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Review

Mechanistic modelling of drug release from polymer-coated and swelling and dissolving polymer matrix systems

Erik Kaunisto[a], Mariagrazia Marucci[b], Per Borgquist[a], Anders Axelsson[a,*]

[a] Department of Chemical Engineering, LTH, Lund University, P.O. Box 124, SE-221 00 Lund, Sweden
[b] AstraZeneca R&D Mölndal, SE-431 83 Mölndal, Sweden

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ABSTRACT

The time required for the design of a new delivery device can be sensibly reduced if the release mechanism is understood and an appropriate mathematical model is used to characterize the system. Once all the model parameters are obtained, *in silico* experiments can be performed, to provide estimates of the release from devices with different geometries and compositions. In this review coated and matrix systems are considered. For coated formulations, models describing the diffusional drug release, the osmotic pumping drug release, and the lag phase of pellets undergoing cracking in the coating due to the build-up of a hydrostatic pressure are reviewed. For matrix systems, models describing pure polymer dissolution, diffusion in the polymer and drug release from swelling and eroding polymer matrix formulations are reviewed. Importantly, the experiments used to characterize the processes occurring during the release and to validate the models are presented and discussed.

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* Corresponding author. Tel.: +46 46 222 3423.
E-mail address: Anders.Axelsson@chemeng.lth.se (A. Axelsson).

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Nomenclature

Symbols

c	concentration (for type see subscript) (kg/m^3)
t	time (s)
x	spatial coordinate × direction (m)
D	diffusion coefficient (for type see subscript and superscript) (m^2/s)
f	factor
F	diffusion coefficient function
$\bar{r}$	dimensionless dissolution velocity
$\bar{t}$	dimensionless time
E	Young's modulus (Pa)
R	gas constant (J/mol/K)
T	temperature (K)
$\hat{V}$	molar volume (m^3/mol)
L	half-thickness of the polymer (or see subscript) (m)
U	function
K	function
G	memory function
k	coefficient/constant
H	Heaviside function
r	spatial coordinate radial direction (or radius) (m)
z	spatial coordinate axial direction (m)
j	flux (kg/m^2/s)
Δc	numerically stable interval (kg/m^3)
Δt	numerically stable interval (s)
n	normal vector
M	molar mass of diffusant (kg/mol)
V	volume (m^3)
A	area (m^2)
m	cumulative absolute amount released (kg)
Z	axial element length (m)
N	volumetric flux between elements (m/s)
s	axial expansion parameter
v	velocity (m/s)
Y	empirical constant
Re	Reynolds number
Sc	Schmidt number
J	volumetric osmotic pumping flow

Greek letters

τ	tortuosity
σ	stress (Pa)
η	normalized spatial coordinate
μ	viscosity/viscosity of the polymer solvent mixture (Pa s)
Π	osmotic pressure (Pa)
λ	numerical constant
δ	see subscript for definition
ρ	density (kg/m^3)
β	concentration dependence parameter
Ω	computational domain (m^2)
χ	Flory's interaction parameter
$(\partial\Omega)_{bnum}$	boundary (m)
κ	solvent shape factor (ranging from 1.5 for rods to 2 for spheres)
α	parameter
υ	Poisson's coefficient (or see subscript)
γ	Flory's exponent for excluded volume
Φ	dissolution term (m/s)
ω	empirical constant
ε	strain

Subscript

1	solvent/diffusant (self-diffusion)
2	polymer (self-diffusion)
12	mutual (solvent/polymer)
v	volume fraction (v/v)
sol	solvent (water) diffusion in the polymer
drug	drug
pol	polymer diffusion in liquid solution
gs	gel–solvent interface (critical value/equilibrium value)
sg	solid–gel interface (threshold value)
front	front
init	initial
coop	cooperative diffusion coefficient
rep	reptation
m	mass transfer coefficient (m/s)
core	core
crys	crystal-unfolding rate (1/s)
a	amorphous
c	crystalline
dis	disentanglement rate (m/s)
w	mass fraction (w/w)
r	radial direction
z	axial direction
gel	gel-layer
lag	lag time
ALE	ALE frame (spatial frame)
b	bound to polymer
pure	in pure solvent
h	hydrodynamic radius of diffusing molecule
e	effective cylindrical radius of a fibre or diffusion coefficient
n	molar fraction (n/n)
o	obstacle
V	average free volume per molecule
VSOL	solvent free volume in the polymer solution
sat	solubility (saturation)
craz	critical for crazing
x, *xx*	*x* direction
g	gel-layer thickness (m)
bnum	boundary number (*bnum* = 1, 2, 3, 4)
screp	screening hydrodynamic interaction parameter
padp	particle dependent parameter
scap	scaling parameter
prop	proportionality factor
tot	total before dissolution
dir	dirac delta function
surf	surface area of device
p	axial discretization index (finite element)/solvent permeability
q	radial discretization index (finite element)
k	index
an	annular element thickness (m)
ON	overall normalized drug concentration
N	normalized drug concentration in the solvent phase
fick	Fickian contribution
caseII	case II contribution
kin	kinetic exponent
∞	infinity (time)
t	time
0	initial (time)
ex	external
in	internal

f	film
part	partition coefficient
coat	coating thickness, (*m*)
refl	reflection coefficient
rel	release medium
mix	flow from release medium into tank
out	flow through pore
pore	pore
poi	Poisson's ratio
diss	dissolved phase
bf	bulk flowing through film
bpore	bulk flowing through pore
d	dissolution rate
*f*0	interface between coating film and internal solution
fh	interface between coating film and external solution
Tank	tank
i	uncoated pellet

Superscript

v	volume-based
es	envelope surface (radial direction)
cs	cross-section (axial direction)
out	external
in	internal
B	bulk
w	solvent (water)
A	drug component
D	diffusive flux
n	empirical constant

1. Introduction

Drug release models can be classified as empirical models or mechanistic models. An empirical approach is based on the experimental behaviour of the system studied. No physical mechanisms are considered in the description of the problem. These kinds of models can often mimic the behaviour of the actual system very well, especially if an appropriate number of parameters are included in the model. However, such a model does not provide any information on the mechanisms that control the process. Consequently, an empirical model cannot be used to predict what effect a change in the conditions, e.g. a change in film thickness of a reservoir system, will have on the release rate. Thus, these models serve the same purpose as any mathematical polynomial with sufficient properties to fit the experimental data. The use of empirical models for simulating drug release profiles is therefore restricted to simple curve-fitting procedures.

Mechanistic drug release models are based on the physical mechanisms that influence the release process. Thus, the model parameters have physical significance, and it is therefore possible to use a mechanistic model to make predictive simulations. However, it is still necessary to confirm the validity of the model against experimental data. In this procedure it is important to validate not only the output of the model, e.g. a release profile, but the values of all the parameters included in the model. This validation is possible because the parameters have physical significance, in contrast to the empirical parameters. Another important issue is to restrict the model to an appropriate level of complexity. A general rule is to identify the rate-limiting processes of the system. This is especially important if the parameter values of the process are unknown and are to be determined from parameter fitting procedures. The more detailed the model description, the more detailed the experimental verification procedure must be. The presentation of the different models should be seen in the light of this leading idea of modelling.

Since 1961, when Higuchi (1961) presented his well-known equation for describing drug release from solid drugs suspended in ointment bases, there have been numerous contributions to empirically and mechanistically model the drug release processes. Several review papers have been published to summarize the drug release models for coated formulations (Siepmann and Siepmann, 2008; Grassi et al., 2007) and for matrices (Siepmann and Siepmann, 2008; Siepmann and Peppas, 2001; Narasimhan, 2001). However, for coated formulations, the discussion of the mathematical models used to describe the processes that occur when the coating is a semi-permeable membrane is not presented. This implies, for example, that the models used to describe the osmotic pumping release from coated formulations or the lag phase for pellets whose coating cracks due to the hydrostatic pressure build-up have not been summarized. Similarly, in the case of matrix systems, the focus has been mostly on models in general and very often only focusing on models including drug release. However, the fundamental basis for understanding drug release from polymer matrix systems is at least twofold, i.e. understanding drug properties and polymer properties. This means that the polymer matrix system should be studied both with and without drug in order to understand the drug release process. Understanding polymer dissolution is therefore vital to be able to design polymer matrix formulations. In earlier reviews of polymer dissolution models and their consequences for drug delivery (Narasimhan, 2001; Miller-Chou and Koenig, 2003) important conclusions from the authors were that an extended knowledge of polymer dissolution is necessary to understand the full applicability of polymers, and that the gap between theoreticians and experimentalists need to be bridged. Several models for polymer dissolution have included parameters that cannot be determined from experiments and numerous experimental results cannot be explained by current theories, thus raising questions regarding their quality.

