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Predictability of drug encapsulation and release from propylene carbonate/PLGA microparticles

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ABSTRACT

Key parameters for microparticle-based parenteral depot formulation development are entrapment efficiency and sustained drug release, which both depend on the intermolecular affinity of the components. Here, partial solubility parameters were evaluated as descriptors for 21 drug substances and 3 polymers in propylene carbonate (PC). Out of these 21 drug substances, eight BCS class II substances (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) were encapsulated using PLGA (Poly (DL-lactide-co-glycolide)) as polymer matrix and PC as a polar aprotic solvent in order to assign microparticle properties to potential affinity-related interactions using partial solubility parameters. Microparticle morphology was highly dependant on the specific glass transition temperature (Tg) of the encapsulated drug substance. A strong correlation (R = 0.912) between the encapsulation efficiency and the difference in total solubility parameter ($\Delta\delta_{t\ API\text{-}PLGA}$) underlined the encapsulation predictability. Moreover, in drug release, a significant impact of $\Delta\delta_{t\ API\text{-}PLGA}$ on initial burst was observed and even more pronounced on the release rate of the encapsulated drug substance. The possibility to predict these important microparticle properties underline the value of including solubility descriptors such as partial solubility parameters into microparticle formulation development.

1. Introduction

In microencapsulation diverse intermolecular affinity-related phenomena between all components in a microparticle system take place. Obviously, excipients as well as the drug substance have a profound effect on different formulation properties, such as the encapsulation efficiency (Vay et al., 2012), drug substance solid state (Vay et al., 2011), the release profile (Gasmi et al., 2015), particle morphology (Katou et al., 2008) etc.

A microencapsulation technique based on an emulsification process usually involves the dissolution of the matrix-forming polymer and, optionally, of the drug. A final solvent elimination step (either by evaporation or extraction, depending on the solvent volatility) is included in order to obtain solid particles which entrap the drug substance. The microparticle matrix is typically formed by a biocompatible and/or biodegradable polymer, whose properties such as the glass transition temperature (Tg) (Li et al., 1995; Vay et al., 2012) and lipophilicity (Parent et al., 2013) significantly influence the properties of the final microparticle formulation. Similarly, also the intrinsic physicochemical properties of the encapsulated drug substance can have a profound impact on the final microparticle properties (Vay et al., 2012). Besides, the type and intrinsic properties of the organic solvent also significantly influence the outcome of the microencapsulation process as well as the final quality of the produced microparticles by means of residual solvents (O'Donnell and McGinity, 1997), which should be kept as low as possible not only based on formulation considerations but also on toxicology-related aspects (Allhenn and Lamprecht, 2011; Viehof et al., 2013). Recently, propylene carbonate (PC) has been identified as a promising solvent candidate of low toxicity, while showing promising properties for microparticle development (Grizić and Lamprecht, 2018).

The description of solubility and miscibility between formulation components from a thermodynamic aspect would be of major interest for explanating the microencapsulation step mechanistically. The most important net force which is including all inter atomic/molecular attraction forces such as Van der Waals interactions, covalent bonds, ionic bonds, hydrogen bonds, electrostatic interactions, induced dipole and permanent dipole interactions, is represented by the cohesive energy (Hancock et al., 1997). The cohesive energy can be quantified in a number of ways, including the expression through the Hildebrand

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solubility parameter δ (Hildebrand and Scott, 1965). Hansen sub-divided this parameter into three components (partial solubility parameters) which express the contributions of different internal forces describing the: dispersion force part (δ_d), polar interactions part (δ_p) and hydrogen bonding force part (δ_h) (Hansen, 2007). The direct relation of partial solubility parameters with some fundamental intrinsic properties of substances such as the surface tension, dipole moment, index of refraction as well as the molar attraction constants was thoroughly described (Koenhen and Smolders, 1975).

Lately, various studies have shown specific relationships between partial solubility parameters and formulation properties. In this manner, the possibility of solute in solvent solubility prediction was described for ibuprofen and ibuprofen lysinate (Kitak et al., 2015) as well as for C_{60} fullerenes (Hansen and Smith, 2004) in different solvent systems. Previous studies also showed that the drug solubility could be predicted using not just binary, but also ternary solvent systems using partial solubility parameters as interaction descriptors (Jouyban et al., 2011). Likewise, it was shown that a connection between microsphere morphology and the use of methylene chloride and its mixture with benzyl alcohol and n-butanol as the organic solvent phase could be observed using partial solubility parameters (Vay et al., 2011).

In this study, the main objective was to evaluate the predictability of the encapsulation and release rates using partial solubility parameters for a PC-based microencapsulation method for poly(DL-lactide-co-glycolide) (PLGA) microparticles. Specific solubility descriptors for 21 different drug substances in PC have built the basis for the selection of 8 drug candidates that have been encapsulated in order to explore the potential to predict encapsulation efficiency and drug release from microparticles.

