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Research Paper

Thermodynamic phase behaviour of indomethacin/PLGA formulations

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ABSTRACT

In the current study, the phase behaviour of indomethacin and poly(lactic-co-glycolic acid) (PLGA) formulations was investigated as a function of the molecular weight and the copolymer composition of PLGA. The formulations were prepared by ball milling, and the phase behaviour, comprised of the glass-transition temperature of the formulations and the solubility of indomethacin in PLGA, was measured using modulated differential scanning calorimetry (mDSC). The results determined that the solubility of indomethacin in PLGA at room temperature was very low and increased with a corresponding decrease in the molecular weight of PLGA. The copolymer composition of PLGA had a minor effect on the indomethacin solubility. The effect of PLGA's molecular weight and copolymer composition on the solubility of indomethacin could be modelled using the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) with a high degree of accuracy when compared with the experimental data. The glass-transition temperatures had a negative deviation from the weighted mean of the glass-transition temperatures of the pure substances, which could be described by the Kwei-equation.

1. Introduction

Poly(lactic-co-glycolic acids) (PLGAs) possess tremendous potential for use as carriers in sustained-release delivery systems for active pharmaceutical ingredients (APIs) due to their appropriate chemical and mechanical properties [1–3]. They are highly biocompatible and also biodegradable, which makes their removal from the body after medication not necessary [4]. PLGA is a copolymer consisting of D-lactic acid (DLA), L-lactic acid (LLA), and glycolic acid (GA) monomer units. Its biological and physicochemical properties are functions of molecular weight, copolymer composition and the chemical composition of the end groups [5,6]. The different PLGA copolymers can be synthesised using an economically attractive process, which also guarantees that the PLGA possesses a specific molecular weight and copolymer composition. This means that a PLGA with favourable properties can be designed for each delivery system [7].

One application of PLGA for a sustained API release is in the formulation of PLGA micro-particles [8] or nanoparticles [9], in which the API is incorporated during PLGA micro- or nanoparticle formation. The API release from these PLGA particles depends on the state (crystalline or amorphous) of the API in the formulation [10], which is determined by its thermodynamic solubility in PLGA. The latter determines how much (amorphous) API can be loaded into the PLGA without forming crystals, even after infinite time. This solubility is a function of the API, the polymer's molecular weight [11] and the copolymer composition [10,12].

Knowledge of the thermodynamic phase behaviour of API/PLGA systems, which includes the API solubility and the glass-transition temperature, is important in screening for an appropriate PLGA for a given API and specific application [13].

Due to the high viscosity of the system, experimental determination of API solubilities in different PLGAs at various temperatures, such as room temperature or body temperature, is a lengthy process (weeks and months). However, the API solubility can be estimated with the application of a thermodynamic model such as the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) [14], which has been used in previous works to predict the API's solubility as a function of the polymer molecular weight [11] and copolymer composition [12].

In this work, both the effects of the molecular weight and the composition of the copolymer on the phase behaviour were measured and modelled for formulations of the poorly-soluble API indomethacin (IND) and various PLGA copolymers (Resomer® RG 502 S, Resomer® RG 752 S, Resomer® RG 755 S, Resomer® RG 756 S and Resomer® RG 750 S) with different molecular weights and different copolymer compositions of LLA, DLA, and GA. Fig. 1 shows the chemical structure of IND as well as that of PLGA.

IND solubility, as well as the glass-transition temperature of the IND/PLGA formulations, was investigated experimentally using modulated differential scanning calorimetry (mDSC) [15]. The

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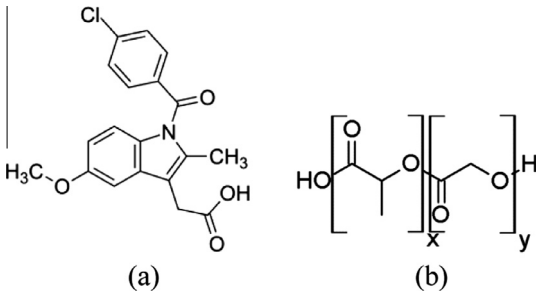

Fig. 1. Chemical structures of IND (a) and PLGA (b) with *x* as the number of units of lactic acid and *y* as the number of units of glycolic acid.

solubility of IND in PLGA was modelled with PC-SAFT as a function of the PLGA molecular weight and copolymer composition, whereas the glass-transition temperature of the IND/PLGA formulations was described using the Kwei-equation [16].

2. Materials and methods

2.1. Materials

IND (γ-polymorph) was purchased from Sigma Aldrich (Steinheim, Germany) with a purity of >99%. The different PLGA copolymers, Resomer® RG 502 S (molar ratio of 50:50 lactic acid (DLLA):glycolic acid (GA), molecular weight M_w of 13,000 g/mol), Resomer® RG 752 S (DLLA:GA ratio of 75:25 and M_w of 13,000 g/mol), Resomer® RG 755 S (DLLA:GA ratio of 75:25 and M_w of 68,000 g/mol), Resomer® RG 756 S (DLLA:GA ratio of 75:25 and M_w of 103,000 g/mol and Resomer® RG 750 S (DLLA:GA ratio of 75:25 and M_w of 128,000 g/mol) were obtained from Evonik (Essen, Germany). All of the copolymers were terminated by an ester-end group. The molecular weights of the different PLGA copolymers were estimated by the inherent viscosity values provided by the supplier. All chemicals were used without further purification.