In this review paper, models for describing the drug release from coated formulations and from swelling and dissolving matrix formulations are presented. Although empirical and mechanistic models are summarized, a special attention was paid to the mechanistic models. The novelty of the part devoted to the coated formulations consists in the description of the models used to describe the lag phase for pellets developing cracks in the coating due to the osmotic pressure build-up, and the drug release by osmotic pumping. A special discussion was presented for the models applied to describe the release from multiple-unit coated systems. Regarding the part devoted to polymer dissolution and polymer matrix formulations, the novelty can be found in the comprehensive presentation of models within these two research fields, since a mechanistic understanding of polymer dissolution plays an integral role in the understanding of polymer matrix formulations. In addition, the importance of experimental data that can help to discriminate between model parameters is discussed.

Moreover, a section was devoted to the experimental characterization of the release mechanism from coated formulations. In the case of polymer dissolution and swelling and dissolving matrix formulations, experimental data for model verification as well as important mechanistic findings are presented.

Due to the huge amount of details and similarities between some models, only relevant equations will be shown/discussed in the text. For specific model details the reader is referred to the original text. Further, the nomenclature in the present work will remain consistent, implying that deviations from the original reference text may occur. Unless stated in the text, the meaning of every symbol occurring can be deduced from the "Nomenclature" section.

2. Coated formulations

2.1. Experimental characterization of the release mechanism

It is fundamental to understand the underlying mechanism of release (i.e. diffusion and/or osmotic pumping) in order to choose the right release model. Drug release occurs by diffusion when the coating is permeable towards the drug investigated. Drug release occurs mainly by osmotic pumping when the film is semi-permeable towards the drug investigated. Unfortunately, models that describe the release by diffusion are often used to fit experimentally determined release data without first ensuring experimentally that the coating film is actually permeable to the drug and that the release occurs by diffusion. This can of course lead to serious errors in the calculations. In order to obtain a complete understanding of the release process, each separate phase of the release must be understood, i.e. the lag phase, the zero-order release phase and the decaying phase. A full understanding of the release mechanisms during the whole release process may be complicated and require several different kinds of experiments. In this section a short summary of the experiments that has been used to characterize the mechanism of release is presented. A more detailed description has been presented by Marucci (2009).

Specially designed dose release experiments can be performed to understand the release process after the lag phase. Diffusional release and osmotic pumping release from coated formulations are often differentiated in an easy and convenient way by performing dose release experiments at different osmotic pressures of the dissolution medium (Zentner et al., 1985; Lindstedt et al., 1989; Ozturk et al., 1990; Verma and Garg, 2004; Marucci et al., 2010). These experiments have been performed also to calculate the fluid permeability of the coating and the diffusion coefficient of the drug in the coating (Zentner et al., 1985; Liu et al., 2007; Marucci et al., 2010). Dose release experiments have been performed at different temperatures to elucidate the state of the coating polymer (i.e. rubbery or glassy) and to explain the change in release mechanism from transport through water-filled pores to transport through the polymer film when the glass transition temperature of the film is higher than the temperature at which release takes place (Frohoff-Hulsmann et al., 1999a).

When the drug delivery device is formulated as a multiple-unit system, the properties of the population of subunits, i.e. the variation of the release-controlling properties, becomes important and will control the overall release characteristics of the device. In some cases erroneous conclusions regarding the release mechanism from multi-particulate formulations can be drawn if only dose experiments are performed (Dappert and Thies, 1978; Hoffman et al., 1986). Hence, in order to properly describe the release characteristics of a multiple-unit system it is appropriate to take into account subunit-to-subunit variations. Single-pellet release has been studied in small vessels and cells (Benita et al., 1988; Jorgensen et al., 1997; Lippold et al., 1999), and in flow-through cells (USP apparatus 4) (Schultz and Kleinebudde, 1997) as well as in an absorbance microplate reader (Folestad et al., 2000; Borgquist et al., 2002, 2004; Marucci et al., 2009b, 2010).

Swelling experiments have been used to study the uptake of water, the mass accumulation inside the pellets and the related hydrostatic pressure build-up during the lag phase, as well as the zero-order release phase and the decaying phase (Schultz and Kleinebudde, 1997; Hjärtstam and Hjertberg, 1998). The accumulation of mass indicates that the coating is semi-permeable to the drug being studied. However, it is not always easy to detect swelling due to the mechanical properties of the coating. Magnetic resonance imaging (Shapiro et al., 1995; Fyfe and Blazek-Welsh, 2000), nuclear magnetic resonance (Ensslin et al., 2008) and electron paramagnetic resonance (Strubing et al., 2007) have been used to study the processes of water uptake and drug dissolution, which can be used to characterize the first step of the release process.

Scanning electron microscopy (SEM) has been widely used to characterize the surface of coated pellets (and in some cases also of free films) and the cross section of the coating, and to crudely identify release paths. Comparison of the coating before and after drug release may help us to understand the effect of the solvent on the coating properties. A sponge-like structure can be observed at the end of the release process in the case of coatings containing leachable substances (Zentner et al., 1985; Marucci et al., 2009b). For formulations coated with a semi-permeable film, the presence of small cracks in the coating at the end of release testifies to the mechanical failure of the coating caused by the swelling of the system due to solvent accumulation (Schultz and Kleinebudde, 1997; Nevsten et al., 2005).

Confocal laser scanning microscopy (CLSM) has been used to measure the film thickness and uniformity of a coated pellet (Haddish-Berhane et al., 2006; Marucci et al., 2009b), and the migration of drug in the coating and explain the unexpected initially high release rate (Felton, 2007).

The leaching of the water-soluble compound from free films and from coating films has been studied to understand the change in the physico-chemical and transport properties of the film during the release (Siepmann et al., 2007; Marucci et al., 2009a,b).

The knowledge of the coating transport properties, i.e. the drug diffusion coefficient in the coating, the water permeability and the drug reflection coefficient, and mechanical properties is fundamental for the description and prediction of the release rate from coated formulation. These parameters can be measured easily in free films. Free films are often used as a convenient model for coating films to explore physico-chemical and mechanical properties and, importantly, how these change from the dry to the wet state (Bodmeier and Paeratakul, 1994; Frohoff-Hulsmann et al., 1999b; Siepmann et al., 2007; Marucci et al., 2009a). Electronic speckle pattern interferometry was used to characterize the nature of free films and made it possible to discriminate between a permeable and a semi-permeable film (Marucci et al., 2006). Special release cells that mimic a coated formulation have been developed (Marucci et al., 2009a, 2006; Okimoto et al., 1999) and free films have also been used to better understand the mechanism of release from coated formulations (Marucci et al., 2006, 2009a) and how these change during the release (Marucci et al., 2009a). Marucci et al. (2009a) developed a release cell equipped with a manometer to measure the pressure build-up inside the cell. The combination of pressure and release data made it possible to easily and accurately characterize the release mechanism from a formulation coated with an ethyl cellulose based film, and how the mechanism changes during the release due to leaching of the water-soluble compound present in the polymer film (Marucci et al., 2009a).

2.2. Modelling of drug release from polymer coated systems

As already described in Section 1, the models can be classified into empirical and mechanistic. In this section a review of the empirical models is presented. Among the mechanistic model, a review of the following models is presented: models that describe drug release by diffusion, models that describe drug release by osmotic pumping and diffusion, models that describe the lag phase for formulations coated with a film undergoing cracking due to the hydrostatic pressure build-up inside the pellet.

2.2.1. Empirical models

Much work has historically been devoted to fitting empirical relations to drug release data from reservoir as well as matrix systems (Ritger and Peppas, 1987; Jorgensen, 1996; Narasimhan et al., 1999; Korsmeyer et al., 1983). The power law equation presented

by Korsmeyer et al. and Ritger and Peppas was originally developed to describe the release from matrix systems, but it has also been applied to curve fitting of reservoir systems (Ritger and Peppas, 1987; Narasimhan et al., 1999):

$$\frac{m_t}{m_\infty} = Y \cdot t^n, \tag{1}$$

where m_t is the amount released and m_∞ is the amount of drug released over an infinite time. Y and n are empirical constants and t is time.