2. Materials and methods

2.1. Materials

PLGA [Poly(DL-lactide-co-glycolide)] (Resomer® RG 502H; lactide:glycolide = 50 : 50) was obtained from Boehringer Ingelheim (Germany). PLA [Poly(DL-lactic acid)](Purasorb® PDL 02A) was obtained from Purac Biomaterials (Netherland). PCL [Poly-E-caprolactone] (70 kDa), rifampicin, mesalazine, L-cystine, glycofurol (syn. tetraglycol), sodium hydroxide and hydrochloric acid were purchased from Sigma-Aldrich (Steinheim, Germany). Celecoxib and clotrimazole were purchased from TCI (Eschborn, Germany). Paracetamol was supplied by Micron Technologies (PA, USA). Erythromycin, indomethacin, theophylline, allopurinol, ascorbic acid, acetylsalicylic acid and histidine were purchased from Fagron (Barsbüttel, Germany). Lopinavir, ritonavir and acyclovir were obtained from Swapnroop Drugs & Pharmaceuticals (Aurangabad, India). Itraconazole was purchased from Alfa Aesar (Karlsruhe, Germany). Sulfathiazole, n-octanol and acetone were obtained from Fisher Scientific (Loughborough, UK). Sodium dodecyl sulfate was purchased from GE Healthcare Life Sciences (Germany). Ibuprofen, chloramphenicol, trometamol and polysorbate 80 were obtained from Caesar & Loretz GmbH (Hilden, Germany). Propylene carbonate was obtained from Merck (Darmstadt, Germany). Propylene glycol (high purity grade) was obtained from Amresco (Ohio, USA). Sodium sulfate and sodium dihydrogen phosphate monohydrate were purchased from Roth (Karlsruhe, Germany). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Determination of partial solubility parameters

Partial solubility parameters were determined by the group contribution method of Hoftyzer and Van Krevelen (Krevelen and Nijenhuis, 2009), using substance specific molar volumes (V) which are equal to the division between molar mass and the true density of the substance. Based on the van der Waals dispersion force (F_{di}), dipole–dipole interaction (E_{pi}), hydrogen bonding energies (E_{hi}) and the molar volume, the following partial solubility parameters were calculated:

$$\delta_d = \frac{\Sigma Fdi}{V} \quad (1)$$

$$\delta_p = \frac{\sqrt{\Sigma F_{pi}^2}}{V} \quad (2)$$

$$\delta_h = \sqrt{\frac{\Sigma E_{hi}}{V}} \quad (3)$$

where δ_d corresponds to the so-called London interaction resulting from the existence of induced dipoles as two molecules approach one another (disperse part), δ_p corresponds to Keesom forces occurring when two permanent dipoles are present (polar part) and δ_h represents hydrogen bonding forces (hydrogen part). Afterwards, the total solubility parameter was obtained by Hansen's method (Hansen, 2007) using the calculated partial solubility parameters using the equation [4]:

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{1/2} \quad (4)$$

Furthermore, the volume-dependant solubility parameter δ_v can be used to describe the miscibility between different components, and can be used for the construction of 2D (Bagley et al., 1971) and 3D graphical representations, predicting the solubility of drug substances in solvents.

$$\delta_v = (\delta_d^2 + \delta_p^2)^{1/2} \quad (5)$$

Finally, different studies have shown that the differences between the total solubility parameters of drug substances and excipients can be used as a tool for drug-carrier solubility/miscibility prediction (Greenhalgh et al., 1999; Li et al., 1995).

$$\Delta\delta_{t\ API-Excipient} = |\delta_{t\ API} - -\delta_{t\ Excipient}| \quad (6)$$

2.2.2. Solubility investigation of polymer–solvent systems

Polymer solubility can be evaluated from a thermodynamic background using the Flory-Huggins solvent-polymer interaction parameter (χ) (Flory, 1945; Huggins, 1942). For this purpose, the Hildebrand solubility parameters for the solvent ($\delta_{solvent}$) and for the polymer ($\delta_{polymer}$) are used for the following equation [7] (Adamska et al., 2016; Lindvig et al., 2002):

$$\chi = \frac{V_{solvent}}{RT} * (\delta_{solvent} - \delta_{polymer})^2 \quad (7)$$

where χ describes the solvent-polymer interaction parameter, $\delta_{solvent}$ corresponds to the Hildebrand solubility parameter for the solvent ($MPa^{1/2}$), $\delta_{polymer}$ corresponds to the Hildebrand solubility parameter for the polymer ($MPa^{1/2}$), $V_{solvent}$ is the molar volume of solvent (mL/mol), R is the gas constant (8.3144621 J/mol K) and T is the temperature of the entire system (296.15 K). Here, solubilities of PLGA, PLA and PCL in PC, propylene glycol, glycofurol, acetone and water were tested and the Flory-Huggins solvent-polymer interaction parameter was calculated. Generally, χ values which are lesser than 1.000 describe mixtures of a completely dissolved polymer in a solvent, while polymer insolubility is observed in cases where χ is greater than 1.000.

2.2.3. Drug solubility in propylene carbonate

The solubility of 21 different drug substances (listed in Table S1) was evaluated according to the following procedure. Approx. 20 mg of pure drug substance was weighted in capped glass vials. Aliquots of PC (50 μL) were gradually added while the mixture was stirred at 200 rpm until a transparent solution was obtained and left overnight. Afterwards, each sample was additionally microscopically observed for the presence of potentially not dissolved drug crystals. All experiments

were performed at 23 °C.

2.2.4. Determination of logP

The determination of logP values for all drug substances used for microencapsulation (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) was done according to the OECD guideline 107, using the shake flask method. Briefly, water and n-octanol were mutually saturated by mixing equal amounts of deionized water and n-octanol in a separation funnel. Afterwards the two phases were split and separately stored. The water phase was used for buffer preparation of appropriate pH values for each tested drug substance. 20–30 mg of the tested substance was weighted in a Falcon® tube and dissolved in 5 mL of n-octanol. An equal volume of buffered water phase was added to the n-octanol phase; the sample was hermetically sealed and placed in a shaking water bath (150 rpm) for 48 h at 37.0 °C ± 0.5 °C. Finally, the two phases were separated, centrifuged at 1000 rpm for 30 min and analyzed using a UV–VIS spectrophotometer (Lambda 12, PerkinElmer UV–Vis spectrophotometer, MA, USA). The respective pH values and wavelenghts for the analysis are shown in Table S2.

