Drug Release Kinetics and Mechanism from PLGA Formulations

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The release kinetics of indomethacin (IND) and hydrochlorothiazide (HCT) from drug/PLGA formulations with different copolymer composition and molecular weight of PLGA were measured in vitro by using a rotating disk system (USP II). The release mechanism of IND and HCT from their PLGA formulations was analyzed using a chemical-potential-gradient model combined with the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT). Furthermore, the release kinetics of IND and HCT from the PLGA formulations with different copolymer composition and molecular weight of PLGA were correlated and predicted in good accordance with the experimental data. It was found that the chemical-potential-gradient model combined with the PC-SAFT helped to understand the drug release mechanism from the drug/PLGA formulations. It also well correlated and predicted the drug release kinetics as function of copolymer composition and molecular weight of PLGA as well as of drug type. It helps to save time and costs for determination of the long-term drug release kinetics, especially for sustained drug release as obtained from the drug/PLGA formulations in this work. © 2016 American Institute of Chemical Engineers *AIChE J*, 62: 4055–4065, 2016
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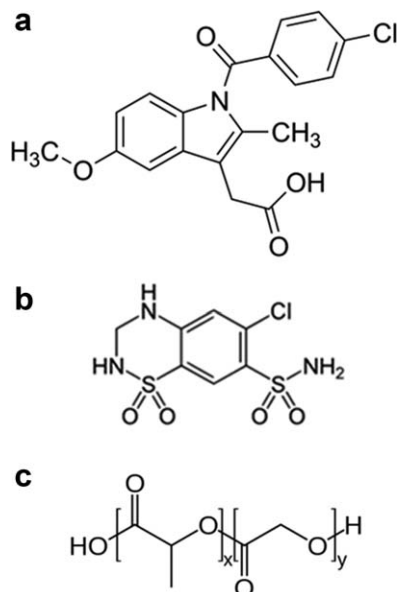
Introduction

Copolymers are often good candidates as excipients for preparing drug formulations since different advantageous properties of monomers can be combined in copolymers. Copolymers poly(D,L-lactic-co-glycolic) acids (PLGAs) are biodegradable, highly biocompatible, FDA, and European Medicine Agency approved in drug formulations and they have tunable mechanical properties.[1–4] Thus, PLGAs have attracted more and more attention as excipients to design sustained- and controlled-drug-release formulations for drugs, proteins and peptides, etc.[5–10] It was reported that the biological and physico-chemical properties of PLGAs are often influenced by their molecular weight and copolymer composition as well as the chemical composition of the end groups.[11,12] For a design of optimized formulations with suitable drug/PLGA combinations and controllable drug release, it is important to characterize the drug release mechanism from PLGA formulations. It is also essential to capture the effects of different influencing factors (e.g., copolymer composition and molecular weight of PLGAs) on the drug release rate. However, as reported in literature, drug release from PLGA-based formulations is rather complex.[13] The complexity of drug release from PLGA-based formulations makes it difficult to understand the drug release mechanism and to predict the drug release kinetics.[13] Various approaches (e.g., by means of observation of the shape of the drug release profile,[13] empirical/semi-empirical models and mechanistic mathematical models,[14] etc.) have been applied to understand drug release mechanisms. However, the results concerning drug release mechanisms differed from each other, which can be due to the complexity of drug release from PLGA formulations.[13] Different drug release mechanisms from PLGA formulations were proposed by many researchers. For example, excipient–drug interactions and drug–drug interactions were considered to control the drug release rate by Gaspar et al.[15] and Zhu and Schwendeman.[16] Dissolution of the drug (in combination with diffusion) as well as hydrolysis and erosion of the excipients were found to be the rate-controlling process in drug release by Wong et al.,[17] Bishara and Domb,[18] and Shah et al.[19]. Diffusion of drugs through water-filled pores or through the polymer excipients as well as water absorption/swelling were regarded as the drug release rate-controlling processes by Kim et al.,[20] Sun et al.,[21] and Mochizuki et al.[22]. More recently, a novel approach, the molecular-based chemical-potential-gradient model,[23] was developed to analyze the drug release mechanisms and to correlate and predict the drug release kinetics. The release kinetics and mechanisms of several crystalline drugs[24–26] and of indomethacin (IND) and naproxen from poly vinylpyrrolidone (PVP K25) formulations[23] were investigated. The purpose of this article is to apply the molecular-based chemical-potential-gradient model to achieve some new insights into the main processes that control the drug release from PLGA formulations.

Therefore, in this work, IND and hydrochlorothiazide (HCT) were selected as model drugs. The PLGAs (Resomer®

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Figure 1. Chemical structures of IND (a), HCT (b), and PLGAs (c) in which x represents the number of monomer units of lactic acid (DLA/LLA) and y represents that of glycolic acid (GA).

RG 502, Resomer® RG 752 S, Resomer® RG 756 S, and Resomer® RG 750 S) with different copolymer composition of D-lactic acid (DLA), L-lactic acid (LLA), and glycolic acid (GA) and with different molecular weights were selected as model PLGA co-polymeric excipients to prepare formulations. The chemical structures of IND, HCT and the PLGAs are shown in Figure 1. The IND/PLGA and HCT/PLGA formulations were prepared by spray drying technique. The drug release kinetics from the PLGA formulations were investigated using a rotating disk system (USP II). The chemical-potential-gradient model[23] was used to study the drug release mechanisms and to correlate and predict the drug release kinetics. As the Perturbed-Chain Statistical Associating Fluid Theory (PC-SAFT) has been successfully applied to model the systems containing drugs,[27–32] electrolytes,[33–35] and polar components,[36,37] in this work, it was used to calculate the solubility and activity coefficients of the model drugs. The effects of copolymer composition and molecular weight of PLGA on drug release kinetics and mechanism were investigated. Furthermore, the release kinetics of IND and HCT from the PLGA formulations were correlated and predicted with a comparison to the experimental measurements.

Theory

Chemical-potential-gradient model

The release process of an amorphous drug/excipient formulation contains at least two consecutive steps.[23,38,39] The first step often involves different processes as the transport of drug from the excipient, solvent penetration into the excipient and the hydration of the drug and excipient and this is called "surface reaction." Accompanied by this step, a solid–liquid interface is formed. The chemical potential difference of the drug or excipient between the solid phase and the solid–liquid interface is the driving force of the surface reaction. The second step includes the diffusion of the hydrated drug and excipient molecules from the solid–liquid interface into the solution bulk phase. In this step, the chemical potential difference of the drug or excipient between the solid-liquid interface and the bulk phase is the driving force of the diffusion. As the chemical-potential-gradient model was introduced in detail in our previous work,[23] it is only introduced briefly in this work.

The dissolution rate of a drug or an excipient J_i is defined as

$$J_i = \frac{1}{A} \cdot V \cdot \frac{dc_i^B}{dt} \tag{1}$$

Here A is the surface area of the dissolving drug or excipient contacting with the dissolution solution in m^2. In this work, A is calculated as the base area of the cylindrical tablet and it is regarded as a constant. V is the volume of the dissolution solution in m^3 and c_i^B the concentration of the drug or excipient in the bulk solution in mol/m^3.