Jorgensen and co-workers developed the "order model", an empirical expression for the release from single, film-coated pellets and ensembles of film-coated pellets (Jorgensen and Christensen, 1996; Jorgensen, 1996; Jorgensen et al., 1997):

$$\frac{m_t}{m_\infty} = 1 - [1 - Y \cdot (1-n)(t - U(t_{init}))]^{1/(1-n)}, \tag{2}$$

where the function, U, allows for exponential behaviour during the lag phase:

$$U(t_{init}) = t_{init}\left(1 - \exp\left(-\frac{t}{abs(t_{init})}\right)\right) \tag{3}$$

These kinds of models, Eqs. (1) and (2), are very successful in fitting drug release profiles – perhaps an obvious statement as the empirical constants n and Y are not based on any physical mechanism. It can be questioned whether the information gained from simple curve fitting increases our knowledge of the release process. The values of the empirical constants can, of course, help us see how release occurs (zero-order, etc.), but gives us very limited information about why it occurs.

2.2.2. Diffusion models

Diffusional mass transfer through the polymer membrane may take place in the (pure) polymer phase and/or in solvent-filled pores or cracks in the membrane (Langer and Peppas, 1983; Good and Lee, 1984; Siegel, 1989; Narasimhan et al., 1999). Therefore, a truly mechanistic description of the transport through a polymer film must include information on numerous important film-properties, e.g. the solute diffusion coefficients in the polymer phase, the solute diffusion coefficient in the water phase, partitioning, porosity, and pore size distribution, see Fig. 1.

Simple models have been derived based on the identification of the transport through the polymer film as the rate-limiting step in the release process. These models, although simple, are based on a solid mechanistic approach as opposed to the empirical models. Assuming that the rate limitation of the drug release is transport through the film, and that the system is at steady state, results in the following expression for a spherical device (Langer and Peppas, 1983; Good and Lee, 1984; Narasimhan et al., 1999):

$$m_t = \frac{4\pi \cdot r_{ex} \cdot r_{in} \cdot D \cdot k_{part} \cdot \Delta c}{r_{ex} - r_{in}} \cdot t \tag{4}$$

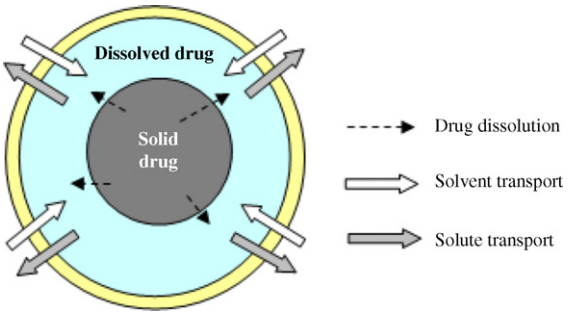

Fig. 1. Schematic picture of drug release from reservoir systems (in this case a film-coated pellet).

where r_{ex} is the external and r_{in} is the internal radius of the reservoir, D is the diffusion coefficient of the drug in the polymer, k_{part} is the partition coefficient and Δc is the concentration difference over the membrane. The use of Eq. (4) is valid when the coating is homogeneous. For heterogeneous coatings, the overall release is affected by the diffusion coefficient and partition coefficient of each phase present in the coating, including obstruction and exclusion effects. Instead of determining these parameters for each phase and the geometry of the different phases, it is convenient to use an effective diffusion coefficient, D_e, which is a lumped parameter that characterizes the transport properties across the film and the partitioning between the water phase and the coating. The driving force for the release can still be written as the difference in the drug concentration across the coating. Eq. (4) only applies in the case of a constant concentration difference, i.e. as long as a saturated solution exists inside the device and if perfect sink conditions are fulfilled. Furthermore, the dissolution rate of the solid drug (if the device is loaded above the drug solubility) is assumed to be rapid, and the external mass transfer resistances are neglected. Therefore, simulations using Eq. (4) are only applicable for the zero-order part of the release profile. The lag time of reservoir systems cannot be described with this model if a constant D_e is assumed, as pointed out by several researchers (Langer and Peppas, 1983; Good and Lee, 1984; Narasimhan et al., 1999). The lag time was explained as the unsteady-state behaviour of the device during the initial phase of the release process, when the concentration gradient is developing. This may be true for the lag time observed for devices with thick polymer films. However, reservoir systems with very thin polymer films can also have substantial lag times.

2.2.3. Single unit

The steady-state film approach has also been used in modelling the release of fertilizers from latex-coated urea balls (Lu and Lee, 1992; Lu and Chen, 1993; Lu and Yu, 1994; Lu, 1994). The models were evaluated against experimental release data from single film-coated urea balls. The first model presented could simulate the release from an initially saturated solution in the core to a less than saturated solution during the declining phase (Lu and Lee, 1992). Dissolution was assumed to be rapid and external mass transfer resistances were neglected. Non-perfect sink conditions were modelled. The model was extended in a further study to include diffusion in the core for the case of unsaturated cores (Lu and Chen, 1993), and to include fast initial release rates due to solid drug in the film (Lu and Yu, 1994; Lu, 1994). Since the polymer film is fairly thick (about 200–400 μm on a 15 mm urea core) it is reasonable to assume that the lag phase in this case is due to film dynamics as discussed above. The effect of the initial conditions in the film on the release profile, i.e. lag phase or fast initial release, was studied later (Lu and Chen, 1995).

The drug release from chitosan-coated tablets, where the film itself dissolves during the release process, has also been modelled using a steady-state film approach (Koizumi et al., 2001). Perfect sink conditions and fast dissolution of the solid drug were assumed, and the external mass transfer hindrances were neglected. The model was fitted to experimental release data. The excellence of the fit is not surprising since the number of fitted model parameters were as many as five, including the lag time.

The release from film-coated matrix systems, i.e. a combination of a reservoir and a matrix system, has been modelled by Lee and co-workers (Lee and Liao, 1995; Liao and Lee, 1997; Chen and Lee, 2001, 2002). The main focus of their studies was the effect of deformations in the coating on the release rate. Unsteady-state diffusion in the matrix core and in the coating was included in the model. The concentration in the matrix was assumed to be less than the saturation concentration, and external mass transfer resistances were neglected. Furthermore, perfect sink conditions were

assumed. It was concluded that the deviation from spherical particles could have a significant effect on the concentration profiles and/or the release rates from different parts of the particle surface. No experimental verification of these detailed models was performed. Recently Haddish-Berhane et al. (2006) developed a rigorous model for drug release from coated (ion-exchange) pellets taking non-uniformities in the coating thickness into account. A Monte Carlo approach was employed for the model simulations and the simulated release curves were found to agree well with experiments performed.

Liu and co-workers studied the release from a coated matrix system where the drug was dispersed in and coated with Eudragit® (Liu et al., 1988). An unsteady-state model was developed taking into account drug and solvent diffusion in the core and film. The diffusivities of the drug and of the solvent are assumed to be concentration-dependent. The diffusivities were obtained by fitting the model to experimental release data from a multiple-unit system. Good agreement with the experimental data was obtained. However, as the experimental study was restricted to a multiple-unit system, it cannot be ruled out that subunit-to-subunit variation could have resulted in erroneous fitting of the parameters.

2.2.4. Multiple unit systems

Several approaches to model the release from film-coated multiple-unit systems have been presented in the literature. A statistically based procedure for modelling diffusional release from multiple-unit systems was introduced by Dappert and Thies (1978), who discussed the relation between release profiles of single-unit and multiple-unit systems. A model for the release from single subunits was derived for an arbitrary geometry based on the assumption of steady-state conditions in the film. In "the general population model" the assumption of "uncoupled" subunit release decreases the complexity of the model to a summation process. The model predicts that, with zero-order release subunits, the release from the multiple-unit system can follow first-order kinetics, depending on the distribution of the release parameters. The model was not verified against experimental data. Gross et al. (1986) further developed the statistical model of Dappert and Thies to allow for a statistical correlation between the parameter that governs the fractional release function and the total single-unit drug loading. It was claimed that the cumulative release kinetics of a multiple-unit system does not characterise the basic release mechanism, which can only be determined from studies on individual units. Donbrow et al. (1988) continued the work of Gross et al. by discussing the possibility of a single-unit lag time, as well as the resulting sigmoid multiple-unit release curve.