2.2.5. Density measurements

In order to evaluate the true density of the employed polymer powders (PLGA, PLA and PCL) and drug substances (listed in Table S1), an AccuPyc 1330 helium pycnometer (Micromeritics Instrument Corporation, USA) was used. For this, 1–2 g of sample was placed in a standard sample holder which was hermetically sealed in the pycnometer and analyzed based on gas displacement. Each sample was running until five consecutive measurements gave a standard deviation lower than 0.01 g/mL at a constant temperature of 23 °C.

2.2.6. Microencapsulation procedure

All microparticles were prepared using an emulsification/solvent extraction method for the excipient combination PLGA/PC, described previously in detail (Grizić and Lamprecht, 2018). Microparticles loaded with lipophilic drug substances were prepared by an o/w emulsification method. At first, 100 mg of PLGA was dissolved in propylene carbonate, giving a 1% internal phase solution. To this solution, 8 BCS class II drug substances (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) were added and stirred for 5 min at 500 rpm at room temperature. The final concentration of drug substances in PC/PLGA was always kept at 20% (related to the final mass of polymer and drug substance). To this internal phase solution, 20 mL of 0.1% polysorbate 80 (external phase) was carefully added, layering it on top of the organic phase solution (a constant o/w ratio of 30/70 was applied for every formulation). These two solutions were stirred for 2 min at 400 rpm using a propeller stirrer (IKA RW 20 digital, 4-bladed stirrer, shaft size 8 mm × 200 mm, stirrer diameter 35 mm), leading to the formation of an o/w emulsion. This emulsion was instantly added to 500 mL of distilled water while stirring at 250 rpm. This was followed by a drop-wise addition of sodium hydroxide solution in order to enhance the solvent extraction, which was described previously in detail (Grizić and Lamprecht, 2018). The obtained microparticles were collected by centrifugation and washed with distilled water. Finally, the microparticles were dried in a desiccator overnight.

2.2.7. Scanning electron microscopy

The morphology of all samples was analyzed using a scanning electron microscope (Hitachi S-2460 N, Tokyo, Japan) at 15 kV. All samples were placed on cover slips mounted on aluminium supports using double-adhesive tape. Prior to imaging, microparticles were gold-coated using a sputter-coater (Polaron SC7640 Sputter Coater, Quorum Technologies Ltd., Newhaven, UK) and finally placed in the scanning electron microscope for observation.

2.2.8. Size and size distribution

The size and size distribution of the microparticles was measured by laser diffraction (Helos, Sympatec®, Clausthal, Zellerfeld, Germany) by re-dispersing all samples in a 0.1% aqueous polysorbate 80 solution while maintaining the optical concentration at 3%. The particle sizes were described as volume distribution of microparticles. All samples were analyzed in triplicates.

2.2.9. Drug content

The drug content expressed as encapsulation efficiency was analyzed on a UV–VIS spectrophotometer (Lambda 12, PerkinElmer UV–VIS spectrophotometer, MA, USA) after a complete dissolution of microparticles for 30 min using propylene carbonate. Celecoxib, clotrimazole, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir were directly measured at their respective λ_{max}, without the use of additional reagents. A modified quantification method based on dehydration was applied for erythromycin (Danielson et al., 1993). In all cases, drug-free microparticles were subjected to the same sample preparation treatments in order to be employed as blanks. Analytical properties such as λ_{max} values and linearity ranges are listed in Table S2.

2.2.10. Quantification of residual propylene carbonate

The residual propylene carbonate amounts were quantified using a method described earlier (Grizić et al., 2016). Briefly, 10 mg of microparticles of every sample was disintegrated using 1 mL of glycofurol, further treated using the three-step HOC method and analyzed at 405 nm. The analytical range was from 25 to 250 µg/mL (R^2 = 0.996). All results were analyzed in triplicates.

2.2.11. In vitro release studies

A weighted amount of dry microparticles was placed in sealed Erlenmeyer flasks containing phosphate buffer pH 7.4 + 0.5% SDS, held constantly at 37.0 °C ± 0.5 °C and shaken at 80 rpm using a shaking water bath (Thermolab GFL 1083, Burgwedel, Germany) over a period of one month. All aliquots were withdrawn at specific time intervals (with buffer replacement), centrifuged at 10 000 rpm for 5 min, filtrated using 0.45 µm polypropylene membrane filters and analyzed using the same quantification procedure as for the drug content. In addition, release rates for each encapsulated drug were calculated from the linear part of the drug release curves starting after the burst release and ending with the reach of the release plateau.

3. Results

The solubility investigation of PLGA, PLA and PCL in propylene carbonate (PC) revealed that only PLGA and PLA were highly soluble (PLGA: 890 mg/mL, PLA: 800 mg/mL), while PCL was insoluble in PC. A similar trend was also observed for glycofurol, while propylene glycol and water were not able to dissolve the polymers. However, all polymers were soluble in acetone. In order to evaluate this phenomenon from a thermodynamic aspect, the Flory-Huggins theory was applied. For comparison purposes, four additional solvents were included (propylene glycol, glycofurol, acetone and water), resulting in specific polymer–solvent interaction parameters (χ) for each mixture (Table 1). In case of PLGA and PLA, the lower solvent-polymer interaction parameter (χ) coincidences with the favourable solubility of these polymers, while the high solvent-polymer interaction parameter underlines the empirically observed insolubility of PCL in PC.

Partial solubility parameters (δ_d, δ_p and δ_h), total solubility parameters (δ_t) and the volume-dependant solubility parameters (δ_v) of 5 solvents, 3 polymers and 21 drug substance were calculated (Table S1). In addition, the densities which were needed for the calculation of the specific molar volumes of each substance as well as the solubility/miscibility of the relevant solvents/polymers/drug substances in PC are also listed in Table S1.