Surface-reaction rate and diffusion rate are described by Eqs. 2 and 3, respectively.

$$J_i = k_S \left(\frac{\mu_i^S}{RT} - \frac{\mu_i^I}{RT} \right) = k_S \left(ln\ a_i^L - ln\ a_i^I \right) \tag{2}$$

$$J_i = k_d \left(\frac{\mu_i^I}{RT} - \frac{\mu_i^B}{RT} \right) = k_d \left(ln\ a_i^I - ln\ a_i^B \right) \tag{3}$$

where μ_i^S, μ_i^I, and μ_i^B are the chemical potentials of the drug or excipient in the solid phase, at the solid–liquid interface and in the bulk phase in J/mol, respectively. a_i^L, a_i^I, and a_i^B are the activities of the drug or excipient in its saturated solution, at the solid–liquid interface and in the bulk phase, respectively. R is the universal ideal gas constant in J/(mol K) and T is the temperature in K. k_S and k_d are the rate constants of surface reaction and diffusion in mol/(m^2 s). Based on the magnitude of the rate constants of surface reaction k_S and diffusion k_d, the rate-controlling step of the drug or excipient release can be determined. Drug or excipient release is controlled by surface reaction, if k_S is smaller than k_d. In the case that k_d is close to or equal to k_S, both surface reaction and diffusion are important and the drug or excipient release is controlled by both steps. If k_d is smaller than k_S, the release is diffusion controlled.

a_i^L and a_i^B can be calculated according to Eqs. 4 and 5, respectively.

$$a_i^L = x_i^L \gamma_i^L \tag{4}$$

$$a_i^B = x_i^B \gamma_i^B \tag{5}$$

where x_i^L, x_i^B are the solubility and bulk concentration (in mole fraction) of drug or excipient, γ_i^L and γ_i^B are the activity coefficients of drug or excipient in its saturated solution and in the bulk phase. The solubility and activity coefficients of drug or excipient can be estimated using a thermodynamic model (in this work PC-SAFT[40]).

The solubility of an amorphous drug in water was determined based on liquid–liquid equilibrium.[23,31] The theory of liquid–liquid equilibrium has been introduced in the literatures[27,41] and will not be repeatedly introduced in this work.

In this work, the buffered solution with a pH of 6.5 was used as a dissolution medium as this pH was commonly used for simulated intestinal fluid test solutions. The solubility of amorphous IND at pH 6.5 was calculated by using the Henderson-Hasselbalch equation.[23,42,43] This was introduced in detail in our previous work.[23] The pK$_a$ value of IND was taken as being 4.5 from literature.[44] As the solubility of amorphous HCT at pH 6.5 is similar to that in pure water, the solubility of amorphous HCT in pure water was used for the modeling.

a_i^I is determined based on the Statistical Rate Theory,[45–47] as described in Eq. 6.

$$J_i = \left(\alpha_1 A_f x_i^L \sqrt{T} + 0.510 \alpha_2 \ \varnothing A_f x_i^L \sqrt{\frac{\omega^3}{v}} \delta^2 \right)$$
$$\left[\exp\left(\frac{\mu_i^S - \mu_i^I}{RT} \right) - \exp\left(\frac{\mu_i^I - \mu_i^S}{RT} \right) \right] \quad (6)$$
$$= \left(\alpha_1 A_f x_i^L \sqrt{T} + 0.510 \alpha_2 \ \varnothing A_f x_i^L \sqrt{\frac{\omega^3}{v}} \delta^2 \right) \left[\frac{a_i^L}{a_i^I} - \frac{a_i^I}{a_i^L} \right]$$

In Eq. 6, x_i^L is the solubility of drug or excipient in mole fraction, α_1 and α_2 are proportionality constants. A_f is the fraction of the area of the interface for molecule transport from the solution and it is treated as a constant. $\varnothing$ is a constant fraction of molecules that strike the solid surface. v is the kinematic viscosity of the solution in m^2/s, δ is the diffusion layer thickness in m, and ω is the stirring speed in round/s.

K_1 and K_2 are set as $K_1 = \alpha_1 A_f$ and $K_2 = \alpha_2 \ \varnothing A_f \delta^2$. By combining Eqs. 2 and 3 with Eq. 6, the parameters k_d, K_1, K_2, and k_s were fitted to the experimental release kinetics data and further the rate-controlling step of the drug or excipient release can be analyzed.

Correlation and prediction of drug or excipient release kinetics

Based on Eqs. 1–3, Eq. 7 could be obtained.

$$J_i = \frac{1}{A} \cdot V \cdot \frac{dc_i^B}{dt} = k_t \left(\frac{\mu_i^S}{RT} - \frac{\mu_i^B}{RT} \right) = \left(\frac{1}{\frac{1}{k_d} + \frac{1}{k_s}} \right) \left(\ln a_i^L - \ln a_i^B \right) \quad (7)$$

where k_t is the rate constant of the whole process of drug or excipient release and it is a function of the rate constants of surface reaction k_s and diffusion k_d as shown in Eq. 7.

By combining Eq. 7 with PC-SAFT for estimating the activity coefficient of a drug or excipient, the release kinetics of the drug or excipient at various conditions can be correlated and predicted.

PC-SAFT

PC-SAFT considers the residual Helmholtz energy a^{res} of a system as the sum of different contributions.[40,48] According to the nature of molecules, PC-SAFT takes into account contributions due to the hard-chain repulsion of the reference system (a^{hc}), van der Waals attractions (dispersive interactions, a^{disp}),[40] association (hydrogen bonding, a^{assoc}),[48] and ionic interactions (a^{elec}),[33–35,49] as described in Eq. 8:

$$a^{res} = a^{hc} + a^{disp} + a^{assoc} + a^{elec} \quad (8)$$

The detailed descriptions of these contributions within PC-SAFT were introduced elsewhere in the literatures,[33–35,40,48] and are not introduced in detail in this work. PC-SAFT considers a molecule as a chain consisting of m^{seg} spherical segments with a diameter of σ. Thus, a non-associating molecule can be modeled using three pure-component parameters: the segment number (m^{seg}), the segment diameter (σ), and the dispersion-energy parameter (u/k_B). For describing associating molecules that are able to interact with each other by hydrogen bonding (e.g., IND and HCT in this work), two additional parameters are required: the association-energy parameter ($\varepsilon_{hb}^{A_iB_i}/k_B$, where k_B is the Boltzmann's constant), and the association-volume

parameter ($\kappa_{hb}^{A_iB_i}$). Moreover, the number of association sites (N^{assoc}), which act as proton donors and acceptors, needs to be considered and it is often determined based on the molecular structure of the substance.

To estimate the Helmholtz energy of binary systems, the Berthelot-Lorentz combining rules are applied to describe the interactions between different components i and j, as presented in Eqs. 9 and 10.

$$\sigma_{ij} = \frac{1}{2} \ (\sigma_i + \sigma_j) \quad (9)$$
$$u_{ij} = (1 - k_{ij}) \sqrt{u_i u_j} \quad (10)$$

In Eq. 10, one adjustable binary interaction parameter (k_{ij}) is considered to correct for the dispersion-energy parameter for the binary mixture of components i and j. If necessary, k_{ij} is a function of temperature as described in Eq. 11.

$$k_{ij} = k_{ij,T} \cdot T + k_{ij,0} \quad (11)$$

In Eq. 11, $k_{ij,T}$ and $k_{ij,0}$ are parameters fitted to binary data.

To describe the cross-association interactions between two different associating components, the simple mixing and combining rules suggested by Wolbach and Sandler[50] are applied as presented in Eqs. 12 and 13. Here, no additional adjustable binary parameter is needed.

$$\varepsilon_{hb}^{A_iB_j} = \frac{1}{2} \ \left(\varepsilon_{hb}^{A_iB_i} + \varepsilon_{hb}^{A_jB_j} \right) \quad (12)$$
$$\kappa_{hb}^{A_iB_j} = \sqrt{\kappa_{hb}^{A_iB_i} \ \kappa_{hb}^{A_jB_j}} \left[\frac{\sqrt{\sigma_{ii}\sigma_{jj}}}{(1/2)(\sigma_{ii} + \sigma_{jj})} \right]^3 \quad (13)$$

Calculation of activity coefficient with PC-SAFT

Once the residual Helmholtz energy (a^{res}) of a system is determined, the residual chemical potential (μ_i^{res}) of the drug or excipient[51] can be described based on Eq. 14.

$$\frac{\mu_i^{res}}{k_B T} = \frac{a^{res}}{k_B T} + Z - 1 + \left[\frac{\partial(a^{res}/k_B T)}{\partial x_i} \right] - \sum_{j=1}^{N} \left[x_j \left(\frac{\partial(a^{res}/k_B T)}{\partial x_j} \right) \right] \quad (14)$$

In Eq. 14, Z is the compressibility factor, which is determined in terms of the residual Helmholtz energy (a^{res})[51] based on Eq. 15.

$$Z = 1 + \rho \left[\frac{\partial(a^{res}/k_B T)}{\partial \rho} \right] \quad (15)$$

Here, ρ is the density of the system in kg/m^3.