A statistical model for the release of fertilizers from polymer-coated granules was presented by Shaviv et al. (2003a). The model is based on a mechanistic model of diffusional release from single granules (Shaviv et al., 2003b), where they modelled the release of urea from single film-coated controlled-release fertilizers. Two possible release mechanisms were presented, the traditional diffusion mechanism and a failure mechanism. Failure of the coating is assumed to occur if the internal pressure exceeds the resistance of the membrane. This results in instantaneous release of the contents of the unit. However, only the diffusion mechanism was considered in their model. The model consists of three stages, a lag phase, a zero-order phase and a declining phase. During the lag phase the release rate is zero. The transport during the zero-order phase was modelled according to Fick's first law. Rapid dissolution kinetics and perfect sink conditions were assumed, and the external mass transfer resistances were neglected. The zero-order phase continues as long as a saturated solution exists in the core. The model was verified against experimental release data from spherical and non-damaged single film-coated granules. It was confirmed that the release rate depends inversely on the product of the granule radius and the coating thickness. The population of coated granules was assumed to have variations only in geometrical factors, i.e. granule radius and coating thickness. Model simulations were performed for populations, varying the granule radius and the coating thickness distributions. The effect of different parameter distributions on the release profile was studied for normally distributed, log-normally distributed, uniformly distributed and polynomially distributed parameters (core radius and film thickness). The model simulations were compared to experimental release data showing good agreement. However, the parameter distributions of the actual experimental population were not determined.

A mechanistically derived model for the release from multiple-unit systems has been presented by Sirotti et al. (2002). They modelled the release from ensembles of ethyl-cellulose-coated theophylline particles, and the phenomena included in the model were dissolution of the solid core and steady-state diffusion through the coating to a non-perfect sink. The population of subunits was modelled in 22 classes having different core radius and film thickness. The model was based on the assumption that the drug loading fraction is independent of subunit size, resulting in a simple relation between subunit size and film thickness. The model was successfully fitted to experimental release data. However, the predictive strength of the model needs to be confirmed since fitting was only performed to the initial part of the release profile, i.e. the zero-order part.

Borgquist et al. (2002), introduced a model for release of remoxipride from ethyl cellulose coated pellets. The model takes into account dissolution of solid material, boundary layer diffusion (based on empirical mass transfer correlations), unsteady state diffusion through the polymer film, and non-sink conditions. The shrinking drug core is modelled as a diffusion-limited dissolution process (Noyes and Whitney, 1897):

$$\frac{dr_{core}}{dt} = -\frac{k_{core} \cdot \Delta c_{core}}{\rho_{core}} \tag{5}$$

The coefficient k_{core}, was assumed to follow an empirical boundary layer correlation (Eq. (6), stationary film hindrance) implying that the coefficient value will increase as the core becomes smaller:

$$k_{core} = \frac{D}{r_{core}} \cdot (1 + 0.3 \cdot Re^{0.5} \cdot Sc^{0.33}) \tag{6}$$

The diffusion in the polymer film was assumed to be Fickian:

$$\frac{\partial c_f}{\partial t} = D_f \cdot \left(\frac{2}{r} \cdot \frac{\partial c_f}{\partial r} + \frac{\partial^2 c_f}{\partial r^2} \right) \tag{7}$$

Flux boundary conditions taking into account stationary film hindrance was employed at both film interfaces. The solution inside the drug pellet was modelled as a mixed tank. Outside the pellet, in the bulk phase, a similar expression was used, implying that non-sink conditions were taken into account. The model was used to simulate the release of remoxipride from EC-coated pellets (approximately size 1 mm in diameter, film thickness corresponding to 40–90 mg coating/g pellet). Model parameters (core radius and film thickness) were fitted to single-subunit release data, keeping the film diffusion coefficient constant. In Fig. 1, a schematic picture of drug release from reservoir systems (in this case a film-coated pellet).

In Fig. 2 the release profiles and model simulations for pellets coated with 70 mg polymer/g pellet are shown, using Eqs. (5)–(7). The fitted film thickness (Fig. 3) shall be viewed as an effective measure of the transport properties, coupled to the Fickian description of the film transport. It is reasonable to assume that the true film thickness will show a Gaussian distribution, hence the deviation from normality shown in Fig. 3 is an indication that other mechanisms than film diffusion are involved in the release process (e.g.

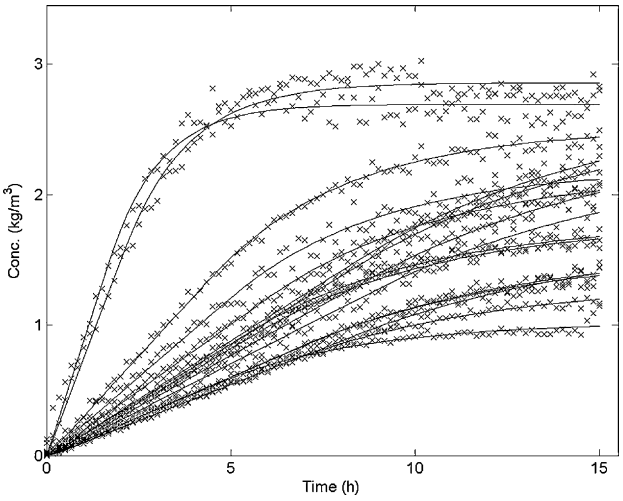

Fig. 2. Experimental data and simulated release profiles. 70 mg coating/g drug.

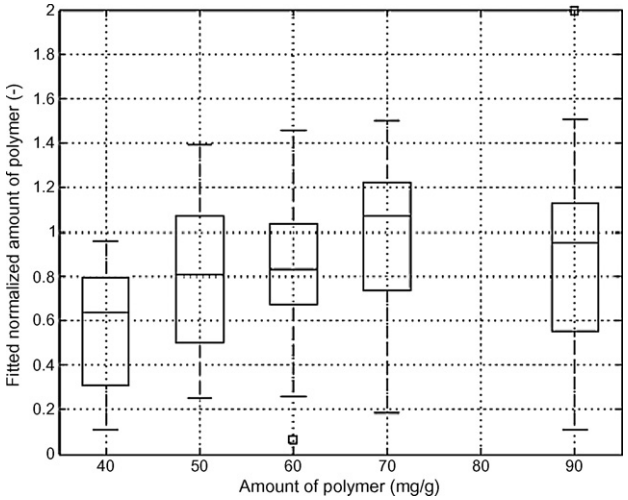

Fig. 4. The fitted film amount (normalized) as a function of the theoretical amount polymer.

osmotically driven release through cracks and defects in the film). The probability of a defect coating is naturally increased for lower amount of coating used. This is also indicated from Fig. 4, where the fitted film thickness, normalised to the theoretical amount, is plotted against the theoretical values of applied coating (i.e. a value of 1 corresponds to a perfect match between the theoretical amount and the fitted value). The deviation is largest for the lower coating levels tested (40–60 mg/g). As it was shown that the film phase reaches stationary conditions fairly quickly, the distributed diffusion expression (Eq. (7)) can be simplified with a lumped parameter without loosing much accuracy. Therefore, the model complexity was reduced in a later work (Borgquist et al., 2004) by exchanging the unsteady state diffusion expression for the film phase into a film mass transfer coefficient. The model was fitted to single-unit release data and used to perform dose release predictions with good results. Fig. 5 illustrates the small variation in dose release profiles that results from a large variation in single-unit release profiles.

Frenning et al. (2003) developed a model for release of salicylic acid from EC-coated pellets. The model included expressions for liquid inflow, drug dissolution and drug diffusion through the polymer film. The granular core was considered to be porous and homogeneous, allowing for a lumped dissolution expression. Three rate constants (related to liquid inflow, drug dissolution and drug diffusion, respectively) were successfully fitted to experimental multiple-unit data, and also the initial lag phase in the experimental data is fairly adequately described by the simulation results. The results therefore could be seen as an indication that liquid influx and drug dissolution is also rate limiting to the release process, and that the release rate is not solely determined by film diffusion. On the other hand, as the parameter fit was performed against multiple-unit data, it is possible that the determined values for the rate constants unintentionally include statistical measures. If so, the physical meaning of the fitted values is somewhat decreased.