Table 1
Polymer-solvent interaction parameters of PLGA, PLA and PCL in propylene carbonate, propylene glycol, glycofurol, acetone and water (at 23 °C).

Polymer Solvent	PLGA Interaction parameter value	Soluble	PLA Interaction parameter value	Soluble	PCL Interaction parameter value	Soluble
Propylene carbonate	0.007	Yes	0.180	Yes	1.928	No
Propylene glycol	1.507	No	2.378	No	5.951	No
Glycofurol	0.0001	Yes	0.189	Yes	2.713	No
Acetone	0.308	Yes	0.057	Yes	0.436	Yes
Water	4.500	No	5.185	No	7.403	No

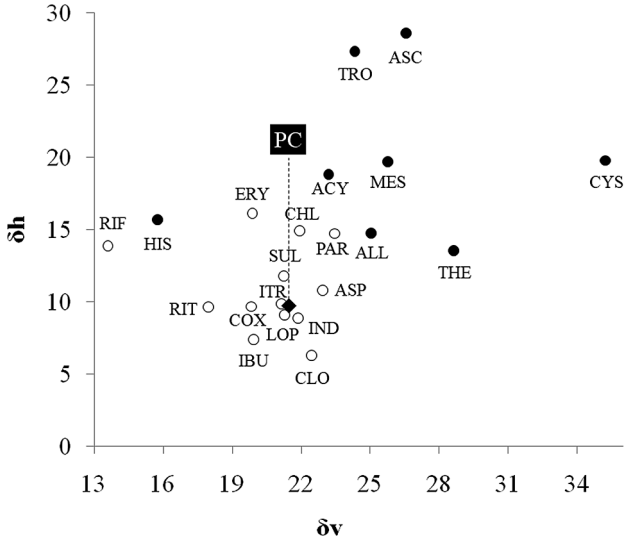

Fig. 1. Drug solubility clustering around PC (closed square) using a Bagley diagram; Soluble substances are depicted as open circles: Acetylsalicylic acid (ASP), Celecoxib (COX), Chloramphenicol (CHL), Clotrimazole (CLO), Erythromicin (ERY), Ibuprofen (IBU), Indomethacin (IND), Itraconazole (ITR), Lopinavir (LOP), Paracetamol (PAR), Rifampicin (RIF), Ritonavir (RIT) and Sulfathiazole (SUL); Insoluble substances are shown as closed circles: Acyclovir (ACY), Allopurinol (ALL), Ascorbic acid (ASC), Histidin (HIS), L-Cystine (CYS), Mesalazine (MES), Theophylline (THE) and Trometamol (TRO). For visualisation purposes, a solubility threshold of 100 μg/mL was chosen to be regarded as soluble.

A 2D Bagley diagram showing partial solubility parameter δ_h versus volume-dependant solubility parameter δ_v leads to a clustering of soluble drug substances around PC (shown in Fig. 1). Drug substances having lower δ_h and δ_v values are most likely to be very well soluble in PC.

Based on the partitioning (logP) and solubility data of all drug substances in PC, eight BCS class II drug substances (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) were microencapsulated. The specific physico-chemical properties, along with the experimentally determined logP values as well as the calculated difference in total solubility parameter between drug substances and PLGA ($\Delta\delta_{t\ API\text{-}PLGA}$) are shown in Table 2.

The particle size of the microparticles varied between 45 μm and 100 μm (Table 3) while the morphology depended solely on the type of the encapsulated drug substance. This dependence can clearly be seen in Fig. 2, which depicts micrographs of freshly prepared and dried microparticle samples as well as the respective Tg values. A clear influence of the microparticle Tg on the specific morphology could be observed. On the other hand, $\Delta\delta_{t\ API\text{-}PLGA}$ did not have any significant influence on the morphology characteristics (values shown in Table 2).

The encapsulation efficiencies were significantly different among all microparticles loaded with different drug substances (lowest for ritonavir-loaded microparticles: 33.9 ± 1.4% and highest for itraconazole-loaded microparticles: 103.7 ± 5.9%). A correlation between the encapsulation efficiency and $\Delta\delta_{t\ API\text{-}PLGA}$ was established (Fig. 3). It

Table 2
Physico-chemical properties of microencapsulated drug substances.

Samples	Mw [g/mol]	pKa	Tg [°C]	Tm [°C]	logP	$\Delta\delta_{t\ API\text{-}PLGA}$ [MPa$^{1/2}$]
Celecoxib	381.37	10.60	50.84[c]	161.80[c]	3.73	1.01
Clotrimazole	344.84	6.62	29.85 [d]	144.85 [d]	5.24	0.23
Erythromicin	733.93	12.45	112.84 [e]	135.8 [e]	2.69	2.46
Ibuprofen	206.29	4.85	−45.15 [d]	76.85 [d]	3.31	1.83
Indomethacin	357.79	3.79	44.85[f]	160.85[f]	4.39	0.49
Itraconazol	705.64	3.91	57.85[f]	167.85[f]	5.67	0.24
Lopinavir	628.81	13.39	77.6[g]	≈ 96[g]	4.68	0.04
Ritonavir	720.95	13.68	48.7[g]	122.2[g]	3.18	2.72

[c] From Ref. (Chawla et al., 2003)
[d] From Ref. (Benmore and Weber, 2011)
[e] From Ref. (Nanakwani et al., 2014)
[f] From Ref. (Alhalaweh et al., 2015).
[g] From Ref. (Wyttenbach and Kuentz, 2017).

Table 3
Microparticle properties regarding size, span value, encapsulation efficiency and yield.

