88:12	85.0	52.0
Methylene chloride:benzyl alcohol	75:25	70:30	82.9	33.8
Methylene chloride:n-butanol	75:25	65:35	80.5	51.5

In pure methylene chloride the polymer and the drug substance show almost the same solubility. The distance calculated by Eq. (20) between drug substance and methylene chloride is 5.46 $\text{MPa}^{1/2}$ and between PLGA and methylene chloride it is 5.51 $\text{MPa}^{1/2}$. The solubility of both was varied by adding different co-solvents in the process. A fraction of methylene chloride was substituted by a better or a poorer solvent for the drug in order to modify the drug distribution in the polymeric phase and the degree of crystallization during the manufacturing process. This is influenced by the drug's solid state solubility (Tse et al., 1999), which in turn has an impact on the release behaviour of the resulting microspheres. Solid dispersions of poor water soluble drugs are often used to enhance the drug dissolution and bioavailability (Chiou and Riegelman, 1971; Vippagunta et al., 2002). In case of a long acting dosage form a low solubility and a crystalline state of the drug is desirable.

Minghetti et al. found, that the release rate of the solved drug was most quickly, when the difference between the solubility parameter of the drug and the polymer matrix was highest due to the maximum thermodynamic activity of the drug substance (Minghetti et al., 1999).

Furthermore co-solvents have been reported to influence the partitioning of the organic phase into the external phase and thus to affect for example drug load and release kinetics of the microspheres (Rawat and Burgess, 2010; Graves et al., 2006).

In the present study we investigated the impact of binary solvent mixtures on the properties of the resulting microspheres. Methylene chloride was used as the basic component in the organic phase, as it is a common solvent for the preparation of PLGA microspheres with the advantage of simple removal by extraction and evaporation. Benzyl alcohol was added in various concentrations to enhance the dissolving power for the drug substance, whereas n-butanol was used to cause the opposite effect.

Consequently, microparticles were prepared with 10%/90% and 25%/75% mixtures of benzyl alcohol and methylene chloride (Table 4) and with a 25%/75% mixture of n-butanol and methylene chloride. With all solvent mixtures spherical, nonaggregated microparticles were obtained. However the particles prepared with 25% benzyl alcohol and n-butanol were not stable during storage at room temperature and agglomerated by and by.

The partial solubility parameters of benzyl alcohol differ from those of methylene chloride especially in their hydrogen bonding component. Benzyl alcohol has a lower δ_h and is a better solvent for the API. As both solvents are only poorly soluble in water with solubilities being in about the same range (benzyl alcohol: 3.9% (m/v), methylene chloride: 2.0% (m/v)) it can be assumed that the extraction process is mainly governed by different evaporation rates. As methylene chloride (b.p. 39.8 °C) is more volatile than benzyl alcohol (b.p. 205 °C), it evaporates faster, thus shifting of the solvent ratio inside the particles (Fig. 5). It can be seen that if the process starts with a benzyl alcohol/methylene chloride ratio of 10:90 or 25:75 the solubility of the polymer in the solvent mixture, expressed as the coordinate distance in the Hansen space, decreases whereas the solubility of on the API increases during evaporation of methylene chloride. Even though the drug again becomes a little bit less soluble toward the end of the process this does not change the fact that there is a net improvement of the drug's solubility after complete removal of methylene chloride. These contrasting changes in solubility, i.e. deterioration in case of PLGA and improvement in case of the drug, support a rapid hardening of the particles and an effective retention of the drug in the particles. At least in case of a 10:90 solvent mixture, causing a 2.6 $\text{MPa}^{1/2}$ net reduction of the drug–solvent coordinate distance during the process, improved encapsulation efficiency could be found in comparison to particles prepared with pure methylene chloride. Only a marginal change of the encapsulation efficiency even in the opposite direction was observed with a 25:75 mixture which is in a certain correlation to the much smaller intra-process distance change of only about 1 $\text{MPa}^{1/2}$. A fraction of more than 25% benzyl alcohol in the organic phase is not beneficial because multinucleated particles are formed the product is not stable and agglomerates during storage. Furthermore a high content of residual benzyl alcohol is undesirable with regard to toxicological aspects.