Petitti et al. (2008) developed a model for a film coated microparticle based on initial water penetration, rapid drug dissolution and perfect mix in the drug core, and unsteady state diffusion through the polymer coating. System characteristics were examined in a sensitivity analysis but no experimental verification was performed. In a follow up paper the model was modified to include expression for hindered pore diffusion, as well as to include effect from the microcapsule size distribution (Petitti et al., 2009). A simplification compared to the original model is that the initial core solution is assumed to be saturated, i.e. no effect from the inlet water penetration is considered. The model was verified with good

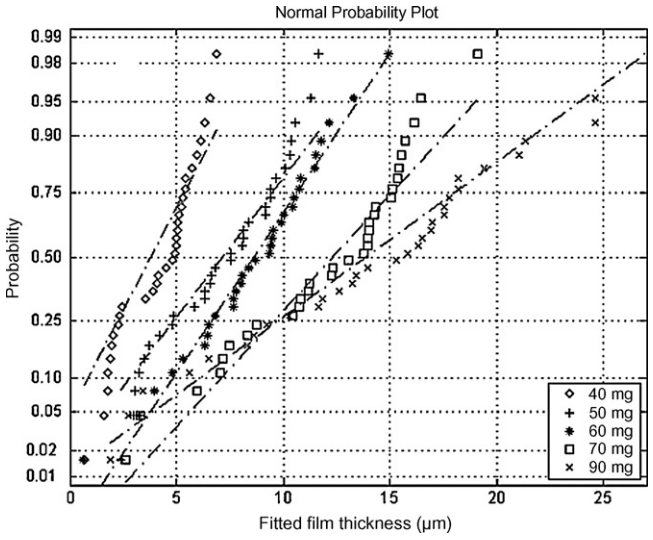

Fig. 3. The fitted film thickness for 40-90 mg polymer/g drug in a normal probability plot.

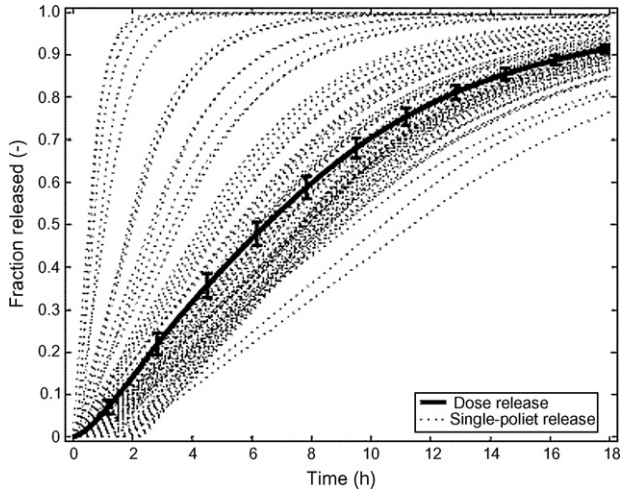

Fig. 5. Average dose simulation (bold) of 100 simulations with 95% confidence interval (bars), and fitted single-pellet simulations (dotted lines, corresponding to the single-pellet experiments performed).

agreement to experimental data for the release of vancomycin from PCL microcapsules. However, as only data points at two different times (in addition to the zero value) were used for model evaluation, it is reasonable to suggest performing additional verification work in order to prove model validity.

The aim of these aforementioned studies was often to calculate D_e by tuning the model to fit the experimental data. However, as the calculations were based on dose release data (Sirotti et al., 2002; Frenning et al., 2003) or on the average size and coating thickness of the sub-unit (Borgquist et al., 2002; Borgquist et al., 2004), the calculated D_e is an averaged parameter. Consequently, as there are differences between the pellets release and the pellets size and coating thickness, the accuracy of D_e is compromised. In some cases the calculated D_e may not have a physical meaning.

Marucci et al. (2009b) have improved the accuracy of the calculation of D_e in a recently presented work. Single-pellet release data were used in the calculations and, uniquely, the pellet size and coating thickness of the pellets used in the single-pellet release experiments were measured using a laser scanning confocal system and a light microscope, respectively. Thus, the value of D_e was not an average value but was truly characteristic of the coating of each individual pellet. The most important advantages of this are: (1) the possibility of accurately studying the homogeneity of the transport properties of the coating on different pellets, and (2) the possibility of relating D_e to the coating thickness for each pellet. In this work, the release profile and mechanism of metoprolol succinate pellets coated with a blend of 70% of a water-insoluble polymer, ethyl cellulose (EC), and 30% of a water-soluble polymer, hydroxypropyl cellulose (HPC), was studied. The release profiles of the single pellets had a sigmoidal shape, i.e. were characterized by an initial lag phase with no or marginal drug release, followed by rapid release (see Fig. 6). The film coating was initially not permeable to metoprolol succinate, the lag time was found to be dependent on the film coating thickness and release started only after a critical amount of the HPC had been leached out. Drug release occurred through the pores created in the coating by the HPC dissolution. As the leaching of the water-soluble polymer makes the film to change from being semi-permeable to permeable, it is probable that release occurs initially by osmotic pumping and diffusion. However, as it was found that diffusion soon became the dominant release mechanism for films made of EC and HPC with 30% HPC when a water-soluble drug is used (Marucci et al., 2009a) a diffusive model could be properly used to describe the release. The effect of HPC leaching on the transport properties of the film was quantitatively characterized. The model developed by Borgquist et al. (2004) was used to fit the experimental data and to calculate the D_e of the drug in the coating. D_e was the only parameter tuned in the model as

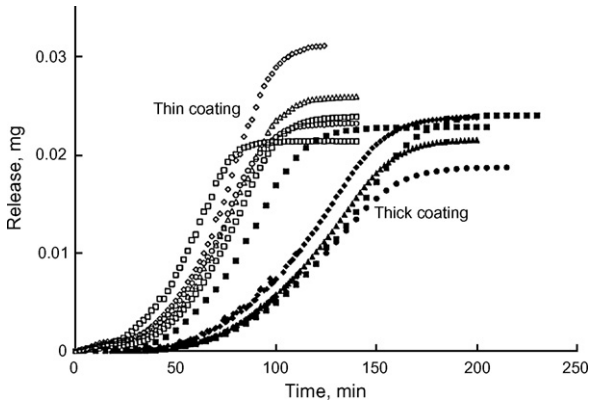

Fig. 6. Single-pellet release profiles.

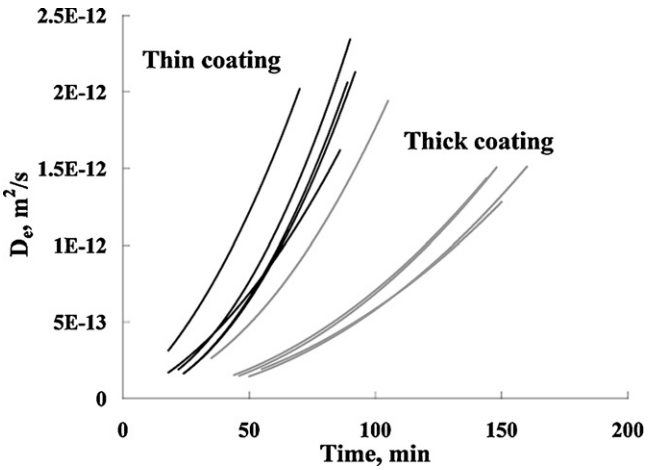

Fig. 7. Calculated effective diffusion coefficient, D_e, of metoprolol succinate in the coating of individual pellets.

each pellet had been characterized in terms of size and film coating thickness before the release experiments. The calculated values of the effective diffusion coefficients are plotted in Fig. 7. D_e increased significantly during release due to an increase in the amount of HPC leached and the consequent increase in the coating porosity. Interestingly, D_e increased more rapidly for pellets coated with a thinner film. This can be explained by the decrease in HPC leaching rate with greater coating film thickness. This finding is quite important, since it implies that the release rate from pellets coated with a blend of polymers, one of which is water-soluble, is not linearly dependent on the inverse o the coating thickness during the whole release period. The effective diffusion coefficient of the drug in the coating was rather homogeneous for pellets having the same coating thickness. This similarity reflects the similarity in the film structure and the pore formation process when the pellets are immersed in the release medium. The accurate calculation of D_e requires the combination of the modelling technique with many experiments. However, it is essential to quantitatively characterize the transport properties of the coating especially for coatings containing a leachable polymer.