Drug-loaded microparticles	Size [μm]	Span	Encapsulation efficiency [%]	Yield [%]
Celecoxib	67.1 ± 0.5	1.55 ± 0.04	63.8 ± 5.5	87.4 ± 4.7
Clotrimazole	63.7 ± 0.7	1.27 ± 0.03	97.3 ± 3.9	89.7 ± 4.8
Erythromicin	59.5 ± 1.3	1.16 ± 0.02	38.1 ± 1.2	93.0 ± 6.3
Ibuprofen	45.1 ± 0.7	1.12 ± 0.02	57.3 ± 3.2	91.8 ± 9.8
Indomethacin	60.2 ± 0.7	1.34 ± 0.01	73.1 ± 1.3	88.6 ± 4.4
Itraconazole	62.6 ± 0.8	1.59 ± 0.02	103.7 ± 5.9	89.0 ± 11.6
Lopinavir	82.6 ± 1.3	2.28 ± 0.04	95.4 ± 0.6	98.1 ± 11.2
Ritonavir	98.9 ± 5.4	2.17 ± 0.11	33.9 ± 1.4	89.3 ± 12.4

could be observed that the encapsulation efficiency is inversely proportional to the difference in total solubility parameter between the drug substances and PLGA ($\Delta\delta_{t\ API\text{-}PLGA}$). This indicates a high impact of the similarity between the total solubility parameter of PLGA and the drug substance on the drug entrapment during microencapsulation.

Based on the qualitative finding of residual PC in the microparticle matrix (data not shown), the residual solvent was quantified and depicted in Fig. 4. The quantities of the residual solvent amount in the microparticle matrix had values between 2.5 ± 0.2% and 4.7 ± 0.2%. No correlation between the residual PC content and the microparticle size could be observed. Also, the residual PC content was not correlating with the difference in total solubility parameter between the drug substances and PC ($\Delta\delta_{t\ API\text{-}PC}$) or with the difference in total solubility parameter between the drug substances and PLGA ($\Delta\delta_{t\ API\text{-}PLGA}$).

The in-vitro release study revealed differences between each drug-loaded microparticle sample (Fig. 5). A potential correlation between release rate and microparticle size was evaluated. Unfortunately, no clear correlation was found (R = 0.02). This is also evident from Table 3, showing similar particle sizes in 5 out of 8 different drug-loaded microparticles, but very different release profiles amongst all samples (Fig. 5).