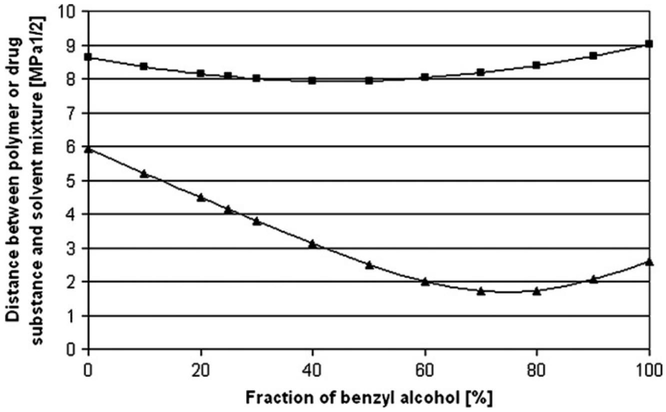

Fig. 5. Distance between polymer (■) and API (▲) and solvent mixture with varying fraction (v/v) of benzyl alcohol.

As a second solvent for the preparation of the microspheres, a 25:75 n-butanol/methylene chloride mixture was employed. n-Butanol differs in its dispersion forces and hydrogen bonding component from methylene chloride and has only a low dissolving power for the API. As n-butanol (b.p. 117.7 °C) is also less volatile than methylene chloride the same consideration as for benzyl alcohol and methylene chloride can be made (Fig. 6). The solubility of the polymer is higher in n-butanol than in methylene chloride with a local maximum at a 60:40-mixture. It is much better than in benzyl alcohol/methylene chloride mixtures. By contrast, the solubility of the drug substance is poorer and decreases strongly from 100% methylene chloride to 100% n-butanol. Consequently a lower retention of the drug has to be expected and was confirmed by an encapsulation rate 3.1% lower than in case of a pure methylene chloride process.

Apart from the effect on the encapsulation efficiency the solvent was found to influence also the morphology of the drug. X-ray diffraction demonstrates that in contrast to methylene chloride or its mixtures with benzyl alcohol (data not shown), which lead to a certain amount of crystalline drug, the n-butanol/methylene chlo-

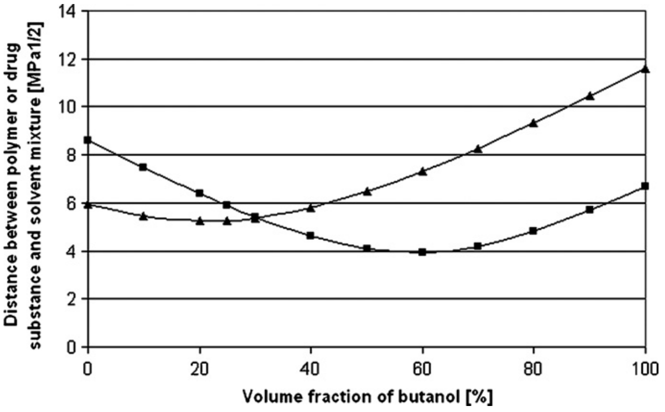

Fig. 6. Distance between polymer (■) and API (▲) and solvent mixture with varying fraction of n-butanol.

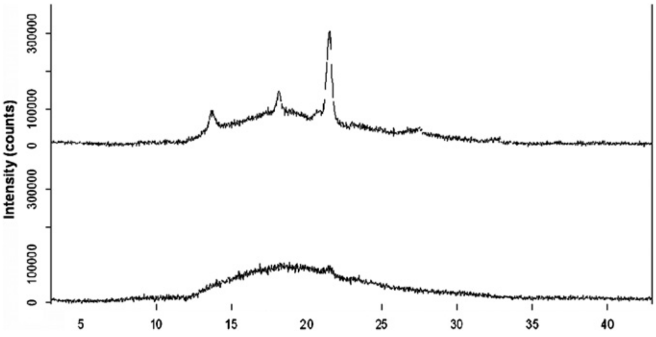

Fig. 7. X-ray diffractogram of microspheres prepared with methylene chloride (top) and with a mixture of methylene chloride and n-butanol (75:25) (bottom).

ride mixture caused deposition of the drug in a totally amorphous form (Fig. 7).