The fugacity coefficient of the drug or excipient in a mixture is determined in terms of its residual chemical potential (μ_i^{res})[51] as presented in Eq. 16.

$$\ln \varphi_i^L = \frac{\mu_i^{res}}{k_B T} - \ln Z \quad (16)$$

The activity coefficient of the drug or excipient is defined as a ratio of its fugacity coefficient φ_i^L in the mixture to that of the pure substance φ_{0i}^L as presented in Eq. 17.

$$\gamma_i^L = \frac{\varphi_i^L}{\varphi_{0i}^L} \quad (17)$$

Table 1. Homogeneity of the IND/PLGA Formulations with an IND Loading of 0.4

Formulation	Homogeneity (%)
IND/RESOMER® RG 502	99.9
IND/RESOMER® RG 752 S	95.4
IND/RESOMER® RG 756 S	95.6
IND/RESOMER® RG 750 S	95.6

Materials and Methods

Materials

IND (γ-polymorph) with a purity of > 99% was purchased from Sigma-Aldrich Co. LLC. (Steinheim, Germany). HCT with a purity of >98% was purchased from Alfa Aesar Co. LLC (Karlsruhe, Germany). The various PLGA copolymers, Resomer® RG 502 (molar ratio of lactic acid (DLLA) to glycolic acid (GA) as 50:50, molecular weight M_w of 13,000 g/mol), Resomer® RG 752 S (DLLA:GA molar ratio of 75:25 and M_w of 13,000 g/mol), Resomer® RG 756 S (DLLA:GA molar ratio of 75:25 and M_w of 103000 g/mol), and Resomer® RG 750 S (DLLA:GA molar ratio of 75:25 and M_w of 128,000 g/mol) were supplied by Evonik (Essen, Germany). All of the selected polymers were ester-terminated. $Na_2HPO_4 \cdot 2H_2O$ and KH_2PO_4 were purchased from Merck KGaA (Darmstadt, Germany) and were used for preparation of buffer solutions. All chemicals were used without any further purification. Water was filtered and deionized using a Millipore purification system and was used to prepare all the aqueous solutions.

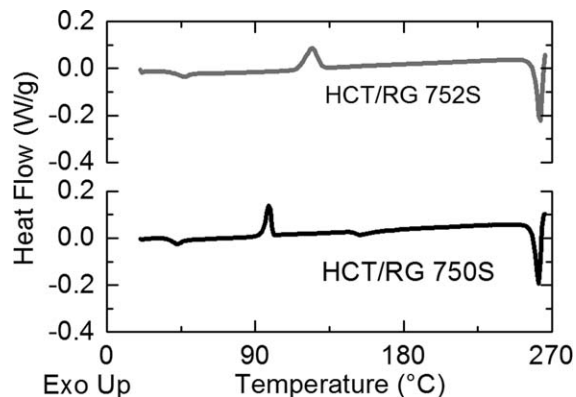### Water sorption measurement of pure PLGAs

The water sorption of pure PLGAs was measured using a gravimetric method. For this purpose, a certain amount of dry pure PLGAs was weighed and then stored in the climate chamber for one week at 298.15 K and at a relative humidity (RH) of 75%. After the storage, the PLGAs were weighed again and the amount of absorbed water was determined by the difference of the PLGA weights before and after storage.

Preparation of drug/PLGA formulations

IND/PLGA and HCT/PLGA formulations with a drug loading of 0.4 were prepared using a Büchi mini spray dryer (B-290) with an inert-loop (B-295) (Büchi Company, Switzerland). For this purpose, the drug and PLGA with a weight ratio of 40:60 were dissolved in acetone at a concentration of 10 g/L. The inlet temperature of the spray dryer was set to 60°C. The aspirator was set to 85%, the feed rate of the solution was 8 mL/min, and the flow rate of nitrogen was 550 L/h. All spray-dried powders were dried in a climate chamber at room temperature and vacuum condition for at least 24 h to remove the remaining water and organic solvent prior to characterization and dissolution measurements. All powders were further stored in the climate chamber at room temperature and vacuum condition.

Analysis of homogeneity

The homogeneity of IND/PLGA formulations was investigated following the procedures in the standard method (ISO 13528:2005).[52] A number *g* (in this work, g ≥ 3) of formulation samples (1.5–4.5 mg for each sample) was selected randomly from each prepared, dried product. The formulation samples were weighed with an accuracy of ±0.3 mg and dissolved in acetonitrile and the concentrations of IND in acetonitrile solution were determined using an UV-Vis
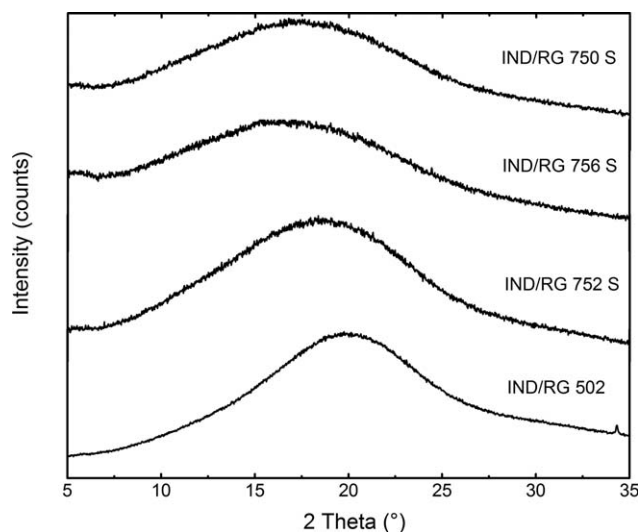

Figure 2. DSC thermograms of HCT formulations in PLGA with HCT loading of 0.4.

The black and gray lines represent the thermograms of HCT/RESOMER® RG 752S and HCT/RG 750S, respectively.

spectrophotometer (Jena, Germany). Each measurement was performed in triplicate. Then the exact IND compositions in the different formulation samples were determined and were used to evaluate the homogeneity according to the standard method (ISO 13528:2005).[52]

Modulated temperature differential scanning calorimetry

The solid state of HCT in HCT/PLGA formulations was characterized by the DSC measurements using a Q 2000 modulated DSC (TA Instruments, Eschborn, Germany). The apparatus was calibrated using indium. Nitrogen was purged into the DSC cell at a flow rate of 50 mL/min to maintain the inert atmosphere. The formulation samples of 5–10 mg were added into aluminum pans and weighed with an accuracy of ±0.3 mg. Then the pans were further sealed with an aluminum lid and heated from 283.15 to 543.15 K at a heating rate of 2 K/min. The samples were equilibrated at 293.15 K for 5 min before heating. The modulation amplitude was set at ±0.318 K, and the modulation period was set to 60 s. The measured results were analyzed mathematically using the TA Universal Analysis 2000 (TA Instruments, Eschborn,

Figure 3. X-ray diffraction spectra (black curves) of the IND/PLGA formulations with an IND loading of 0.4.