Different samples showed release completion at different time

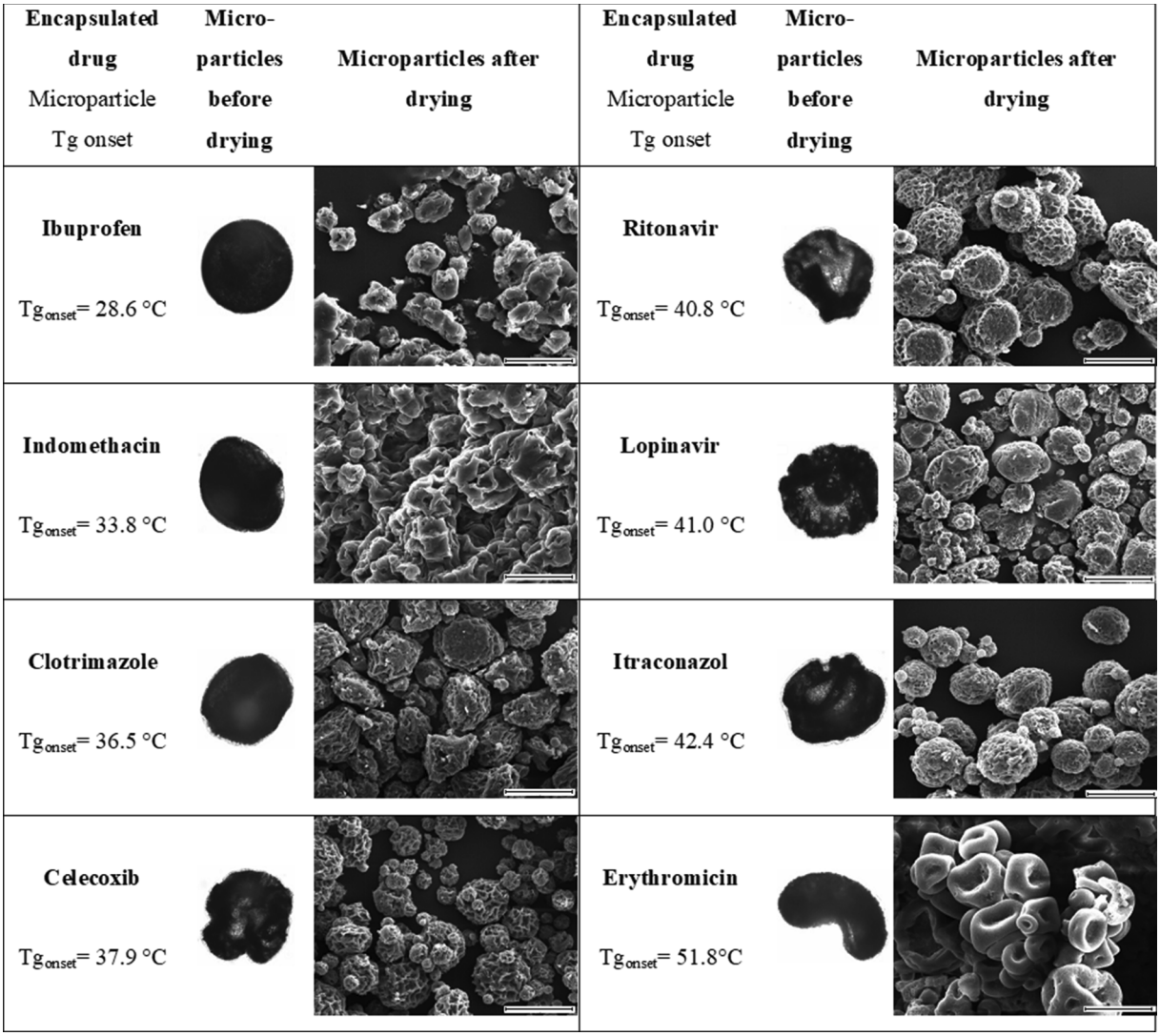

Fig. 2. Influence of the glass transition temperature of drug-loaded microparticles (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) on the specific microparticle morphology. Micrographs show the specific microparticle before drying (freshly after preparation) using an optical microscope and after drying using SEM. All SEM images are taken at a magnification of 500x. The scale bar represents 60 μm.

points. Celecoxib showed the fastest release completion after 5 days, while itraconazole showed a complete release after 25 days. Even though we observe a trend when correlating the difference in partial solubility parameter and time for complete release (lower $\Delta\delta_{t\ API\text{-}PLGA}$ values foster a longer time for complete release), the correlation of the trend for this behaviour is not high enough for the claim of this trend ($R = 0.33$). Additionally, it could be observed that all samples showed an initial burst release within the first two hours. An increased burst release was observed for samples with higher $\Delta\delta_{t\ API\text{-}PLGA}$ values (the highest burst amount being around 36% for erythromycin) while decreased $\Delta\delta_{t\ API\text{-}PLGA}$ values fostered a low burst release (the lowest being around 8% for itraconazole). However, no indicative correlation could be shown between the $\Delta\delta_{t\ API\text{-}PLGA}$ values and the burst release amongst all eight microparticle samples. Oppositely, a clear trend could be observed between the $\Delta\delta_{t\ API\text{-}PLGA}$ values and the release rates of all microparticle samples. In Fig. 6, it can be observed that higher $\Delta\delta_{t\ API\text{-}PLGA}$ values fostered higher release rates (e.g. Ritonavir), while lower release rates were observed with lower $\Delta\delta_{t\ API\text{-}PLGA}$ values (e.g. Lopinavir).

4. Discussion

Data on microencapsulation are most often comprising of empirical parameters such as morphology, encapsulation efficiency, release rate etc. However, the intermolecular interaction phenomena which lead to the empirical observation of these microparticle properties are often related to intrinsic solubility affinities between the polymer, drug substance and polymer which play, at best, a secondary role in the respective scientific reports. Nevertheless, the knowledge of the mechanistic background of such properties is of high value for a deeper understanding of the observed formulation properties (Choi et al., 2002) and maybe a helpful tool in predicting the properties.

As PLGA, PLA and PCL are very frequently employed as biodegradable polymers for microparticle formulations, the evaluation of solubility differences amongst all these polymers was of a great interest. The solubility differences between PLGA, PLA and PCL evaluated by the Flory-Huggins interaction parameter were in agreement with earlier observations of the degree of affinity between solvent and polymer in binary systems (Safronov and Zubarev, 2001; Wu et al., 2012). Even though all three polymers possess hydrophobic properties (positive χ values point to a lack of hydrogen bonding between the solvent and the solute (Kluge et al., 2009)), which usually ensures a good solubility in lipophilic organic solvents, favourable thermodynamic interactions between the PLGA and PLA polymer chains and the PC molecules exist, finally leading to a good solubility of these polymers in the solvent but

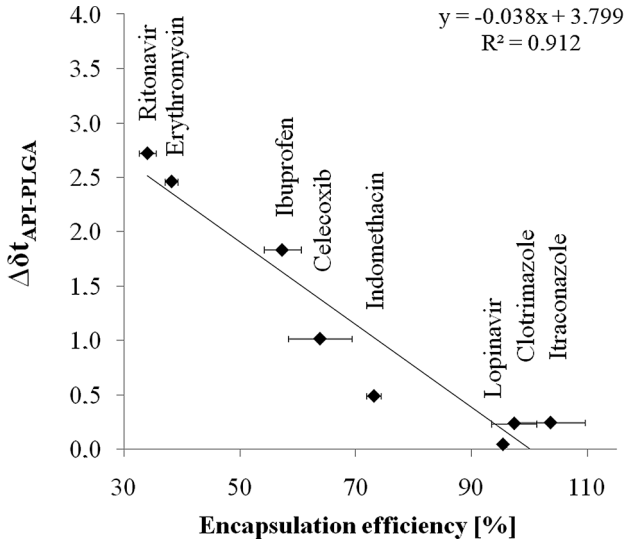

Fig. 3. Correlation between the encapsulation efficiency of drug-loaded microparticles (celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir) and $\Delta\delta_{tAPI\text{-}PLGA}$ (mean ± SD, n = 3).

not for PCL. In this way, the Flory-Huggins interaction parameter proved to be a descriptor which can contribute complementary information in polymer screening for future microparticle developments.

PC is an aprotic organic solvent, which explains the fact that δ_h is a strong influencing parameter for the solubility limitation. It was shown previously that PC is weak hydrogen-bond acidic and mainly hydrogen-bond basic (Karunasekara and Poole, 2011). Especially in cases where the solvent lacks any hydrogen donating groups, the solubility can be hindered (van Eupen et al., 2009). However, the high polarity of PC (Pawlak et al., 1982) enables a good solubility of drug substances possessing a wide range of δ_d and δ_p values. Accordingly, the solubility assessment of various drugs here, in line with the solubility descriptors, revealed that drug substances having hydrophilic properties could not be dissolved.