2.2. Ball milling

Ball milling of the IND/PLGA formulations was performed with a Pulverisette 23 ball mill (Fritsch, Idar-Oberstein, Germany) at room temperature with a total powder weight of 100 mg. The IND/PLGA formulations contained different weight fractions of IND (w_{IND} of 0.2, 0.4, 0.6 and 0.9) and were ball milled for 1 h with a frequency of 15 s^{-1}. The sample holders (5 ml volume) as well as the ball (10 mm diameter) were made of stainless steel.

2.3. Thermal analysis

The temperatures at the end point of IND dissolution (T_{end}) in PLGA, as well as the glass-transition temperatures (T_g) of the formulations, were measured using mDSC (Q2000 from TA instruments, Eschborn, Germany). The apparatus was calibrated with indium and purged with nitrogen (flow rate of 40 ml/min) to maintain an inert atmosphere; 10–15 mg of the IND/PLGA formulation was transferred into an aluminium pan that was hermetically sealed.

The mDSC method that was performed consisted of three steps. The offset of the temperature at the end point of the IND dissolution in PLGA was measured in the first step by heating the sample from 293.15 K till 443.15 K with a heating rate of 2 K/min with a modulation period of 60 s and with an amplitude of 0.318 K. The IND concentration in the PLGA, known from the sample preparation, is the solubility at the determined dissolution-end point temperature T_{end}. In the second step, the samples were quench-cooled with a cooling rate of 10 K/min, a modulation period of 60 s, and an amplitude of 1.592 K. Finally, the sample was reheated again in a third step following the same parameters as the first step to determine the glass-transition temperature of the IND/PLGA formulation.

It was checked whether the heating rate had an influence on the measured dissolution-end point temperature as well as glass-transition temperature. The influence was small and no linear correlation between measured values and heating rate could be observed. Therefore, it was assumed that the heating rate of 2 K/min as used in this work was slow enough to determine the dissolution-end point temperature and glass-transition temperature values, which were used for modelling.

3. Modelling

3.1. IND solubility in PLGA

The solubility of IND in PLGA x^L_{IND} (mole fraction of indomethacin in PLGA) was determined by calculating the solid–liquid equilibrium of the formulation based on the assumption that the solid phase consists of pure IND, according to [17]

$$x^L_{IND} = \frac{1}{\gamma^L_{IND}} \exp\left[-\frac{\Delta h^{SL}_{IND}}{RT}\left(1-\frac{T}{T^{SL}_{IND}}\right) - \frac{\Delta c^{SL}_{p,IND}}{R}\left(ln\left(\frac{T^{SL}_{IND}}{T}\right) - \frac{T^{SL}_{IND}}{T} + 1\right)\right] \quad (1)$$

The melting temperature T^L_{IND}, the heat of fusion Δh^{SL}_{IND} and the difference in the heat capacities of the liquid and solid state of IND $\Delta c^{SL}_{p,IND}$ represent the melting properties of indomethacin. In this work, the γ-polymorph of IND was considered, which has a melting temperature of 433.25 K, a heat of fusion of 31.5 kJ/mol and a difference in heat capacities of 116.95 J/(K mol) [18].

The activity coefficient γ^L_{IND} required for the solubility calculations, was estimated with PC-SAFT [19].

3.2. PC-SAFT

In PC-SAFT, the residual Helmholtz energy a^{res} of a system is calculated according to [14,20]

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} \quad (2)$$

where a^{hc}, a^{disp} and a^{assoc} represent the different contributions resulting from the repulsion (a^{hc}), van der Waals attraction (a^{disp}, disp stands for dispersion) and hydrogen bonding (a^{assoc}, where assoc stands for association) between the molecules in a system. The detailed description of PC-SAFT and the different contributions can be found elsewhere [14,20] and will not be further explained here.

In calculating the different contributions to the Helmholtz energy a^{res}, each molecule is described by three pure-component parameters: a segment number m^{seg}_i, a segment diameter σ_i and a dispersion-energy parameter u_i/k_B with k_B being the Boltzmann constant. In the case of IND and other molecules that are able to form hydrogen bonds, two more pure-component parameters, namely the association-volume parameter κ^{AiBi} and association-energy parameter ε_{AiBi}/k_B, have to be applied. These parameters are required to determine the association contribution to the residual Helmholtz energy. Moreover, the number of association sites N^{assoc} has to be defined for the different molecules based on their chemical structures. In the case of IND, six association sites (three proton donors and three proton acceptors) were assumed (Fig. 1). The association volume κ^{AiBi} of these sites was set to a value of 0.02 [19]. The remaining pure-component parameters of IND were

Table 1
PC-SAFT pure-component parameters of IND, PDLA, PLLA and PGA.

	m^{seg}/M $\left(\frac{mol}{g}\right)$	σ (Å)	u/k_B (K)	ε^{AB}/k_B (K)	κ^{AB} (–)	N^{assoc} (–)	Ref.
IND	0.0399	3.54	262.791	886.4	0.02	3/3	[11]
PLLA	0.0455	2.92	230	–	–	–	[23]
PDLA	0.0369	3.12	240	–	–	–	[23]
PGA	0.0313	2.86	233.9	–	–	–	[24,25]

fitted to its solubility data in organic solvents that had been published in a previous work [11] and are listed in Table 1.

