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Modeling and analysis of dissolution of paracetamol/Eudragit® formulations

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ABSTRACT

In this work, amorphous paracetamol/Eudragit® formulations for four Eudragit® (polymeric excipients) were prepared by spray drying technique. The simultaneous dissolution kinetics of paracetamol and Eudragit® from these formulations were measured as function of pH in vitro using a rotating disk system (USP II). Paracetamol dissolution mechanisms were analyzed by comparing the dissolution rates of paracetamol and excipient. It was found that a controlled paracetamol dissolution was achieved from Eudragit® L 100-55 and Eudragit® E PO formulations at pH 5.0, 6.5, and 7.2. Furthermore, a controlled paracetamol dissolution was also achieved from Eudragit® L 100 formulations at pH 6.51 and 7.27 as well as from Eudragit® S 100 formulations at pH 7.27. Paracetamol dissolution rates were controlled by both paracetamol and excipient from Eudragit® L 100 and S 100 formulations at other pH values. Moreover, a chemical-potential-gradient model combined with PC-SAFT was used to model the dissolution kinetics of PARA from these formulations in good accordance with the experimental data.

1. Introduction

Controlled drug formulation has been an increasingly important strategy in therapeutic treatment (Giri et al., 2012; Tran et al., 2011). In a controlled drug formulation, the pharmacological effect can be maintained by releasing a drug at a controlled rate for an extended period of time (Tran et al., 2011). Controlled drug formulations often have the advantage of reducing dosing frequency and total dose amount, reducing side effects, achieving a more uniform blood concentration/response and improving therapy and patient compliance/convenience (De Haan and Lerk, 1984). Therefore, controlled drug formulations have attracted great interests and efforts of researchers in recent years. A controlled dissolution of paracetamol (PARA) from amylodextrin tablets was reported by van der Veen et al. (1994). Other controlled drug formulations were also reported, such as hydrophilic and hydrophobic polymeric excipients (Reza et al., 2003; Tiwari et al., 2003; Tran et al., 2011), polymer microspheres (Freiberg and Zhu, 2004), polymer microneedles (Park et al., 2006) and polymer blends (Siepmann et al., 2008). One representative example of polymeric excipients is the application of different types of Eudragit® (Aceves et al., 2000; Higashi et al., 2015; Mehta et al., 2001; Wu et al., 2003). Eudragit® are methacrylic copolymers with various side group compositions (Barea et al., 2012). They are synthetic copolymers combining both mucoadhesive and pH-dependent dissolution strategies (Hua, 2014). It was reported that Eudragit® could be applied to achieve colon-targeted drug dissolution via oral routes of administration (Hua, 2014).

Besides the widespread investigations on designing and manufacturing oral drug/polymer formulations for controlled drug dissolution, few reports interpreting the mechanisms for controlled drug dissolution are available (Tran et al., 2011). In addition to that, as stated by Giri et al. (2012), an accurate description of drug dissolution kinetics by theoretical modeling is particularly important for designing and characterizing controlled drug formulations. Various mathematical models (e.g. the Weibull model (Vudathala and Rogers, 1992), the Higuchi model

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Nomenclature

Roman symbols

a	Activity
a	Helmholtz energy per total particle number, J
A	Surface area of tablet, m^2
c	Concentration, mol/m^3
J	Dissolution rate, $mol/(m^2\ s)$
k_B	Boltzmann's constant $1.38065 \cdot 10^{-23}$ J/K
k_{ij}	Binary interaction parameter
k_t	Rate constant of the whole drug dissolution, $mol/(m^2\ s)$
m^{seg}	Segment number
M	Average molar mass, g/mol
N^{assoc}	Number of association sites
R_{drug}	Drug dissolution order
R	Universal ideal gas constant, J/(mol K)
t	Time, s or min.
T	Temperature, K
V	Volume of media, m^3
x	Mole fraction
Z	Compressibility factor