When subsequently dissolving PLGA and the eight model drug substances together in PC, in view of their encapsulation, the differences in total solubility parameters between each of the eight drugs and PLGA ($\Delta\delta_{t\ API\text{-}PLGA}$) were lower than 7.0 $MPa^{1/2}$, which was according to Greenhalgh's approach (Greenhalgh et al., 1999) a solubility/miscibility defining limit (lower values indicate higher solubility/miscibility).

The morphology of drug-loaded microparticles varied according to the type of the encapsulated drug substance. Interestingly, the morphology was highly dependent on the glass transition temperature (Tg) while the difference in total solubility parameter between the drug substance and the polymer did not impact the structure. It is well known that homogenously dispersed substances in a polymer matrix contribute to the overall glass transition temperature of the microparticles (Gasmi et al., 2015), which is the major phenomenon contributing to the specific morphology in this study. According to previous work done with PLGA microparticles, a significant influence of the final Tg on particle morphology exists (Vay et al., 2012). It is stated that the time span at which the preparation process takes place above the Tg of the sample, influences the resulting final microparticle morphology as the polymer chains are flexible at that time. This is influenced on one hand by the speed of organic solvent diffusion and on the other hand by the speed of microparticle hardening (which is influenced by the final microparticle Tg). As the droplet-to-particle process progresses, the overall microparticle Tg value increases until the solidification is completed and the final microparticle Tg value is reached. As all microparticle samples in this study are prepared under identical conditions, PC diffusion is progressing at the same rate during preparation. However, samples having higher Tg values also have a shorter time at which they reside above the Tg values during solidification, which relates to a shorter time during which polymer chains are flexible. This in turn relates to a faster solidification of the outer layer, making the microparticle rigid. As the Tg values increased, more spherical microparticles were obtained after drying compared to low Tg samples as these did not collapse during drying. However, too high Tg values lead to structures as in case of erythromycin, which had the highest Tg value of all encapsulated substances. Here, the microparticles appeared spherical but collapsed; not during drying, but during microparticle preparation. In this case, the outer droplet surface hardens so fast (due to the very high Tg value) that the rigid outer layer hinders the fluidity of the solidifying polymer solution and a consecutive collapse of the inner structure in fresh state is eminent. Oppositely, on the example of ibuprofen-loaded microparticles which have the lowest Tg value, the particle hardening is slow. As the final Tg value is low, the sample resides for a longer time above the Tg value during solidification, which relates to a longer time during which polymer chains are flexible including also the outer polymer layer. This leads to a homogenously formed spherical particle in fresh state, which drastically changes during drying as the inner structure collapses during

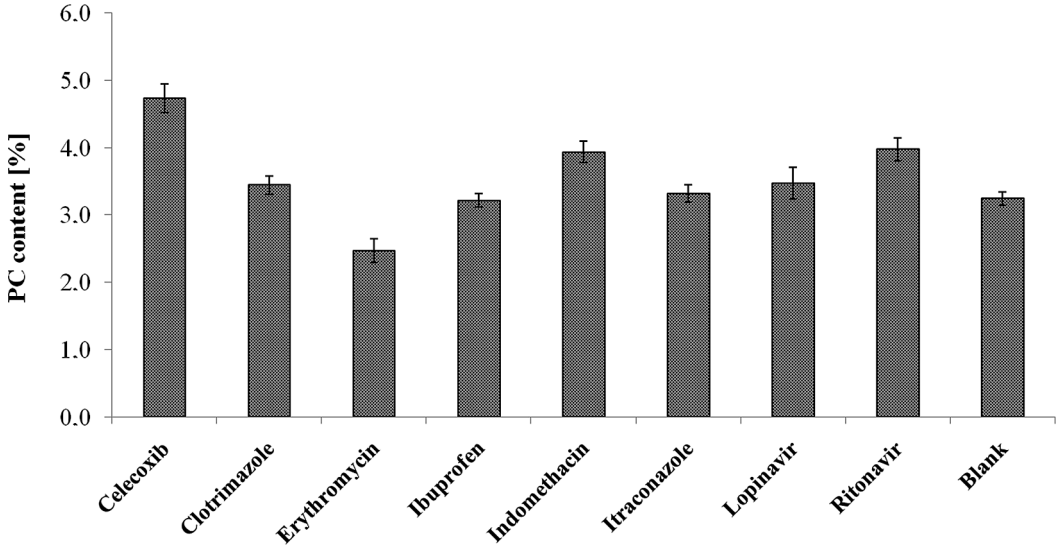

Fig. 4. Residual PC amounts of all drug-loaded microparticles (mean ± SD, n = 3).

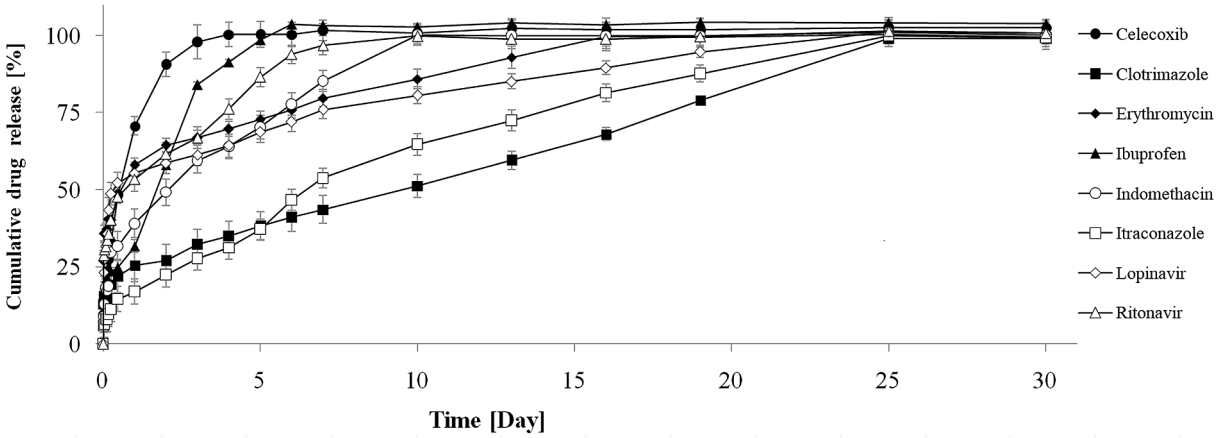

Fig. 5. Release profiles of microparticle samples loaded with celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir (mean ± SD, n = 3).