3.3. PLGA modelling using PC-SAFT

PLGA is a copolymer consisting of three different monomer units: LLA, DLA, and GA. Within PC-SAFT, it is possible to characterise copolymers as a chain consisting of segments that differ in segment diameter σ and energy parameters u/k$_B$, which represent the different monomer units in the copolymer backbone [21,22]. The polymer segments LLA, DLA and GA can be described by the pure-component parameters of the homopolymers poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA) and poly(glycolic acid) (PGA), respectively. PLLA, PDLA, and PGA were modelled as non-associating compounds and could therefore be described by only three pure-component parameters.

Pure-component parameters of PLLA and PDLA were taken from the literature [23] and PGA pure-component parameters were calculated according to a group-contribution method developed by Peters et al. [24,25]. All of the model parameters are summarised in Table 1.

In this work, different compositions of PLGA were investigated, having DLLA:GA molar ratios of 50:50 and 75:25. It was assumed that the PLGA consisted of the same amount of the DLA and LLA monomer units and that the monomer units were in alternating order. Fig. 2 schematically shows how PLGA is treated within the PC-SAFT modelling when the monomer units of LLA and DLA were presented by two segments and GA was present by one segment.

The segment number of PLGA m^{seg}_{PLGA} is calculated as the sum of the numbers of the three different segments representing the different monomer units LLA, DLA, and GA:

$$m^{seg}_{PLGA} = m^{seg}_{PLGA,LLA} + m^{seg}_{PLGA,DLA} + m^{seg}_{PLGA,GA} \quad (3)$$

The numbers of segments for each monomer type $m^{seg}_{PLGA,LLA}$, $m^{seg}_{PLGA,DLA}$ and $m^{seg}_{PLGA,GA}$ (which are usually not equal to the number of monomer units in PLGA because a monomer unit may consist of more than one segment) were calculated from the weight fractions of the monomer units LLA ($w_{PLGA,LLA}$), DLA ($w_{PLGA,DLA}$) and GA ($w_{PLGA,GA}$) in PLGA and the pure-component parameters (m^{seg}/M, segment number divided by the molecular weight) of the homopolymers PLLA, PDLA, and PGA:

$$m^{seg}_{PLGA,LLA} = (m^{seg}/M)_{LLA} \cdot w_{PLGA,LLA} \cdot M_{PLGA} \quad (4)$$

$$m^{seg}_{PLGA,DLA} = (m^{seg}/M)_{DLA} \cdot w_{PLGA,DLA} \cdot M_{PLGA} \quad (5)$$

$$m^{seg}_{PLGA,GA} = (m^{seg}/M)_{GA} \cdot w_{PLGA,GA} \cdot M_{PLGA} \quad (6)$$

The weight fractions of the different monomer units were obtained according to their molar fractions in the copolymer, which are given in Table 2.

The amount of the LLA, DLA, and GA segments in the PLGA chain can be described by the segment fractions $z_{PLGA,LLA}$, $z_{PLGA,DLA}$ and $z_{PLGA,GA}$ according to