Table 2. Water Sorption of Pure PLGAs After Storage for 1 Week at 298.15 K and at a RH of 75%

Polymer	$m_{before\ storage}$ [g]	$m_{after\ storage}$ [g]	w [g_{water}/$g_{polymer}$]
RESOMER® RG 502	1.3163	1.3197	0.0026
RESOMER® RG 752 S	1.2827	1.2839	0.0009
RESOMER® RG 756 S	1.3448	1.3465	0.0013
RESOMER® RG 750 S	1.2410	1.2449	0.0031

Germany). The degree of HCT crystallinity, β_{HCT} (%) in HCT/PLGA formulations was estimated from the melting enthalpies of the formulations and pure HCT using the following Eq. 18.

$$\beta_{HCT}\ (\%) = \frac{\Delta h^{SL}_{F,\ HCT}}{\Delta h^{SL}_{0HCT} \times w_{HCT}} \times 100 \qquad (18)$$

where Δh^{SL}_{0HCT} and $\Delta h^{SL}_{F,HCT}$ are the melting enthalpies of pure HCT and HCT in the formulation, respectively. $\Delta h^{SL}_{F,HCT}$ was measured in this work by mDSC and Δh^{SL}_{0HCT} was taken from a literature.[31]

Powder X-ray diffraction measurements

The solid state of IND in IND/PLGA formulations was characterized by powder X-ray diffraction (PXRD). The Powder X-ray Diffractometer Mini Flex 600 from Rigaku (Ettlingen, Germany) was operated with Cu-K alpha irradiation, a voltage of 40 kV and a current of 15 mA. The data were collected in step scan mode in the region of $10° \leq 2\theta \leq 40°$ with a step size of 0.02°.

Preparation of dissolution media

A certain amount of $Na_2HPO_4 \cdot 2H_2O$ and KH_2PO_4 was weighed and dissolved in water to prepare the dissolution media with a pH value of 6.5.[23,24] The exact pH value of the media was detected with a pH meter (Mettler-Toledo GmbH, Gießen, Germany). To remove the air bubbles in the media, the media were degassed by purging helium into the media for 90 min prior to the dissolution experiments.

In-vitro intrinsic dissolution measurement

The release kinetics of IND and HCT from drug/PLGA formulations in a buffered solution with a pH value of 6.5 were measured in vitro using a rotating disk system (USP II). The cylindrical tablets (with a diameter of 8 mm) of drug/PLGA formulations were prepared by pressing 200 mg (± 1 mg) powders in the disk die with a force of 2 kN. The disk was then inserted into the dissolution vessel containing 500 mL medium at 310.15K (± 0.3 K). As the influences of stirring speed on drug release kinetics and mechanism were already investigated in our

Table 4. Binary Interaction Parameters k_{ij} Between Drug and Water, Between Ion and Water, Between Cation and Anion Within PC-SAFT Used in this Work

System	$k_{ij,T}$	$k_{ij,0}$	References
IND/water	0.000169	−0.110	24
HCT/water	0.000161	−0.113	31
K^+/water	−0.00401	1.40	49
Na^+/water	−0.00798	2.38	49
$H_2PO_4^-$/water	0	0.25	49
HPO_4^{2-}/water	0	0.25	49
K^+/$H_2PO_4^-$	0	0.0182	49
K^+/HPO_4^{2-}	0	1	49
Na^+/$H_2PO_4^-$	0	−0.0709	49
Na^+/HPO_4^{2-}	0	−1	49

previous work (Ji et al., 2015; Paus et al., 2016), it will not be investigated in this work. The disk was rotated at a stirring speed of 50 rpm as this speed was commonly used in the experiments. The temperature and stirring speed were monitored during each experiment. Sample analysis was performed in spectrometer flow cells. The release kinetics of IND and HCT from drug/PLGA formulations were measured automatically at wavelengths of 320 and 317 nm, respectively, using an UV-Vis spectrophotometer (Jena, Germany). Each measurement was performed in triplicate and the average data were reported.

Results

Homogeneity analysis

The exact concentration of IND in IND/PLGA formulations as well as the homogeneity of these formulations was investigated and the results are presented in Table 1. As shown in Table 1, the homogeneity of all the investigated formulations is higher than 95%. This indicates that IND is homogeneously dispersed in IND/PLGA formulations prepared by spray drying in this work.

Analysis of degree of drug crystallinity using DSC

Figure 2 shows the DSC thermograms of HCT formulations in PLGAs. For HCT/RESOMER® RG 752 S and HCT/RG 750 S formulations, there are obvious endothermal melting peaks shown in Figure 2. Based on the melting enthalpies of pure HCT Δh^{SL}_{0HCT} (38.65 kJ/mol from Ref. 31) and that of HCT in the formulations $\Delta h^{SL}_{F,HCT}$ (determined from Figure 2), the degree of HCT crystallinity in the formulations was calculated. The degree of HCT crystallinity in HCT/RESOMER® RG 752S and HCT/RG 750S formulations were determined as 47.80 and 41.72%, respectively. This indicates that both HCT/PLGA formulations are more than 50% amorphous.

Table 3. Molecular Weights and Pure-Component PC-SAFT Parameters of IND, HCT, Water, and Ions Used in this Work

Component [Ref.]	M (g/mol)	m^{seg} (–)	σ (Å)	u/k_B (K)	$\varepsilon^{A_iB_i}_{hb}/k_B$ (K)	$k^{A_iB_i}_{hb}$ (–)	N^{assoc} (–)
IND[27]	357.79	14.283	3.535	262.79	886.4	0.02	3/3
HCT[31]	297.74	11.961	2.938	179.849	2173.62	0.03	4/4
Water[53]	18.02	1.205	σ_{water}[a]	353.95	2425.7	0.0451	1/1
K^{+}[49]	39.10	1	3.342	200	–	–	–
Na^{+}[49]	22.99	1	2.823	230	–	–	–
$H_2PO_4^{-}$[49]	96.99	1	3.651	95	–	–	–
HPO_4^{2-}[49]	95.98	1	2.162	146.02	–	–	–

[a]$\sigma_{water} = 2.7927 + 10.11 \cdot exp(−0.01775 \cdot T) − 1.417 \cdot exp(−0.01146 \cdot T)$.[53]

Table 5. Solubility (Mole Fraction) of Amorphous IND in a Buffered Solution at pH 6.5 and that of HCT in Water at 310.15 K

Amorphous drug	x_{drug}^L (−)
IND	5.9967×10^{-4} (pH 6.5)
HCT	7.6481×10^{-4} (water)

Analysis of drug solid state using PXRD

The solid state of the IND/PLGA formulations with an IND loading of 0.4 was characterized by PXRD, and their diffraction patterns are shown in Figure 3.

As presented in Figure 3, the X-ray diffraction patterns show amorphous halos without diffraction peaks for all the investigated IND/PLGA formulations. This indicates the amorphous state of IND in these formulations.

Water sorption of pure PLGAs

The water sorption of pure PLGAs after storage for one week at 298.15 K and at a RH of 75% was measured and the results are shown in Table 2. As observed from Table 2, PLGAs absorbed a little water (≤ 0.0031 g$_{water}$/g$_{polymer}$) after storage for 1 week at RH of 75%. For RESOMER® RG 502 and RG 752 S which have different copolymer compositions but have almost the same molecular weight, it was found that RG 502 absorbed more water than RG 752 S. For RESOMER® RG 752 S, RG 756 S, and RG 750 S which have different molecular weights but have the same copolymer composition, it was found that the PLGA with higher molecular weight absorbed more water (RG 750 S > RG 756 S > RG 752 S).

Discussions
PC-SAFT parameters

The pure-component PC-SAFT parameters of IND, HCT, water, and ions and the binary interaction parameters between drug and water as well as those between ions and water are listed in Tables 3 and 4.

Drug solubility in solution

The solubilities of amorphous IND and HCT in water at 310.15 K were taken from literature.[23,31] The solubility of IND in a buffered solution at pH 6.5 was calculated based on a previous work[23] by using the Henderson-Hasselbalch equation. The calculated solubilities of amorphous IND at pH 6.5 and that of HCT in water are listed in Table 5.

As shown in Table 5, the solubility of amorphous IND at pH 6.5 is smaller than that of amorphous HCT in water.

Drug release kinetics and mechanism from PLGA formulations

The release kinetics of IND and HCT from drug/PLGA formulations were measured and compared with those of pure crystalline drugs. The influence of copolymer composition and molecular weight of PLGA as well as type of drug on drug release rate was investigated.