2.3. Release by osmotic pumping and diffusion

When describing the release process in (a) pellets coated with a semi-permeable film containing a sufficient amount of a leachable substance to create channels of limited volume during release and (b) pellets coated with a semi-permeable film undergoing cracking in a way that channels of limited volume are formed, it is important to differentiate between the processes taking place during the lag phase, i.e. before channels are created, and those that take place after the lag phase. Assuming that the coating is perfectly semi-permeable, i.e. it is not permeable to the drug, the processes that occur during the lag phase are: inflow of solvent, driven by the difference in osmotic pressure across the coating, dissolution of the solid drug, swelling of the pellet due to mass accumulation, and the build-up of hydrostatic pressure inside the pellet. During the lag phase, the release from a pellet coated with a perfectly semi-permeable film, is zero. The lag phase ends when one or more channels are formed.

The processes that occur after the lag phase are: inflow of solvent, driven by the difference in osmotic pressure across the coating, dissolution of the solid drug, outflow of the drug solution, driven by the difference in hydrostatic pressure across the channels in the coating, and, finally, release of the drug by osmotic pumping and diffusion. Fig. 8 shows a schematic illustration of the main

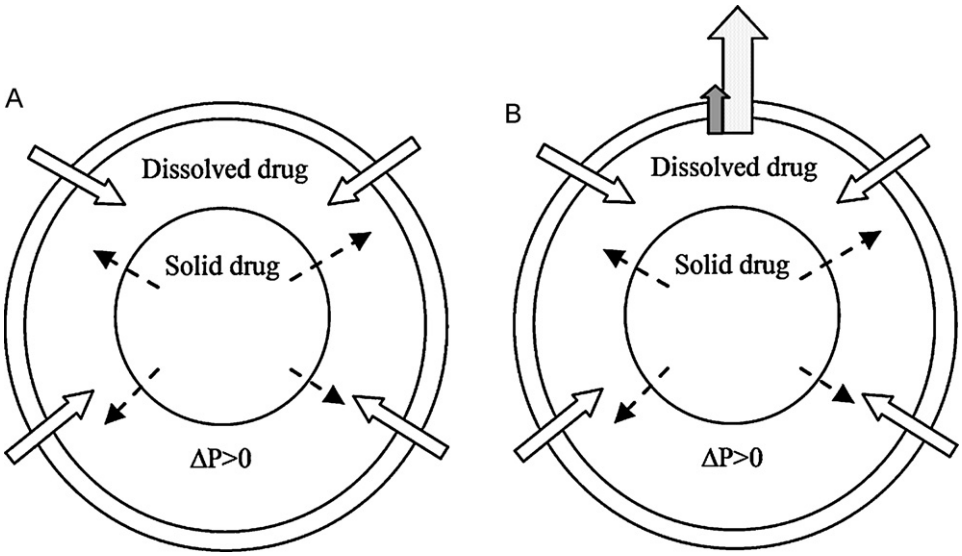

Fig. 8. Schematic illustration of the drug release process occurring during the lag phase (A) and after the lag phase (B). ⇨, diffusive transport of the solvent; ⟹, convective transport of the drug solution, - - →, dissolution of the drug; ⇨, diffusive transport of the drug.

processes occurring during the lag phase and once channels (one is shown in the figure) are created.

Despite the fact that osmotic pumping plays a fundamental role in oral modified-drug release formulations, surprisingly few studies have been published on the modelling of drug release by osmotic pumping, and, consequently, the field has not been included in the reviews of mathematical modelling of drug release (Grassi et al., 2007; Siepmann and Siepmann, 2008). This may be because drug release by osmotic pumping is a more complicated process than drug release by diffusion from pellets coated with a permeable film, as phenomena such as hydrostatic pressure build-up inside the formulation and formulation swelling take place. Moreover, the theoretical calculation of the tensile stress distribution across the coating of a tablet can be an extremely difficult task. However, for a spherical geometry, the relationship between the hydrostatic pressure and the tensile stress is known.

The studies published to date have usually been aimed at describing the drug release rate during the zero-order release phase and during the decaying phase (Theeuwes, 1975; Zentner et al., 1985; Marucci et al., 2007). The description of the solvent uptake and, consequently, of the drug release, have been based on the irreversible thermodynamics theory (Theeuwes, 1975). The pressure build-up, which affects the water uptake, is usually neglected also due to the already mentioned difficulties in calculations for non-spherical formulations. This is often acceptable at steady state and during the decaying phase as, during these phases, the difference in hydrostatic pressure across the coating is usually much smaller than $\Delta\prod$. The drug release rate, from a formulation containing only solid and dispersed drug, is thus expressed as:

$$\frac{dm}{dt} = \frac{L_p}{\delta_{coat}} \cdot A \cdot k_{refl} \cdot \Delta\Pi \cdot c_{diss} \tag{8}$$

where A, δ_{coat}, L_p and k_{refl} are the area, the thickness, the solvent permeability and the reflection coefficient of the coating, respectively, and c_{diss} is the drug concentration in the dispensed liquid inside the formulation. The model can be easily adapted to describe in a similar way also the release from formulations containing a push layer (Swanson et al., 1987) by taking into account the surface of each layer present in the formulation and the effect of the degree of hydration of the polymer present in the push layer on the difference in osmotic pressure across the coating. In this simplified description of the release process, variables such as the pressure build-up, pellet swelling and the drug concentration profile inside the pores/cracks are not considered. However, it is necessary to model these variables to fully understand the importance of osmotic pumping in relation to diffusional release through pores and cracks, and the effects of the area of the pores/cracks, the coating thickness and pellet size on the drug release mechanism and release rate.

A more complicated mechanistic model of drug release by osmotic pumping and diffusion from pellets coated with a semipermeable film developing pores of limited volume was developed by Marucci et al. (2010). The model describes all the release phases and all the processes listed above were modelled. The main assumptions made were that the pellets were spherical, with a coating of a uniform thickness, and that the coating is ideally elastic and deformations took place according to Hooke's law. The equations reported in that work were based on the assumption that only one pore is created. However, the model can easily be implemented to account for the formation of different pores at different times. As the coating was not permeable to the drug, the release started only once a pore was formed. The drug release rate was described as:

$$\frac{d(V_{rel} \cdot c_{rel})}{dt} = (J_{mix} + J_{out}) \cdot c_t - J_{mix} \cdot c_{rel} \tag{9}$$

where V_{rel} is the volume of the release medium, c_{rel} the drug concentration in the release medium, J_{out} the volumetric osmotic pumping flow through the pore, c_t the drug concentration in a small well mixed tank which is assumed to be located at the end of the pore and J_{mix} the flow from the release medium into the tank. The tank was assumed in order to derive the boundary condition at the outside of the coating. J_{out} was written according to:

$$J_{out} = \frac{L_{p,pore}}{\delta_{coat}} \cdot A_{pore} \cdot \Delta P \tag{10}$$

where A_{pore} is the area of the pore, $L_{p,pore}$ is the water permeability of the pore and ΔP is the hydrostatic pressure difference across the coating. Assuming the pore to have a constant radius, r_{pore}, $L_{p,pore}$ can be derived from the Poiseuilles equation if the flow inside the pore is laminar and can be written as:

$$L_{p,pore} = \frac{r_{pore}^2}{8 \cdot \mu} \tag{11}$$

where μ is the viscosity of the drug solution. The pressure difference across the coating is zero at the beginning of the release experiment. A hydrostatic pressure is built up inside the pellet due

to the accumulation of mass and pellet swelling, and a tensile stress acts on the coating due to the resistance of the coating to swell. For spherical geometry, the pressure inside the pellet is related to the growth in the radius, Δr, according to Eq. (12).

$$\Delta P = \frac{E((\Delta r)/(r_{init}/1-\upsilon))\cdot 2\cdot \delta_{coat}}{r} \quad (12)$$