$$z_{PLGA,LLA} = \frac{m^{seg}_{PLGA,LLA}}{m^{seg}_{PLGA}} \quad (7)$$

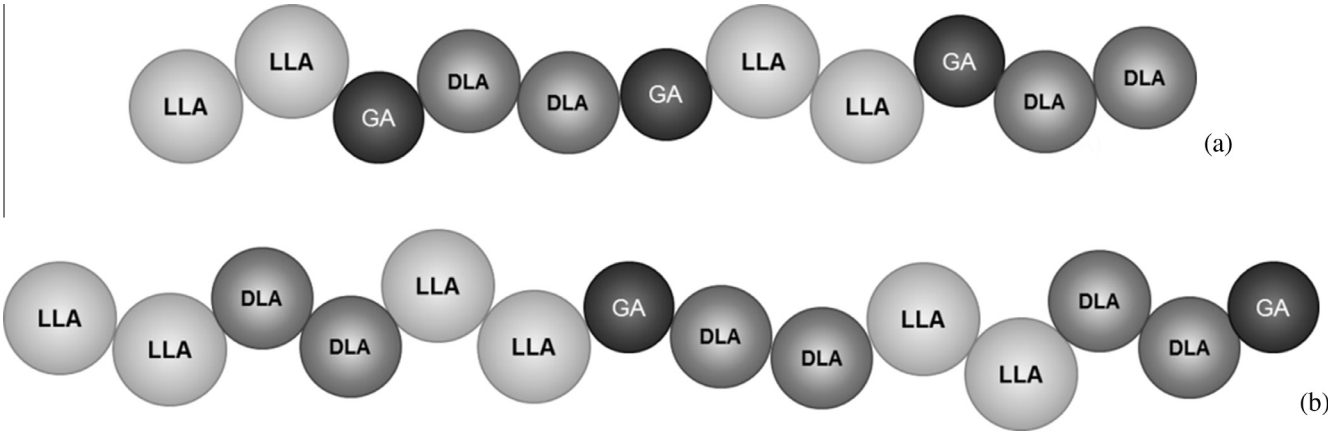

Fig. 2. PC-SAFT scheme of the PLGA copolymer consisting of three different types of segments LLA, DLA and GA with a DLLA:GA molar ratio of 50:50 (a) and 75:25 (b).

Table 2
Mole fractions of the LLA, DLA and GA monomer units in PLGA, molecular weights of the different PLGAs as well as the determined segment fractions for the PLGA modelling with PC-SAFT.

	mol% LLA (–)	mol% DLA (–)	mol% GA (–)	$M_{w,PLGA}$ (g/mol)	$z_{PLGA,LLA}$ (–)	$z_{PLGA,DLA}$ (–)	$z_{PLGA,GA}$ (–)
Resomer® RG 502 S	25	25	50	12,880[a]	0.342	0.278	0.380
Resomer® RG 752 S	37.5	37.5	25	13,073[a]	0.458	0.373	0.169
Resomer® RG 755 S	37.5	37.5	25	68,233[a]	0.458	0.373	0.169
Resomer® RG 756 S	37.5	37.5	25	103,313[a]	0.458	0.373	0.169
Resomer® RG 750 S	37.5	37.5	25	127,909[a]	0.458	0.373	0.169

[a] Calculated from the inherent viscosity determined by the supplier.

$$z_{PLGA,DLA} = \frac{m^{seg}_{PLGA,DLA}}{m^{seg}_{PLGA}} \quad (8)$$

$$z_{PLGA,GA} = \frac{m^{seg}_{PLGA,GA}}{m^{seg}_{PLGA}} \quad (9)$$

The segment fractions $z_{PLGA,LLA}$, $z_{PLGA,DLA}$ and $z_{PLGA,GA}$ that were determined for the polymers investigated in this work are listed in Table 2.

In addition to the amount of each monomer unit, the different arrangements of the segments within the PLGA chain are also taken into account within PC-SAFT by the fractions of different possible bonds between the two segments (bond fractions). The bond fraction $B_{LLA,LLA}$ describes the fraction of bonds within a copolymer which is formed between two LLA segments, whereas the bond fraction $B_{LLA,DLA}$ describes the fraction of bonds which are formed between an LLA segment and a DLA segment.

All bond fractions can be calculated according to the equations shown in Table 3 from the chemical structure of PLGA. In these equations, $\eta_{PLGA,LLA}$, $\eta_{PLGA,DLA}$ and $\eta_{PLGA,GA}$ represent the mole number of monomer units LLA, DLA and GA, respectively, in PLGA. The bond fractions $B_{LLA,LLA}$, $B_{LLA,DLA}$, $B_{LLA,GA}$, $B_{DLA,DLA}$, $B_{DLA,GA}$ and $B_{GA,GA}$ depend on the PLGA composition but not on the molecular weight of the PLGA. The bond fraction $B_{LLA,DLA}$ is different in PLGAs with DLLA:GA molar ratios of 50:50 and 75:25. According to the PLGA schematic in Fig. 2, it was assumed that no DLA or LLA segments were bonded to each other in PLGA with a DLLA:GA molar ratio of 50:50 (RG 502 S), whereas there is a number of DLA/LLA bonds in PLGA with a DLLA:GA molar ratio of 75:25. The bond fractions can be estimated from equations found in Table 3.

It becomes clear from Eqs. (3)–(9) and Table 3 that PLGA can be described within PC-SAFT solely based on the pure-component parameters of the homopolymers PLLA, PDLA, and PGA and the structural information of the PLGA composition without the need for fitting any additional parameters.

For the modelling of mixtures, such as IND/PLGA, so-called mixing rules are applied to determine the segment diameter σ_{ij} and dispersion-energy parameter u_{ij}/k_B in a mixture consisting of compounds i and j as follows:

$$\sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \quad (10)$$

$$u_{ij} = \sqrt{u_i \cdot u_j}(1 - k_{ij}) \quad (11)$$

The binary interaction parameter k_{ij} in Eq. (11) may be a function of temperature, according to Eq. (12), and corrects for the deviation of the mixture-energy parameter u_{ij} from the geometric mean of the two pure-component parameters.

$$k_{ij} = k_{ij,T} \cdot T + k_{ij,b} \quad (12)$$

In total, six different binary interaction parameters k_{ij} can be defined for the systems considered within this work: one between IND and each of the different monomer-unit segments DLA, LLA and GA and one between each pair of different polymer segments within PLGA. In this work, only the k_{ij}'s between IND and the different polymer segments were fitted to the experimental IND solubility data in PLGA, whereas the other k_{ij}'s were set to zero.