In addition, the chemical-potential-gradient model combined with PC-SAFT as described in the 2nd section was used to analyze the drug release mechanism from PLGA formulations and will be discussed in detail in the following text. In the modeling, the molar density and kinematic viscosity of water at 310.15 K were calculated based on the following correlations according to the reported data in literature[54]:

$$\rho/(\text{mol/L}) = -0.0003 \cdot (T/^{\circ}C)^2 - 0.0008 \cdot (T/^{\circ}C) + 55.525 \tag{19}$$

$$v/(\text{m}^2/\text{s}) = 2.248 \cdot 10^{-10} (T/^{\circ}C)^2 - 3.195 \cdot 10^{-8} (T/^{\circ}C) + 1.572 \cdot 10^{-6} \tag{20}$$

The parameters (k_d, k_s, K_1, and K_2) were fitted to the experimental IND and HCT release kinetics from PLGA formulations and are summarized in Table 6. Assuming a linear relationship of the surface-reaction rate constant and diffusion rate constant of IND release from PLGA formulations with PLGA molecular weight, the parameters k_s and k_d for IND release from RESOMER® RG 750 S were predicted and the results are presented in Table 7.

To evaluate the accuracy of the correlated or predicted drug release kinetics, the average relative deviation (ARD (%)) between the correlated or predicted and experimental data was analyzed according to Eq. 21. The obtained ARDs are presented in Tables 6 and 7.

$$ARD \ (\%) = 100 \ \frac{1}{n_{\text{exp}}} \sum_{m=1}^{n_{\text{exp}}} \left| \frac{x_m^{\text{exp}} - x_m^{model}}{x_m^{\text{exp}}} \right| \tag{21}$$

Effect of drug type on drug release from PLGA formulations

The influence of drug type on drug release kinetics and mechanism from PLGA formulations was investigated for IND and HCT at pH 6.5. IND and HCT release rates from PLGA formulations were compared with those of the pure crystalline drugs.[24,55] The results are presented in Figures 4a, b.

As observed in Figure 4a, the type of drug has an obvious influence on the drug release kinetics from PLGA formulations. IND release rate from RG 752 S is smaller than that of HCT, while IND release rate from RG 750 S is greater than that of HCT. As discussed in literature,[23,56,57] the drug release from a formulation can be considered as excipient-controlled if the drug release rate is independent on drug type. Based on

Table 6. Parameters $k_s, k_d, K_1,$ and K_2 Fitted to the Experimental IND and HCT Release Kinetics from PLGA Formulations in the Buffered Solutions at pH 6.5, 310.15 K and at 50 rpm

System	k_s	k_d	K_1	K_2	k_t	ARD (%)
IND/RESOMER® RG 502	1.25×10^{-7}	4.32×10^{-6}	1.25×10^{-9}	2.48×10^{-10}	1.21×10^{-7}	22.93
IND/RESOMER® RG 752 S	5.23×10^{-8}	4.41×10^{-6}	3.90×10^{-10}	4.50×10^{-11}	5.17×10^{-8}	18.18
IND/RESOMER® RG 756 S	1.26×10^{-6}	3.79×10^{-6}	9.23×10^{-8}	5.62×10^{-8}	9.46×10^{-7}	15.02
HCT/RESOMER® RG 752 S	2.37×10^{-7}	9.22×10^{-6}	3.60×10^{-9}	1.90×10^{-10}	2.31×10^{-7}	26.22
HCT/RESOMER® RG 750 S	3.05×10^{-7}	6.54×10^{-6}	1.05×10^{-8}	1.22×10^{-9}	2.91×10^{-7}	25.99

Table 7. The Predicted Surface-Reaction Rate Constant k_s and Diffusion Rate Constant k_d as Well as the ARD Between the Predicted and Experimental Data for IND Release from RESOMER® RG 750 S in the Buffered Solution at pH 6.5, 310.15 K and at 50 rpm According to the Following Linear Relationship with PLGA Molecular Weight: $k_s/(mol/(m^2 s)) = 1.3451 \cdot 10^{-11} \cdot (M_w/(g/mol)) - 1.2261 \cdot 10^{-7}$; $k_d/(mol/(m^2 s)) = -6.8633 \cdot 10^{-12} \cdot (M_w/(g/mol)) + 4.4968 \cdot 10^{-6}$

System	k_s	k_d	k_t	ARD
IND/RESOMER® RG 750 S	1.60×10^{-6}	3.62×10^{-6}	1.11×10^{-6}	13.59%

this, the drug release from IND/PLGA and HCT/PLGA formulations were not excipient-controlled.

Compared to the release rate of pure IND, IND/RESOMER® RG 750 S formulations improved the IND release rate, which is due to the fact that IND is dissolved in RG 750 S and is thus amorphous. However, IND/RG 752 S formulations obtained a sustained IND release, which implies that the release of excipient (RG 752 S) also plays an important role for IND release. Furthermore, compared to the release rate of pure HCT, both HCT/RG 752 S and HCT/RG 750 S obtained a sustained HCT release at pH 6.5. It shows that the release of both excipients (RG 752 S and RG 750 S) plays an important role for HCT release. It was further found that HCT release rate from RG 750 S was greater than that from RG 752 S, which can be explained by the fact that RG 750 S absorbed more water than RG 752 S, and accelerated the hydration process (within surface reaction step) of HCT in RG 750 S. All these information reveal that drug release from IND/PLGA and HCT/PLGA formulations were not only drug-controlled, but controlled by the release of both drug and excipient.
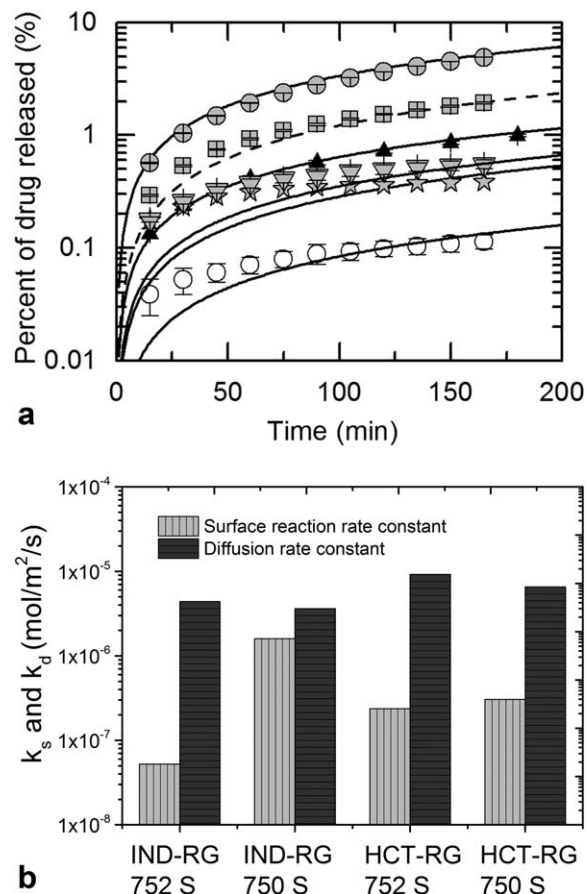
The drug release mechanism analysis (Figure 4b) shows that both IND and HCT release were controlled by surface reaction, which is related to the transport of drug from the PLGA, water penetration into the PLGA, the hydration of the drug and PLGA. As presented in Figure 4b, for HCT release from RG 752 S, both surface-reaction rate constant and diffusion rate constant of HCT are higher than that of IND, which led to higher HCT release rate from RG 752 S than IND. For IND and HCT release from PLGA formulations, although the diffusion rate constant of HCT from RG 750 S is higher than that of IND from RG 750 S, the surface-reaction rate constant of HCT from RG 750 S is lower than that of IND, which led to lower HCT release rate from RG 750 S than IND from the same PLGA.