Greek symbols

γ	Activity coefficient
$\varepsilon^{A_iB_i}/k_B$	Association-energy parameter, K
φ	Fugacity coefficient
ν	Kinematic viscosity, m^2/s
u/k_B	Dispersion-energy parameter, K
$\kappa^{A_iB_i}$	Association-volume parameter
μ	Chemical potential, J/mol
ρ	Density, $mol/Å^3$ or mol/l or kg/m^3
σ	Segment diameter, Å

Subscripts

t or T	Total
i, j, ij	Component indices
0	Pure substance

Superscripts

A_iB_j	Association sites A and B of molecule i
assoc	Association
B	Bulk phase
disp	Dispersion
L	Liquid phase
hc	Hard chain
res	Residual
S	Solid phase
seg	Segment
model	Modeled result
exp	Experimental data

Abbreviations

ARD	Average relative deviation
PARA	Paracetamol
PC-SAFT	Perturbed-Chain Statistical Association Fluid Theory

(Higuchi, 1961, 1963), the Hixson-crowell model (de Almeida et al., 1997; Hixson and Crowell, 1931), the Baker–Lonsdale model (Baker and Lonsdale, 1974), and the Korsmeyer–Peppas model (Korsmeyer et al., 1983), etc.) have already been developed and applied to describe drug dissolution kinetics from controlled formulations. These models are mainly empirical or semi-empirical and their performance of prediction is often limited. Recently, a novel molecular-based chemical-potential-gradient model, was developed and applied to describe and predict drug dissolution kinetics (Ji et al., 2016, 2015; Paus and Ji, 2016; Paus et al., 2015a,b,c).

The purpose of this work was to investigate the drug dissolution kinetics and to interpret the drug dissolution mechanism from drug/Eudragit® formulations. As paracetamol (PARA) is hepatotoxic at high PARA concentration levels (Ammar and Khalil, 1997), it was selected as a model drug. PARA dissolution mechanisms from the PARA/Eudragit® formulations were analyzed at different pH. Furthermore, the chemical-potential-gradient model (Ji et al., 2015) was used to model the PARA dissolution kinetics and the modeled results were compared with the experimental findings.

2. Theory

2.1. Chemical-potential-gradient model

The drug dissolution rate from a drug formulation is defined as

$$J_{drug} = \frac{1}{A} \cdot V \cdot \frac{dc^B_{drug}}{dt} \tag{1}$$

Here A is the surface area of the dissolving drug contacting with the dissolution solution in m^2. For intrinsic dissolution, A is calculated as the base area of the cylindrical tablet and can be regarded as a constant. V is the volume of the dissolution solution in m^3 and c^B_{drug} is the concentration of the drug in the bulk solution in mol/m^3.

The drug dissolution kinetics from a drug/Eudragit® formulation was described by Eq. (2).

$$J_{drug} = k_t \left(\frac{\mu^S_{drug}}{RT} - \frac{\mu^B_{drug}}{RT} \right)^{R_{drug}} \tag{2}$$

where k_t is the rate constant of the whole drug dissolution process in $mol/(m^2\ s)$. R_{drug} is the drug dissolution order. As studied in previous works (Ji et al., 2015; Paus and Ji, 2016; Paus et al., 2015a,b,c), it was suitable to assume R_{drug} as being one as the modeled and predicted results were in good agreement with the experimental data. Therefore, the same R_{drug} value was applied in this work. μ^S_{drug} and μ^B_{drug} are the chemical potentials of the drug in the solid and in the liquid bulk phase in J/mol, respectively. R is the universal ideal gas constant in J/(mol K) and T is the temperature in K.

Based on the phase-equilibrium principles, the chemical potential of the drug in the solid phase μ^S_{drug} equals that in its saturated solution according to Eq. (3).

$$\mu^S_{drug} = \mu^L_{drug} = \mu^L_{0drug} + RT \ln a^L_{drug} \tag{3}$$

Here, μ^L_{drug} and a^L_{drug} are the chemical potential and thermodynamic activity of the drug in its saturated solution, respectively. μ^L_{0drug} is the chemical potential of the drug in the standard state (here the pure component).