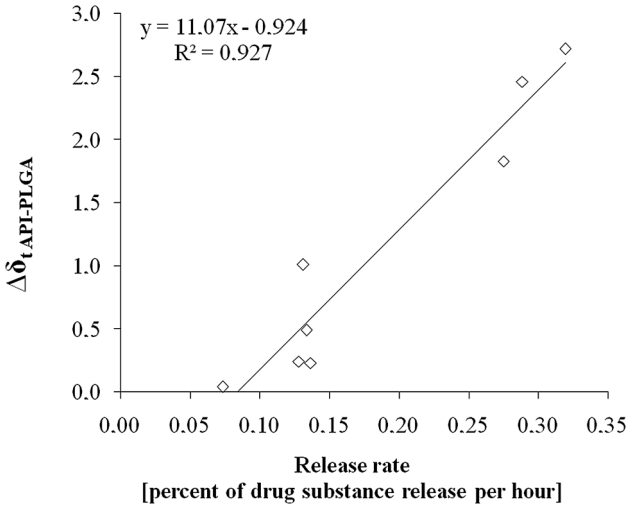

Fig. 6. Relationship between $\Delta\delta_{t\ API\text{-}PLGA}$ and the release rate of microparticle samples loaded with celecoxib, clotrimazole, erythromycin, ibuprofen, indomethacin, itraconazole, lopinavir and ritonavir.

drying.

In addition to morphological differences, the microparticle size also differed amongst drug-loaded microparticles. It is interesting to note that for ritonavir which has the biggest particles size, the lowest encapsulation efficiency is observed. Compared to other drug substances, ritonavir has a lower lipophilicity (logP = 3.18), which is probably leading to an enhanced loss towards the external aqueous phase during the microparticle solidification, regardless of size.

Generally, the observed correlation between the encapsulation efficiency and $\Delta\delta_{t\ API\text{-}PLGA}$ revealed two things. Firstly, higher similarity between δ_t of PLGA and the drug substance fosters an increased encapsulation. These findings can be connected with the previous statement that the miscibility of polymer and drug is promoted as the values for their solubility parameters approach each other (Liu et al., 2004). Also, miscibility screenings between lipophilic drug substances like itraconazole and a broad variety of polymers for the development of solid dispersions by means of differences in total solubility parameters were successfully implemented previously (Piccinni et al., 2016). Secondly, higher drug substance lipophilicity influences the encapsulation positively. Similar insights were given previously for PLGA microparticles when glycofurol was used as the organic solvent (Allhenn and Lamprecht, 2011). In line with these earlier results, the lowest encapsulation efficiency in our study is observed for ritonavir-loaded microparticles, which had the highest differences in total solubility parameter while itraconazole-loaded microparticles had the highest encapsulation efficiency and the lowest differences in total solubility parameter. In addition, even though ritonavir and lopinavir could be considered as being similar in view of their physicochemical properties, the large differences in total solubility parameter have seemingly a strong influence on the encapsulation efficiency. We showed that this partial solubility parameter-based approach can be successfully implemented for the prediction of the microparticle encapsulation efficiency. In this way, predictive calculative screenings could be performed for potential drug candidates, which could be encapsulated with high encapsulation efficiencies.

In drug release experiments, the release rate correlated strongly with $\Delta\delta_{t\ API/PLGA}$. Similarly, previous work on drug release from polymeric films revealed that the release is fastest when the total solubility parameter difference ($\Delta\delta_{t\ API\text{-}PLGA}$) was highest due to the maximum thermodynamic activity of the drug substance (Minghetti et al., 1999). However, such a clear relationship could not be observed for the burst release, probably due to the reason that it is influenced also by other factors simultaneously, such as drug substance distribution, microparticle morphology, drug substance solid state, particle size, porosity etc. (Hassan et al., 2009), which differs in this case among all drug-loaded microparticles.

In general, the deeper thermodynamic insight through partial solubility parameters for microparticle drug delivery systems based on PLGA and PC obtained in this work show the benefit in terms of predictability. The fact that strong correlations indicate a good predictability (for both, encapsulation efficiency as well as for the release rate) makes this approach attractive for a drug substance screening for microencapsulation using PLGA and PC.

5. Conclusion

Even though the interplay between all components of a microparticle system can be complex, a deeper insight by means of solubility descriptors can be beneficial for the development of such systems. The partial solubility parameter-based approach showed on the one hand the importance of the impaled hydrogen bonding part for drug solubilisation in PC and on the other hand a strong prediction possibility of specific microparticle properties such as the encapsulation efficiency as well as the release rate for microparticles prepared with PLGA as the matrix polymer and PC as the solvent.

CRediT authorship contribution statement

Daris Grizić: Conceptualization, Investigation, Formal analysis, Visualization, Writing - original draft. **Alf Lamprecht:** Supervision,

Writing - review & editing, Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.119601.

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