Effect of copolymer composition on drug release from PLGA formulations

To evaluate the copolymer composition of PLGA on drug release kinetics and mechanism, RESOMER® RG 502 and RG 752 S which have different copolymer compositions but have almost the same molecular weight were selected as the copolymeric excipients. The release kinetics and mechanism of IND from these formulations at pH 6.5 and 310.15 K are shown in Figures 5a, b.
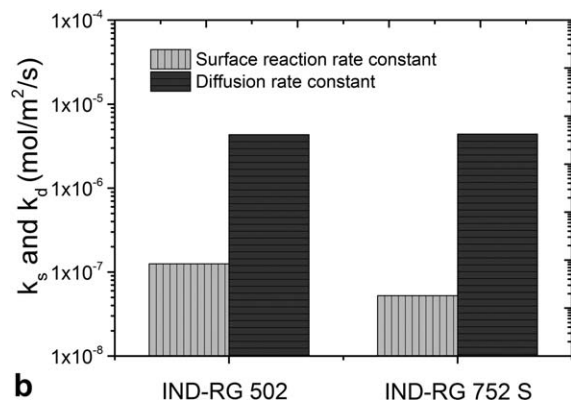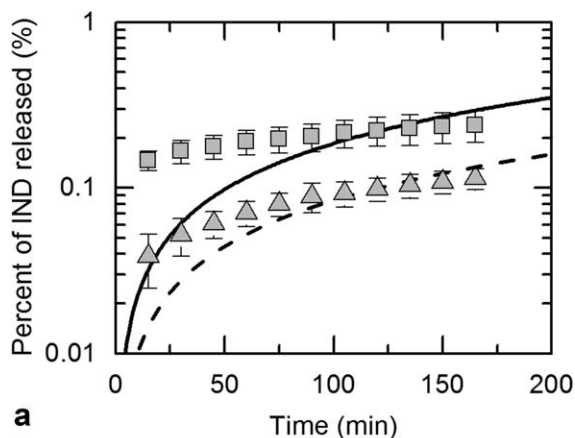
As shown in Figure 5a, copolymer composition of PLGA has obvious influence on IND release kinetics at pH 6.5, and IND release rate from RG 502 is higher than that from RG 752 S. This shows that IND release rate is higher from the PLGA with more amount of GA monomer unit as RG 502 (DLLA: GA molar ratio of 50:50) contains more amount of GA monomer unit than RG 752 S (DLLA: GA molar ratio of 75:25). This observation agrees with the results for estradiol *in vitro* release from PLGA formulations with different copolymer compositions as found by Mittal et al.[58].

As analyzed from Figure 5b, compared to IND release from RESOMER® RG 752 S, the surface-reaction rate constant of IND from RG 502 is obviously higher than that from RG 752 S. The diffusion rate constant of IND from RG 502 is similar to that from

a

b

Figure 4. (a) Release kinetics of pure IND (black triangles) in buffered solution (pH 6.5),[24] of IND from RESOMER® RG 752 S (gray hollow circles), RG 750 S (gray squares) formulations, and of pure HCT in pure water (gray circles)[55] as well as of HCT from RG 752 S (gray stars) and RG 750S (gray triangles) formulations in buffered solution (pH 6.5) at 310.15 K and at a stirring speed of 50 rpm. The full lines represent the correlated IND and HCT release kinetics and the dashed line represents the predicted IND release kinetics using the chemical-potential-gradient model. The release kinetics of IND from RG 750 S was predicted. (b) Surface-reaction and diffusion rate constants of IND and HCT release from RG 752 S and RG 750 S, respectively, at pH 6.5, 310.15 K and at 50 rpm.

13,000 g/mol), RG 756 S (M_w of 103,000 g/mol), and RG 750 S (M_w of 128,000 g/mol) which have different molecular weights but have the same copolymer composition (DLLA: GA molar ratio of 75:25) were selected as the copolymeric excipients. The release kinetics and mechanism analysis results of IND from these formulations at pH 6.5 and 310.15 K are shown in Figures 6a, b.

As shown in Figure 6a, the molecular weight of PLGA has an obvious influence on IND release kinetics at pH 6.5. The highest IND release rate was observed from RESOMER® RG 750 S and the lowest from RG 752 S. Generally, IND release rate increased with an increase in PLGA molecular weight.

As analyzed from Figure 6b, IND release from all these three PLGA formulations was controlled by surface reaction. This means that the factors related to the transport of IND from the PLGAs, water penetration into the PLGAs, the hydration of IND and PLGAs in local aqueous medium played important roles for IND release rate.

Figure 5. (a) Release kinetics of IND from RESOMER® RG 502 (gray squares) and RG 752 S (gray triangles) formulations in buffered solution (pH 6.5) at 310.15 K and at a stirring speed of 50 rpm. The dashed and full lines represent the correlated IND release kinetics from RG 502 and RG 752 S, respectively, using the chemical-potential-gradient model. (b) Surface-reaction and diffusion rate constants of IND release from RG 502 and RG 752 S, respectively, at pH 6.5, 310.15 K and at 50 rpm.

Figure 6. (a) Release kinetics of IND from RESOMER® RG 752 S (gray circles), RG 756 S (gray squares), and RG 750 S (gray triangles) formulations in buffered solution (pH 6.5) at 310.15 K and at a stirring speed of 50 rpm. The dotted and dashed lines represent the correlated IND release kinetics from RG 752 S and RG 756 S, respectively, using the chemical-potential-gradient model; the full line represents the predicted IND release kinetics from RG 750 S using the same model. (b) Surface-reaction and diffusion rate constants of IND release from RG 752 S, RG 756 S, and RG 750 S, respectively, at pH 6.5, 310.15 K and at 50 rpm.

RG 752 S, which might be explained by the fact that the viscosity of RG 502 is almost the same as that of RG 752 S. This analysis shows that the higher IND release rate from RG 502 is mainly attributed to the higher surface-reaction rate constant of IND, which is related to the transport of IND from RG 502, water penetration into the RG 502 and the hydration of IND and RG 502.

As found in our previous work,[29] IND solubility in RG 752 S is slightly higher than that in RG 502. The larger IND solubility in PLGA is, the slower IND release rate from the excipient. Furthermore, the water sorption of the pure PLGAs was experimentally observed in this work at 298.15 K and at a RH of 75%. It was found that RG 502 absorbed more water than RG 752 S, which accelerated the hydration process of IND in RG 502. All these observations support the release mechanism analysis by the chemical-potential-gradient model.
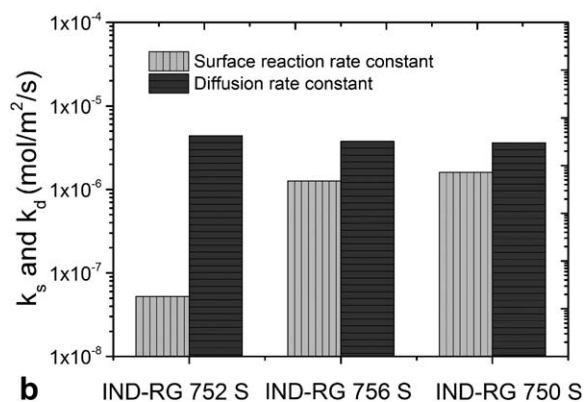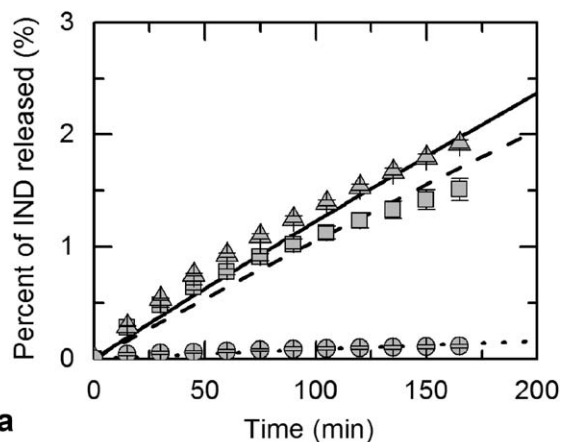
Effect of PLGA molecular weight on drug release from PLGA formulations

To evaluate the molecular weight of PLGA on drug release kinetics and mechanism, RESOMER® RG 752 S (M_w of

With an increase in PLGA molecular weight, the diffusion rate constant of IND in aqueous media from PLGA was decreased, which can be explained by the fact that the viscosity of PLGA solution is increased with increasing PLGA molecular weight. However, IND release rate was still enhanced with an increase in PLGA molecular weight due to the improved surface reaction.