In Eq. (12) E is the modulus of elasticity of the coating, υ is the Poisson coefficient of the coating, r is the radius of the coating and r_{init} is the radius of the pellet at time zero. In order to solve the problem, the total mass balance for the whole pellet before and after pore formation, the drug mass balance in the dissolved phase within the pellet before and after pore formation, the drug mass balance in the pore, the drug mass balance and in the tank, and the boundary conditions at the end of the pore and the initial conditions need to be added. Here only the mass balances after pore formation is reported. For a complete description of the mathematical problem, the reader is referred to the original paper. Assuming planar geometry, the total mass balance for the whole pellet after pore formation was written as:

$$\rho_{core}\frac{dV_{core}}{dt} + \rho_{core}\frac{dV_{diss}}{dt} + V_{diss}\frac{d\rho_{diss}}{dt} = \rho_{bf}\frac{L_p}{\delta_{coat}}\cdot(4\cdot\pi\cdot r_i - A_{pore}) \times (k_{refl}\cdot\Delta\Pi - \Delta P) - \rho_{bpore}\frac{L_{p,pore}}{\delta_{coat}}\cdot A_{pore}\cdot\Delta P \quad (13)$$

where V_{core} is the volume of the solid core, V_{diss} is the volume of the dissolved phase inside the coated pellet, ρ_{core}, ρ_{bpore} and ρ_{diss} are the densities of the solid core, of the bulk flowing through the pore and of the dissolved phase inside the pellet, respectively. The first term on the right-hand side of Eq. (13) is the diffusive flow from the release medium into the dissolved phase inside the pellet through the coating film. The second term on the right-hand side of Eq. (13) is the convective osmotic pumping flow from the dissolved phase inside the pellet into the release medium through the pore and is equal to zero during the lag phase. The mathematical expression for the two flows was derived from irreversible thermodynamics theory (Mulder, 1991).

After pore formation, the drug mass balance in the dissolved phase inside the pellet was written as follows:

$$V_{diss}\cdot\frac{dc_{diss}}{dt} + c_{diss}\cdot\frac{dV_{diss}}{dt} = ,4\cdot\pi\cdot r_{core}^2\cdot k_d\cdot(c_{sat}-c_{diss}) - J_{out}\cdot c_{pore}\Big|_{x=x_{f0}} + A_{pore}\cdot D\cdot\frac{\partial c_{pore}}{\partial x}\Big|_{x=x_{f0}} \quad (14)$$

where D_{drug} is the diffusion coefficient of the drug in an aqueous solution, k_d is the dissolution rate constant, c_{diss} is the drug concentration in the dissolved phase within the pellet, c_{sat} is the drug concentration at the solid surface, and is assumed to be at saturation, the subscript $f0$ denotes the position at the interface between the coating and the internal solution, and $c_{pore}\big|_{x=x_{f0}}$ is the drug concentration inside the pore at the interface between the coating film and the internal solution.

The mass balance in a pore was written as follows:

$$A_{pore}\cdot\frac{\partial c_{pore}}{\partial t} = A_{pore}\cdot\frac{\partial}{\partial x}\left(D\cdot\frac{\partial c_{pore}}{\partial x}\right) - J_{out}\cdot\frac{\partial c_{pore}}{\partial x} \quad (15)$$

The mass balance in the tank was written as:

$$V_{Tank}\frac{dc_{Tank}}{dt} = J_{out}\,c_{pore}\Big|_{x=x_{fh}} - A_{pore}D\,\frac{\partial c_{pore}}{\partial x}\Big|_{x=x_{fh}} - J_{out}\cdot c_{Tank} + J_{mix}c_{rel} - J_{mix}c_{tank} \quad (16)$$

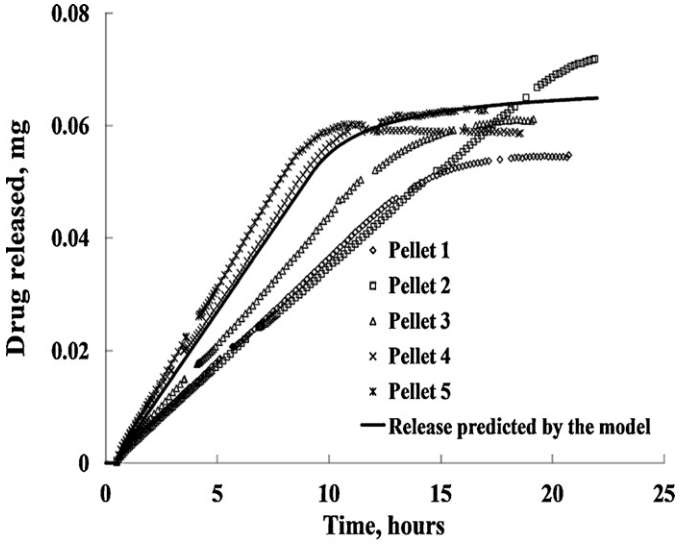

Fig. 9. Comparison between the release profile predicted by the model for an average coated pellet and experimental single-pellet release profiles. The experimental data were translated in time so that the release started after 30 min to simplify comparison of the release profiles.

where V_{Tank} is the volume of the tank and c_{Tank} the drug concentration inside the tank.

The boundary condition on the inside of the pore at the interface with the internal dissolved phase is:

$$c_{pore}\Big|_{x=x_{f0}} = c_{diss} \quad (17)$$

The model was validated by comparison with the release profile of single metoprolol succinate pellets coated with a film made of ethyl cellulose and hydroxypropyl cellulose (80:20). This system was chosen as it was shown that the release mechanism was osmotic pumping, and that the release occurred through small pores created in the coating by hydroxypropyl cellulose (HPC) leaching. Single-pellet release data were used for the model validation instead of dose release data, as the dose release profile was not representative of the release of an average pellet, due to the large variations in the lag phase of individual pellets. The model is rather complex and many parameters are required. However, all of them were either measured or were deduced from values found in the literature and average values were used for the geometric input of the model. As the model is not able to calculate the lag time associated with the time necessary for a channel to be created, which is itself related to the dissolution of HPC, a lag time of 30 min was assumed in the model and the release profiles of the single pellets obtained experimentally were translated in time to enable a comparison between the predicted and the experimental profiles. It should be pointed out that no parameter fitting was performed and that the simulated release shown in Fig. 9 is based only on measured parameters. The good agreement found between the predicted release and the experimental data confirmed the validity of the model and its prediction capacity. The model can also be used to simulate variables that are difficult or impossible to measure, e.g. the pressure build-up, water uptake and drug concentration profile in the channel. Some of the model outputs are shown in Fig. 10. The water influx reaches a maximum almost instantly and then decreases, although the concentration of the dissolved phase inside the pellet, as well as the difference in osmotic pressure across the coating, are both constant. The decrease in the water influx can be explained by the rise in pressure inside the pellet caused by the accumulation of mass (see Fig. 10). The opening of the pore allows the convective out-

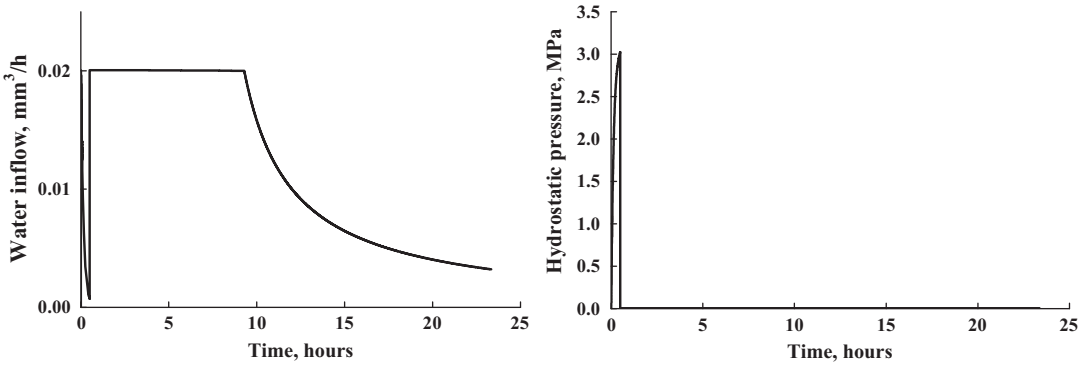

Fig. 10. Some of the model outputs. (A) Water inflow profile; (B) hydrostatic pressure build-up.

flow of the drug solution from the coated pellet into the release medium. The pressure drops after 30 min to a value close to zero, as shown in Fig. 10, and the water inflow increases again. The water inflow starts to decrease again as the solid drug inside the pellet is completely dissolved and the drug concentration in the dissolved phase inside the pellet decreases. A very low pressure after the creation of a pore was sufficient to allow convective flow through the pore.