When the concentration of n-butanol rises during the process as described above and thus the solubility of the drug substance in the solvent mixture inside the microspheres decreases, the partition of the drug between solvent regions and polymeric phase shifts in favor of the latter. Because the polymer acts as a crystallization inhibitor the drug will not precipitate in a crystalline but in an amorphous state. In solid dosage forms normally the most stable polymorph of a drug substance is preferred, as an amorphous drug substance is thermodynamically less stable (Yu et al., 2003) and tends to undergo uncontrollable alterations during storage.

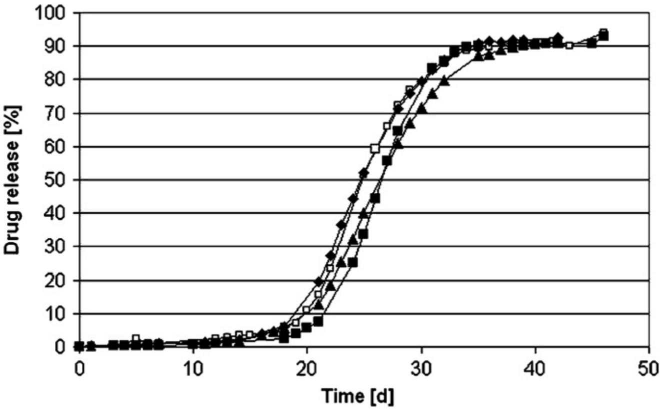

Fig. 8. Drug release of microspheres prepared with different organic solvents: methylene chloride (▲), methylene chloride/n-butanol 75:25 (w/w) (□), benzyl alcohol/methylene chloride 75:25 (w/w) (■) and 90:10 (w/w) (♦).

Surprisingly, in case of the studied microspheres the presence of amorphous API had about no influence on the drug release profile (Fig. 8). Regarding the drug release of the microspheres prepared with benzyl alcohol and methylene chloride also no influence could be shown. All curves were within the variation limits obtained with different batches from a pure methylene chloride process.

It could be shown by DSC measurements that already on the second day of the release test the amorphous fraction had disappeared and a recrystallization peak could not be observed anymore. This indicates that the morphological state of the embedded drug is irrelevant for the release kinetics because recrystallization occurs upon the first contact with water and subsequently the drug is always released from a crystalline solid. Thus any potential recrystallization during storage is not likely to have a major impact on drug release.

4. Conclusions

The partial solubility parameters of 3-{2-[4-(6-Fluor-1,2-benzisoxazol-3-yl)piperidino]ethyl}-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-on were determined by three different methods, of which the experimental approach appears to provide the most reliable values. The structure of this drug substance is rather complex for the calculation by group contribution methods. For some structural elements of the molecule no values are tabulated. From the solubility parameters of the API and of PLGA a fraction of 12.6% of the drug was calculated to be dissolved in the polymer matrix. This order of magnitude could also be verified by DSC measurements.

Methylene chloride is one of the most commonly used solvents for the preparation of PLGA microspheres by emulsion-solvent evaporation. It is highly volatile and easily extractable from the microspheres. On the basis of partial solubility parameters two co-solvents were chosen as additional solvent components. Benzyl alcohol was selected as it enhances and n-butanol as it diminishes the dissolving power for the drug substance. Three different co-solvent/methylene chloride mixtures were analyzed with regard to their particle characteristics and drug release behaviour. The encapsulation efficiency was slightly increased if the drug became better soluble in the solvent mixture during the process and it was diminished if the extraction process led to a mixture with a lower dissolving power for the drug. Moreover, the solvent selection showed an influence on the morphology of the drug and it could be shown, that the addition of n-butanol caused an almost completely amorphous state of the API. It is remarkable, that these particles produced nearly the same drug release profile as particles, which contained the drug in a crystalline state. Recrystallization upon the first contact with dissolution medium was found to be the reason for this behaviour. Thus, microspheres which contain the drug or fractions of the drug in an amorphous state are not to be considered as prone to instabilities influencing the drug release kinetics.

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