As observed in our previous work,[29] IND solubility in PLGA was generally increased with decreased PLGA molecular weight. The slower IND release rate will be obtained in an aqueous medium when IND solubility in PLGA is larger. This information partly explains why IND release rate was increased with increasing PLGA molecular weight. Furthermore, the water sorption observations of the pure PLGAs at 298.15 K and at RH of 75% found that more water was absorbed by PLGAs with higher molecular weight (RG 750 S > RG 756 S > RG 752 S). The absorbed water accelerates the hydration process of IND in the PLGA.

In addition to that, as observed in our previous work,[29] the glass-transition temperatures (Tg) of the IND/PLGA formulations increased with an increase in the molecular weight of PLGA. The amorphous IND in PLGA formulations can be stabilized if the temperature is kept below the Tg of the formulations.[27] The mobility of molecules is drastically reduced and the recrystallization rate of the amorphous IND is decreased. Therefore, IND/PLGA formulations with higher PLGA molecular weights are more stable as they have higher Tg. For IND release from RG 752 S, the temperature of the solution (310.15 K) is higher than the Tg of the IND/RG 752 S (300.30 K), which indicates a high possibility that the amorphous IND recrystallizes in RG 752 S during IND release. The recrystallized IND is less soluble in the aqueous solution than the amorphous one and decreased IND release rate. For IND formulations with RG 756 S and RG 750 S, the release temperature is lower than the Tg of these two formulations. It can therefore be assumed that IND does not crystallize in these PLGAs during release. All these information support the release mechanism analyzed by the chemical-potential-gradient model that the IND release rate was enhanced by improving the surface reaction step for increasing PLGA molecular weight.

Correlation and prediction of drug release kinetics from drug/PLGA formulations

Based on the correlated and predicted rate constants of surface reaction and diffusion (as shown in Tables 6 and 7), the release kinetics of IND and HCT from PLGAs were correlated and predicted. The correlated and predicted results are also presented in Figures 4a, 5a, and 6a. As shown in Figures 4a–6a, the correlated results are generally in good accordance with the experimental data, which was verified by the ARDs between the correlated results and the experimental data. As found in Figure 6a, the predicted IND release kinetics from RG 750 S at pH 6.5 is in good agreement with the experimental data with a low ARD of 13.59%. However, for IND release from RESOMER® RG 502, RG 752 S and for HCT release from RG 752 S and RG 750 S, the correlated drug release kinetics at early stage (before 60 min) was lower than the experimental data. It can be due to the low drug release rate and the low released drug concentration from these PLGAs in the media. Furthermore, for the release kinetics of IND from RESOMER® RG 502 and RG 752 S as shown in Figure 5a, at a later stage (after 120 min), the amount of drug released into

the bulk solutions increases very slowly from the experimental measurement, while the correlated results shows evidently increasing IND amount. This may be because that the slow PLGA release influences the IND release during the experiments, as analyzed in above text that IND release rate is controlled by the release of both drug and excipient. This work generally shows that the chemical-potential-gradient model combined with PC-SAFT is a useful tool to correlate and even predict the release kinetics of IND and HCT from PLGA formulations as function of drug type, copolymer composition as well as of molecular weight of PLGA in a good accordance with the experimental data.

One main contribution of this work is to achieve a better understanding of the influence mechanism of copolymer composition and molecular weight of PLGA as well as of drug type on drug release using a chemical-potential-gradient model. For the cases of the PLGA formulations which obtain sustained drug release, it often takes quite a lot of time to measure the drug release kinetics. Therefore, the accurate correlation and prediction of drug release kinetics from PLGA formulations for a long time as required could save considerable time and costs. This is the other main contribution of this work to the field of drug formulation development.

Conclusions

In this work, the release kinetics of IND and HCT from drug/PLGA formulations with different copolymer composition and molecular weight of PLGA were measured *in vitro* by using a rotating disk system. It was found that the copolymer composition and the molecular weight of PLGA as well as the drug type had obvious influence on drug release kinetics at pH 6.5. Generally, drug release rate was increased from the PLGA with more amount of GA monomer unit and with an increase in PLGA molecular weight.

In addition to that, a chemical-potential-gradient model combined with the PC-SAFT was used to investigate the release mechanism of IND and HCT from their PLGA formulations. This analysis gave a better understanding of the influence mechanism of copolymer composition and molecular weight of PLGA as well as of drug type on drug release. As found in this work, the drug release rates from IND/PLGA and HCT/PLGA formulations were controlled by the release of the excipient PLGA as well as by the surface reaction of the drug. The latter is related to the transport of drug from the PLGA, water penetration into the PLGA and the hydration of the drug and PLGA.

Furthermore, the release kinetics of IND and HCT from the PLGA formulations were correlated and even predicted as function of copolymer composition and molecular weight of PLGAs in a good accordance with the experimental data. It was shown that the chemical-potential-gradient model combined with the PC-SAFT can be used to well correlate and predict the drug release kinetics from PLGA formulations as function of copolymer composition and molecular weight of PLGA. It helps to save time and costs for the long-term drug release kinetics measurement, especially for the sustained drug release as obtained from the drug/PLGA formulations in this work.

Acknowledgments

Literature Cited

1. Wischke C, Schwendeman SP. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. *Int J Pharm*. 2008;364:298–327.

2. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers (Basel)* 2011;3:1377–1397.

3. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Preat V. PLGA-based nanoparticles: an overview of biomedical applications. *J Control Release* 2012;161:505–522.

4. Jain RA. The manufacturing techniques of various drug loaded biodegradable poly(lactide-co-glycolide) (PLGA) devices. *Biomaterials* 2000;21:2475–2490.

5. Corrigan OI, Li X. Quantifying drug release from PLGA nanoparticulates. *Eur J Pharm Sci*. 2009;37:477–485.

6. Zhang Y, Schwendeman SP. Minimizing acylation of peptides in PLGA microspheres. *J Control Release* 2012;162:119–126.

7. Gasmi H, Danede F, Siepmann J, Siepmann F. Does PLGA microparticle swelling control drug release? New insight based on single particle swelling studies. *J Control Release* 2015;213:120–127.

8. Feng SB, Nie L, Zou P, Suo JP. Effects of drug and polymer molecular weight on drug release from PLGA-mPEG microspheres. *J Appl Polym Sci*. 2015;132:41431–41438.

9. Martín-Sabroso C, Fraquas-Sánchez AI, Aparicio-Blanco J, Cano-Abad MF, Torres-Suárez AI. Critical attributes of formulation and of elaboration process of PLGA-protein microparticles. *Int J Pharm*. 2015;480:27–36.

10. Sanna V, Roqqio AM, Pala N, Marceddu S, Lubinu G, Mariani A, Sechi M. Effect of chitosan concentration on PLGA microcapsules for controlled release and stability of resveratrol. *Int J Biol Macromol*. 2015;72:531–536.

11. Gilding DK, Reed AM. Biodegradable polymers for use in surgery-polyglycolic/poly(actic acid) homo- and copolymers: 1. *Polymer* 1979;20:1459–1464.

12. Reed AM, Gilding DK. Biodegradable polymers for use in surgery-poly(glycolic)/poly(lactic acid) homo and copolymers: 2. *In vitro* degradation. *Polymer* 1981;22:494–498.

13. Fredenberg S, Wahlgren M, Reslow M, Axelsson A. The mechanisms of drug release in poly(lactic-co-glycolic acid)-based drug delivery systems-a review. *Int J Pharm*. 2011;415:34–52.

14. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. *Int J Pharm*. 2008;364:328–343.

15. Gasper MM, Blanco D, Cruz ME, Alonso MJ. Formulation of L-asparaginase-loaded poly(lactide-co-glycolide) nanoparticles: influence of polymer properties on enzyme loading, activity and in vitro release. *J Control Release* 1998;52:53–62.