Table 3
Calculations of bond fractions for PLGA modelling within PC-SAFT.

	LLA	DLA	GA
LLA	$= \frac{z_{PLGA,LLA} m^{seg}_{PLGA} - n_{PLGA,LLA}}{m^{seg}_{PLGA} - 1}$	= 0 (only for RG 502 S) $= \frac{n_{PLGA,LLA} + n_{PLGA,DLA} - n_{PLGA,GA}}{m^{seg}_{PLGA} - 1}$	$= \frac{n_{PLGA,GA}}{m^{seg}_{PLGA} - 1}$
DLA	= 0 (only for RG 502 S) $= \frac{n_{PLGA,LLA} + n_{PLGA,DLA} - n_{PLGA,GA}}{m^{seg}_{PLGA} - 1}$	$= \frac{z_{PLGA,DLA} m^{seg}_{PLGA} - n_{PLGA,DLA}}{m^{seg}_{PLGA} - 1}$	$= \frac{n_{PLGA,GA} - 1}{m^{seg}_{PLGA} - 1}$
GA	$= \frac{n_{PLGA,GA}}{m^{seg}_{PLGA} - 1}$	$= \frac{n_{PLGA,GA} - 1}{m^{seg}_{PLGA} - 1}$	$= \frac{z_{PLGA,GA} m^{seg}_{PLGA} - n_{PLGA,GA}}{m^{seg}_{PLGA} - 1}$

3.4. Glass-transition temperature of the IND/PLGA formulations

The glass-transition temperatures T_g of the IND/PLGA formulations were calculated using the Kwei-equation (as shown in Eq. (13)), which is an extension of the commonly-used Gordon-Taylor Equation. For that purpose, the glass-transition temperatures as well as the densities of pure IND and pure PLGA were required to calculate the quantity K according to Eq. (14). q is an additional parameter that was fitted to the experimental glass-transition temperatures of the IND/PLGA formulations.

$$T_g = \frac{w_{IND} \cdot T_{g,IND} + K \cdot w_{PLGA} \cdot T_{g,PLGA}}{w_{IND} + K \cdot w_{PLGA}} + q \cdot w_{IND} \cdot w_{PLGA} \quad (13)$$

$$K \approx \frac{\rho_{IND} \cdot T_{g,IND}}{\rho_{PLGA} \cdot T_{g,PLGA}} \quad (14)$$

4. Results and discussion

4.1. Dissolution-end point temperature T_{end} and glass-transition temperature T_g

The dissolution-end point temperatures (T_{end}), as well as the glass-transition temperatures T_g for the IND formulations with Resomer® RG 502 S, Resomer® RG 752 S, Resomer® RG 755 S, Resomer® RG 756 S and Resomer® RG 750 S were measured using mDSC. The results are shown in Table 4.

As explained in the "Thermal analysis" section, the weight fraction of IND in the IND/PLGA formulation, which was known from the sample preparation, is the solubility of IND in PLGA at the measured T_{end}. As shown in Table 4 and later in Figs. 3 and 4, the dissolution-end point temperatures T_{end} increased with an increase of the IND weight fraction w_{IND} in all of the IND/PLGA formulations. This means that the solubility of IND in PLGA increased with a corresponding increase in temperature, as was expected.

At a given temperature, the solubility of IND in PLGA increased in the order of Resomer® RG 750 S ($M_w \approx 128{,}000$ g/mol) < Resomer® RG 756 S ($M_w \approx 133{,}000$ g/mol) < Resomer® RG 755 S ($M_w \approx 68{,}000$ g/mol) < Resomer® RG 502 S ($M_w \approx 13{,}000$ g/mol) < Resomer® RG 752 S ($M_w \approx 13{,}000$ g/mol).

Moreover, IND became more soluble when the molecular weight of PLGA decreased. This was also found for PLGA formulations with dexamethasone and flutamide that were investigated in the literature [10].

The DLLA/GA ratio in PLGA had only a minor effect on IND solubility compared to the effect of the molecular weight of PLGA; this was demonstrated by the fact that the experimental results for the IND solubility in the formulations with Resomer® RG 502 S (DLLA:GA ratio of 50:50) and Resomer® RG 752 S (DLLA:GA ratio of 75:25) were almost identical.

The glass-transition temperatures of the IND/PLGA formulations decreased with a corresponding decrease in the molecular weight of PLGA as well as with an increase in the amount of DLA and LLA monomer units in the copolymer (see also Figs 3 and 4).

The determined dissolution-end point temperatures (solubilities) and glass-transition temperatures were further modelled using PC-SAFT and the Kwei-equation, respectively. This will be discussed in subsequent sections.