16. Zhu G, Schwendeman SP. Stabilization of proteins encapsulated in cylindrical poly(lactide-co-glycolide) implants: mechanism of stabilization by basic additives. *Pharm Res*. 2000;17:351–357.

17. Wong HM, Wang JJ, Wang CH. In vitro sustained release of human immunoglobulin G from biodegradable microspheres. *Ind Eng Chem Res*. 2001;40:933–948.

18. Bishara A, Domb AJ. PLA stereocomplexes for controlled release of somatostatin analogue. *J Control Release* 2005;107:474–483.

19. Shah SS, Cha Y, Pitt CG. Poly(glycolic acid-co-DL-lactic acid): diffusion or degradation controlled drug delivery? *J Control Release* 1992;18:261–270.

20. Kim HK, Chung HJ, Park TG. Biodegradable polymeric microspheres with "open/closed" pores for sustained release of human growth hormone. *J Control Release*. 2006;112:167–174.

21. Sun Y, Wang J, Zhang X, Zhang Z, Zheng Y, Chen D, Zhang Q. Synchronic release of two hormonal contraceptives for about one month from the PLGA microspheres: in vitro and in vivo studies. *J Control Release* 2008;129:192–199.

22. Mochizuki A, Niikawa T, Omura I, Yamashita S. Controlled release of argatroban from PLA film—effect of hydroxylesters as additives on enhancement of drug release. *J Appl Polym Sci*. 2008;108:3353–3360.

23. Ji YH, Paus R, Prudic A, Lübbert C, Sadowski G. A novel approach for analyzing the dissolution mechanism of solid dispersions. *Pharm Res*. 2015;32:2559–2578.

24. Paus R, Ji YH, Braak F, Sadowski G. Dissolution of crystalline pharmaceuticals: experimental investigation and thermodynamic modeling. *Ind Eng Chem Res*. 2015;54:731–742.

25. Paus R, Prudic A, Ji YH. Influence of excipients on solubility and dissolution of pharmaceuticals. *Int J Pharm*. 2015;485:277–287.

26. Paus R, Hart E, Ji YH. A novel approach for predicting the dissolution profiles of pharmaceutical tablets. *Eur J Pharm Biopharm*. 2015;96:53–64.

27. Prudic A, Ji YH, Sadowski G. Thermodynamic phase behavior of API/polymer solid dispersions. *Mol Pharm*. 2014;11:2294–2304.

28. Prudic A, Kleetz T, Korf M, Ji YH, Sadowski G. Influence of copolymer composition on the phase behavior of solid dispersions. *Mol Pharm*. 2014;11:4189–4198.

29. Prudic A, Lesniak AK, Ji YH, Sadowski G. Thermodynamic phase behaviour of indomethacin/PLGA formulations. *Eur J Pharm Biopharm*. 2015;93:88–94.

30. Prudic A, Ji YH, Luebbert C, Sadowski G. Influence of humidity on the phase behavior of API/polymer formulations. *Eur J Pharm Biopharm*. 2015;94:352–362.

31. Paus R, Ji YH, Vahle L, Sadowski G. Predicting the solubility advantage of amorphous pharmaceuticals: a novel thermodynamic approach. *Mol Pharm*. 2015;12:2823–2833.

32. Paus R, Hart E, Ji YH, Sadowski G. Solubility and caloric properties of cinnarizine. *J Chem Eng Data* 2015;60:2256–2261.

33. Held C, Cameretti LF, Sadowski G. Modeling aqueous electrolyte solutions: part 1. fully dissociated electrolytes. *Fluid Phase Equilib*. 2008;270:87–96.

34. Held C, Sadowski G. Modeling aqueous electrolyte solutions. Part 2. weak electrolytes. *Fluid Phase Equilib*. 2009;279:141–148.

35. Reschke T, Naeem S, Sadowski G. Osmotic coefficients of aqueous weak electrolyte solutions: influence of dissociation on data reduction and modeling. *J Phys Chem B*. 2012;116:7479–7491.

36. Tumakaka F, Sadowski G. Application of the perturbed-chain SAFT equation of state to polar systems. *Fluid Phase Equilib*. 2004;217:233–239.

37. Kleiner M, Gross J. An equation of state contribution for polar components: polarizable dipoles. *AIChE J*. 2006;52:1951–1961.

38. Ji YH, Ji XY, Liu C, Feng X, Lu XH. Modelling of mass transfer coupling with crystallization kinetics in microscale. *Chem Eng Sci*. 2010;65:2649–2655.

39. Lu XH, Ji YH, Liu HL. Non-equilibrium thermodynamics analysis and its application in interfacial mass transfer. *Sci China Chem*. 2011;54:1659–1666.

40. Gross J, Sadowski G. Perturbed-chain SAFT: an equation of state based on a perturbation theory for chain molecules. *Ind Eng Chem Res*. 2001;40:1244–1260.

41. Prausnitz JM, Lichtenthaler RN, de Azevedo EG. *Molecular thermodynamics of fluid-phase equilibria*. Upper Saddle River: Prentice Hall PTR, 1999.

42. Henderson LJ. Concerning the relationship between the strength of acids and their capacity to preserve neutrality. *Am J Physiol*. 1908;21:173–179.

43. Henderson LJ. The theory of neutrality regulation in the animal organism. *Am J Physiol*. 1908;21:427–448.

44. Tirkkonen S, Urtti A, Paronen P. Buffer controlled release of indomethacin from ethylcellulose microcapsules. *Int J Pharm*. 1995;124:219–229.

45. Ward CA, Findlay RD, Rizk M. Statistical rate theory of interfacial transport. I theoretical development, *J Chem Phys*. 1982;76:5599–5605.

46. Ward CA, Rizk M, Tucker AS. Statistical rate theory of interfacial transport. II. Rate of isothermal bubble evolution in a liquid-gas solution. *J Chem Phys*. 1982;76:5606–5614.

47. Dejmek M, Ward CA. A statistical rate theory study of interface concentration during crystal growth or dissolution. *J Chem Phys*. 1998;108:8698–8704.

48. Gross J, Sadowski G. Application of the perturbed-chain SAFT equation of state to associating systems. *Ind Eng Chem Res*. 2002;41:5510–5515.

49. Held C, Reschke T, Mohammad S, Luza A, Sadowski G. ePC-SAFT revised. *Chem Eng Res Des*. 2014;92:2884–2897.

50. Wolbach JP, Sandler SI. Using molecular orbital calculations to describe the phase behavior of cross-associating mixtures. *Ind Eng Chem Res*. 1998;37:2917–2928.

51. Ruether F, Sadowski G. Modeling the solubility of pharmaceuticals in pure solvents and solvent mixtures for drug process design. *J Pharm Sci*. 2009;98:4205–4215.

52. DIN ISO 13528, Statistical methods for use in proficiency testing by interlaboratory comparisons (ISO 13528:2005), DIN Deutsches Institut für Normung e.V. 2009; 98–100.

53. Fuchs D, Fischer J, Tumakaka F, Sadowski G. Solubility of amino acids: influence of the pH value and the addition of alcoholic cosolvents on aqueous solubility. *Ind Eng Chem Res*. 2006; 45:6578–6584.

54. Kestin J, Sokolov M, Wakeham WA. Viscosity of liquid water in the range −8°C to 150°C. *J Phys Chem Ref Data* 1978;7:941–948.

55. Paus R, Ji YH. Modeling and predicting the influence of variable factors on dissolution of crystalline pharmaceuticals. *Chem Eng Sci*. 2016;145:10–20.

56. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int J Pharm*. 2002;231:131–144.

57. Mehta KA, Kislalioglu MS, Phuapradit W, Malick AW, Shah NH. Effect of formulation and process variables on matrix erosion and drug release from a multiunit erosion matrix of a poorly soluble drug. *Pharm Technol*. 2002;2:26–34.

58. Mittal G, Sahana DK, Bhardwaj V, Kumar MNR. Estradiol loaded PLGA nanoparticles for oral administration: effect of polymer molecular weight and copolymer composition on release behavior in vitro and in vivo. *J Control Release* 2007;119:77–85.