Table 4
Dissolution-end point temperatures (T_{end}) and glass-transition temperatures (T_g) as function of the IND/PLGA composition (solubility).

PLGA	w_{IND} (g/g)							
	0.2		0.4		0.6		0.9	
	T_g (°C)	T_{end} (°C)	T_g (°C)	T_{end} (°C)	T_g (°C)	T_{end} (°C)	T_g (°C)	T_{end} (°C)
RG 502 S	30.35 ± 0.5	145.65 ± 2.8	29.05 ± 1.8	152.35 ± 1.3	25.85 ± 1.2	155.05 ± 1.2	33.85 ± 1.4	159.05 ± 0.1
RG 752 S	25.05 ± 1.0	143.25 ± 0.8	27.15 ± 1.4	151.25 ± 0.4	26.85 ± 0.6	154.35 ± 0.4	32.95 ± 0.3	159.35 ± 0.6
RG 755 S	39.75 ± 0.7	148.35 ± 5.1	35.95 ± 1.7	151.55 ± 0.8	33.05 ± 3.0	155.75 ± 1.0	35.65 ± 1.8	159.25 ± 0.2
RG 756 S	42.65 ± 0.1	151.75 ± 0.4	39.05 ± 0.7	157.55 ± 1.5	36.75 ± 2.4	158.55 ± 0.8	36.55 ± 2.8	159.75 ± 0.3
RG 750 S	40.65 ± 5.2	154.75 ± 0.3	40.05 ± 1.1	158.35 ± 0.2	35.35 ± 1.0	158.05 ± 0.01	–	–

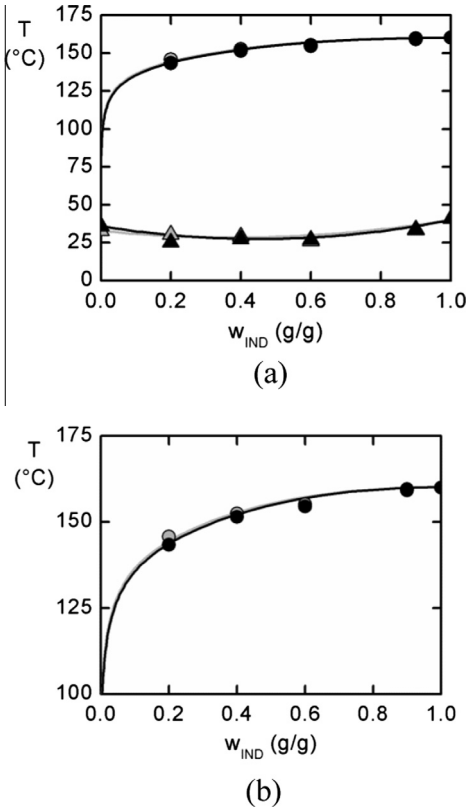

Fig. 3. IND solubility (circles) in PLGAs with different copolymer compositions as well as the glass-transition temperatures of these formulations (triangles). The light grey and black symbols represent the experimental data for the IND formulations with Resomer® RG 502 S and Resomer® RG 752 S, respectively. Lines represent the modelling results with PC-SAFT (IND solubility) and the Kwei-equation (glass-transition temperatures T_g). Fig. 3(b) shows the same results as 3(a) but is zoomed in on the solubility data.

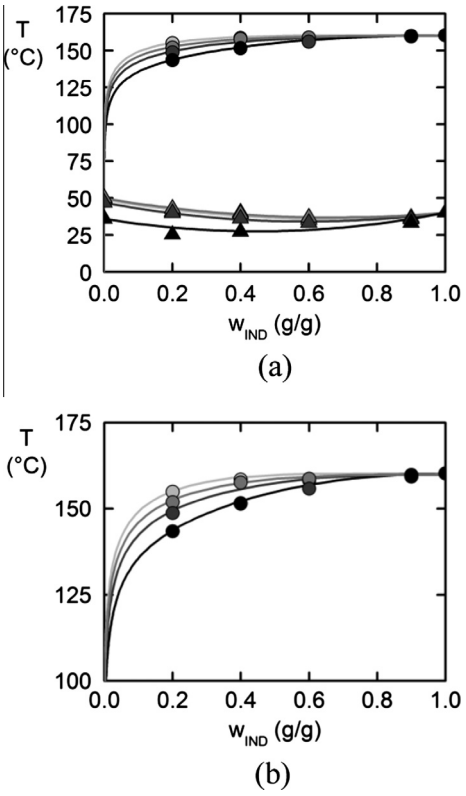

Fig. 4. IND solubility (circles) in PLGAs with different molecular weights as well as the glass-transition temperatures of these formulations (triangles). The symbols represent experimental data for IND formulations with Resomer® RG 752 S (black), Resomer® RG 755 S (dark grey), Resomer® RG 756 S (grey) and Resomer® RG 750 S (light grey). Lines represent the modelling results with PC-SAFT (IND solubility) and the Kwei-equation (glass-transition temperatures T_g). (b) shows the same results as (a) but is zoomed in on the solubility data.

4.2. Modelling IND solubility in PLGA

To reduce the number of adjustable binary interaction parameters k_{ij}'s from six to two, as mentioned in the Section "PLGA modelling using PC-SAFT", we made the following assumptions:

- k_{ij}'s between the different monomer units DLA, LLA and GA in PLGA were set to zero.
- The k_{ij} between IND and DLA equals that between IND and LLA.

Based on these assumptions, temperature-dependent k_{ij}'s between IND and the monomer units DLA, LLA, and GA were fitted to the experimental solubility data of IND in RG 502 S and RG 752 S listed in Table 4.

The influence of PLGA's molecular weight on the values of k_{ij} was taken into account using the solubility data of IND in RG 752 S and RG 755 S, which had the same copolymer composition (DLLA:GA molar ratio of 75:25) but different molecular weights (≈13,000 g/mol and ≈68,000 g/mol, respectively). The obtained k_{ij}'s between IND and the three different monomer units DLA, LLA and GA are listed in Table 5.

Using the parameters from Tables 1 and 5, the solubility of IND in RG 756 S ($M_w \approx 133{,}000$ g/mol) and RG 750 S ($M_w \approx 128{,}000$ g/mol) could be fully predicted. These results are included in Fig. 4.

4.3. Modelling the glass-transition temperatures of the IND/PLGA formulations

In modelling the glass-transition temperatures of the IND/PLGA formulations, the densities as well as the glass-transition temperatures T_g of pure IND and each PLGA composition were required for

Table 5
Binary interaction parameters k_{ij} between IND and the different monomer units LLA, DLA, and GA used in this work.

Monomer unit	$k_{ij,b}$ (–)	$k_{ij,T}$ (–)
DLA	$= 4.35 \cdot 10^{-08} \cdot M_{w,PLGA} + 6.93 \cdot 10^{-03}$	$-3.12 \cdot 10^{-04}$
LLA	$= 4.35 \cdot 10^{-08} \cdot M_{w,PLGA} + 6.93 \cdot 10^{-03}$	$-3.12 \cdot 10^{-04}$
GA	$= 4.35 \cdot 10^{-08} \cdot M_{w,PLGA} + 9.43 \cdot 10^{-03}$	$-3.12 \cdot 10^{-04}$

Table 6
Densities and glass-transition temperatures of the PLGAs and the fitted q-parameters of the IND/PLGA formulations used for the T_g-calculations using the Kwei-equation (Eq. (13)).

	ρ (g/cm^3)	T_g (°C)	q (K)
Resomer® RG 502 S	1.25[a]	32.74[b]	−30.06
Resomer® RG 752 S	1.25[a]	35.82[b]	−41.59
Resomer® RG 755 S	1.25[a]	46.74[b]	−36.58
Resomer® RG 756 S	1.25[a]	49.76[b]	−28.99
Resomer® RG 750 S	1.25[a]	49[b]	−32.05

[a] Information from the supplier.
[b] Measured in this work.

use in Eq. (13) and Eq. (14). The densities and glass-transition temperatures of the different PLGAs are listed in Table 6, and the density and the glass-transition temperature of pure IND were 1.32 g/cm^3 [26] and 317.6 K [12], respectively.

Because the glass-transition temperatures T_g of the IND/PLGA formulations had a negative deviation from the weighted mean of the glass-transition temperatures of the pure substances, as observed in Figs. 3 and 4, a negative parameter q was fitted to the experimental data. This means that there are only small attractive interactions between IND and PLGA [27], which also explains the low solubility of IND in all of the PLGAs. The obtained q parameters are also included in Table 6.

4.4. Comparison of the modelling results with the experimental data

The experimental results for the IND solubility in RG 502 S and RG 752 S as well as for the glass transition temperatures of the corresponding IND formulations are plotted in Fig. 3. This visualises the effect of the PLGA copolymer composition on the phase behaviour of the IND/PLGA formulations. Both copolymers had almost the same molecular weight but different copolymer compositions (Table 2). The modelling results with PC-SAFT (IND solubility in the PLGAs) and the Kwei-equation (T_g of the IND/PLGA formulations) are also inserted into Fig. 3.

As shown in Fig. 3(a) and (b), there was almost no influence of the PLGA composition on the phase behaviour of the IND/PLGA formulations. The phase behaviour of IND/Resomer® RG 502 S (DLLA:GA molar ratio of 50:50) and that of IND/Resomer® RG 752 S (DLLA:GA molar ratio of 75:25) showed only small differences at weight fractions of 0.2. The solubility of IND in both PLGAs at room temperature was predicted to be almost zero. This means that at this temperature, amorphous IND is not thermodynamically stable in IND/PLGA formulations and will recrystallise at all weight fractions of the IND.

The glass-transition temperatures of the formulations of IND with Resomer® RG 502 S and with Resomer® RG 752 S were at approximately room temperature for all of the weight fractions of IND, which means that recrystallisation of IND was not kinetically inhibited at this temperature. Using PC-SAFT and the Kwei-equation, the full phase diagram of IND/PLGA formulations could be modelled and the modelling results were in good accordance with the experimental data.

Fig. 4 shows the solubility data of IND in Resomer® RG 752 S, Resomer® RG 755 S, Resomer® RG 756 S and Resomer® RG 750 S as well as the glass-transition temperatures of the corresponding IND/PLGA formulations. Additionally, the modelling results are also included in Fig. 4. All of these PLGAs had the same DLLA/GA monomer-unit ratio (75:25) but differ in molecular weight (Table 2).

As observed in Fig. 4, the IND solubility increased and the glass-transition temperature of IND/PLGA formulations decreased with a corresponding decrease in the molecular weight of the PLGA. The effect of the (co)polymer molecular weight on the solubility of IND was also found in a previous work for formulations with PEG [11] and can be predicted with PC-SAFT. In this work, the solubility of IND in Resomer® RG 755 S and Resomer® RG 756 S was fully predicted and was found to be in good accordance with the experimental data.

The glass-transition temperatures of all of the investigated IND/PLGA formulations showed a negative deviation from the weighted mean of the glass-transition temperatures of the pure substances and could be correlated using the Kwei-equation.

For a better evaluation of the modelling performance, the maximum relative deviation (MRD) and the average relative deviation (ARD) between the experimental data and the modelling results were determined according to Eqs. (15) and (16), and these values are listed in Table 7.

$$\mathrm{MRD} = 100 \cdot \max_{i=1,n_{exp}} \left| \frac{w_{IND,calc,i} - w_{IND,exp,i}}{w_{IND,exp,i}} \right| \tag{15}$$

$$\mathrm{ARD} = 100 \cdot \frac{1}{n_{exp}} \sum_{i=1}^{n_{exp}} \left| \frac{w_{IND,calc,i} - w_{IND,exp,i}}{w_{IND,exp,i}} \right| \tag{16}$$

As observed in Table 7, the ARD values determined for all of the calculations of the IND solubility in PLGA (PC-SAFT) were below 25%. The highest deviations (MRD up to 46%) were always found for IND/PLGA formulations with $w_{IND} = 0.6$, which increased the ARD between the modelling and experimental results of the corresponding system. The ARD of the glass-transition-temperature calculation with the Kwei-equation and the experimental results for all systems was below 30%. These results demonstrated a good accuracy of PC-SAFT as well as of the Kwei-equation to describe the phase behaviour of the IND/PLGA formulations and the ability to construct a whole phase diagram.

The phase diagrams of the IND/PLGA formulations, as shown in Figs. 3 and 4, show that IND has only weak attractive interactions with each considered PLGA, resulting in a low solubility and a negative deviation from the weighted mean of the glass-transition temperatures of pure IND and PLGA. This implies that none of the PLGA samples investigated in this work is a preferred excipient to stabilise the amorphous state of IND at room temperature. This can of course be true for other APIs. The amorphous state of the API in PLGA formulations is not required for all applications. Especially a long-term API release over several months can also be achieved by

Table 7
MRD and ARD of the IND solubility in PLGA modelled with PC-SAFT as well as of the IND concentration in the formulations at a given glass-transition temperature (T_g) calculated with the Kwei-equation.

	PC-SAFT		Kwei-equation	
	MRD (%)	ARD (%)	MRD (%)	ARD (%)
Resomer® RG 502 S	17.16	12.06	40.11	29.09
Resomer® RG 752 S	19.07	9.07	37.40	25.23
Resomer® RG 755 S	36.58	24.33	11.07	6.64
Resomer® RG 756 S	14.7	7.17	25.61	11.56
Resomer® RG 750 S	45.72	21.17	29.00	17.88

the crystalline state of the API. However even in these cases, the knowledge of the phase behaviour is a useful prerequisite for designing PLGA formulations in which the solid state of the API is of importance.

5. Conclusions

The focus of this work was to investigate the influence of the molecular weight and copolymer composition of PLGA on the phase behaviour of IND/PLGA formulations. For that purpose, five different PLGAs (Resomer® RG 502 S, Resomer® RG 752 S, Resomer® RG 755 S, Resomer® RG 756 S and Resomer® RG 750 S), which differ in molecular weight and copolymer composition, were selected as model excipients.

It was found that the solubility of IND in PLGA increased with a corresponding increase in the ratio of DLLA:GA monomer units in the copolymer and with a corresponding decrease in the molecular weight of PLGA. The copolymer composition has a minor influence on the IND solubility compared with the molecular weight of PLGA.

The thermodynamic model PC-SAFT is capable of describing and even predicting the solubility of IND in different PLGA compositions as a function of the PLGA molecular weight and copolymer composition and based on the knowledge of the respective homopolymer systems only.

Moreover, it was shown that the glass-transition temperature of these formulations can be described with a high degree of accuracy using the Kwei-equation.

This approach can also be applied to model the phase behaviour of PLGA formulations with any other API and thus can be utilised as an improved screening process when searching for an appropriate PLGA/API delivery system.

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