2.4. Lag time for pellets developing cracks in the coating due to hydrostatic pressure-build-up

Delayed release systems are often coated with a film developing cracks due to the hydrostatic pressure build-up. The film is a semi-permeable film without drilled holes neither a sufficient amount of leachable substance for pores to be created. The main processes that occur during the lag phase are: the inflow of solvent, driven by the difference in osmotic pressure across the coating, dissolution of the drug, the release of the drug by diffusion, resisted by the inward convective flow of solvent, swelling of the pellet due to mass accumulation, the build-up of hydrostatic pressure inside the formulation, and finally, the cracking of the coating when the tensile stress acting on the coating is equal to the tensile strength. Fig. 11 shows a schematic illustration of the major processes occurring during the lag phase.

Only a few modelling studies have been published in this field; some of them on pellets and others on tablets. For a spherical geometry, the relationship between the hydrostatic pressure and the tensile stress is known. However, the theoretical calculation of the tensile stress distribution across the coating of a tablet is an extremely difficult task.

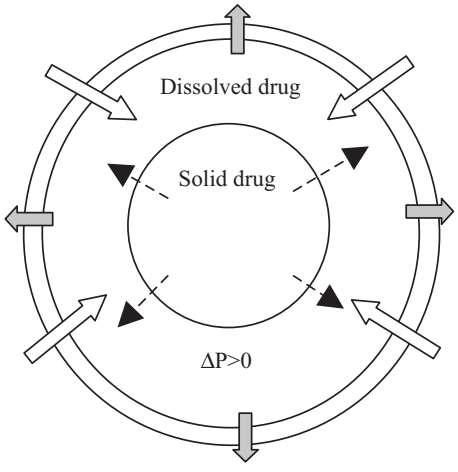

Fig. 11. Schematic illustration of the drug release process. ⇨, Diffusive transport of the solvent; ⇒, diffusive transport of the drug; - - →, dissolution of the drug.

Already in 1991, Kuethe et al. (1992) developed a model to calculate the lag time for a coated capsule whose coating cracks due to hydrostatic pressure build-up. The transport equation for the water uptake is basically that of irreversible thermodynamics, despite the fact that the reflection coefficient of the coating is not considered. The authors assumed that the core contained only a dissolved phase, and that the concentration inside the core was at saturation, thus the model cannot be applied to pellets with a dissolving solid core. However, the model includes rigorous treatment of the water uptake process, as it considers the effect of the pressure increase on the water transport, and of the tensile stresses acting on the coating, which is described using solid mechanics theory. The authors described the process as a function of two non-dimensional parameters, and estimated the lag time as a function of the pellet radius and coating thickness. Unfortunately, the model was not validated with experimental data. Surprisingly, the models developed afterwards for pulse release suffered from the fact that hydrostatic pressure was not included in the calculation of the water uptake.

Hartman Kok et al. (2001) modelled the lag time for a multiparticulate delayed-release system coated with an EC-based film. The lag time was predicted from the knowledge of the maximum extension of the coating at fracture and, thus, from the maximum increase in the volume. The water uptake was described using the Stefan-Maxwell approach. However, no information was given on how the strain in the coating was calculated. Moreover, the fact that the pressure rise influences the water uptake was not considered.

Shaviv et al. (2003a,b) presented a model to describe the lag time for spherical pellets. The lag time was related to the maximum amount of water acceptable inside the coated pellet. Also in this case the effect of the hydrostatic pressure build up on the water uptake was not considered.

Zhu and Zheng (2005) presented a model to predict the lag time for tablets containing a swelling core. However the model does not give a mechanistic description of the processes occurring. The prediction was based instead on an semi-empirical parameter, an apparent diffusion coefficient of water in the coating. This parameter was calculated using a simplified equation and is therefore dependent not only on the transport properties of the film but also on the swelling behaviour of the tablet and on the mechanical properties of the film.

Marucci et al. (2008) developed a model which all the processes occurring during the lag phase listed above. The main assumptions employed in the model are: the pellets are spherical or ellipsoidal, with a coating of a uniform thickness, the coating is ideally elastic and deformations take place according to Hooke's law, and the transport properties of the coating are uniform over the whole surface of the pellet before the formation of a crack in the coating.

Planar geometry was assumed and the total mass balance for the whole pellet was written as:

$$\rho_{core}\frac{dV_{core}}{dt}+\rho_{diss}\frac{dV_{diss}}{dt}+V_{diss}\cdot\frac{d\rho_{diss}}{dt}=\rho_{bf}\cdot\frac{L_p}{\delta_{coat}}\cdot 4\cdot\pi\cdot r_i^2\times(k_{refl}\cdot\Delta\Pi-\Delta P) \quad (18)$$

The term in the right-hand side of Eq. (18) is the net bulk flow through the coating and has been derived from irreversible thermodynamics theory (Mulder, 1991). As $\Delta P < k_{refl}\ \Delta\prod$, during the lag phase there is a net in-flow from the release medium around the pellet into the pellet, causing it to swell. The amount of drug in the dissolved phase inside the pellet is $V_{diss}c_{diss}$, and the mass balance in the dissolved phase was written as follows:

$$V_{diss}\cdot\frac{dc_{diss}}{dt}+c_{diss}\cdot\frac{dV_{diss}}{dt}=4\pi r_{core}^2\cdot k_d\cdot(c_{sat}-c_{diss})-\left[\frac{D_e}{\delta_{coat}}\cdot 4\pi r_i^2\cdot(c_{diss}-c_{rel})-\frac{(c_{diss}+c_{rel})}{2}\cdot(1-k_{refl})\cdot J_v\right] \quad (19)$$

where D_e is the effective diffusion coefficient of the drug in the coating, J_v is the net inward volumetric bulk flow through the coating, and c_{rel} is the drug concentration in the release medium.

The mass balance for the release medium was written as:

$$\frac{d(V_{rel}\cdot c_{rel})}{dt}=\frac{D_e}{\delta_{coat}}\cdot 4\cdot\pi\cdot r_i^2\cdot(c_{diss}-c_{rel})-\frac{(c_{diss}+c_{rel})}{2}\cdot(1-k_{refl})\cdot J_v \quad (20)$$

The pressure difference across the coating, ΔP, is zero at the beginning of the release experiment. A hydrostatic pressure is built up inside the pellet due to the accumulation of mass and pellet swelling, and a tensile stress acts on the coating due to the resistance of the coating to swelling. For spherical geometry, it can be shown from solid mechanics theory that the stress acting in the circumferential direction and that acting in the radial direction are identical, and are not dependent on the position of the element on the surface of the pellet. The pressure inside the pellet is related to the tensile stress of the coating according to Eq. (21).

$$\Delta P=\frac{\sigma\cdot 2\cdot\delta_{coat}}{r_i} \quad (21)$$

The tensile stress, σ, can be correlated to the strain in the coating of the pellet, ε. For a spherical pellet the following relationship is valid.

$$\sigma=E\cdot\frac{\varepsilon}{1-\upsilon} \quad (22)$$

In Eq. (23) E is the modulus of elasticity of the coating and υ is the Poisson coefficient. The strain in the coating, ε is geometrically related to the increase in the radius of the sphere, Δr_i.

$$\varepsilon=\frac{\Delta r_i}{r_{i,init}} \quad (23)$$

where $r_{i,init}$ is the radius of the uncoated pellet at time zero. If planar geometry cannot be assumed, Eq. (23) must be modified (Bodelind and Persson, 1999).

Remoxipride pellets coated with a film made of EC and triethyl citrate were used to validate the model that describes the lag phase of pellets developing cracks on the coating (Marucci et al., 2008). This system was chosen as it has been shown that the film was semi-permeable to the coated drug (Marucci et al., 2007), that the pellets swelled during the lag phase (Zackrisson, 1993) and that the hydrostatic pressure built up inside the pellet was responsible of the microcracks present in the film at the end of the release experiments (Nevsten et al., 2005). It was considered convenient to use the dose-release profile, average pellet size and average film thickness data for model validation. The choice was dictated by the fact that one of the major parameters used in the model, the tensile strength of the coating film, was not known. If the model had been validated using single-pellet release data, accurate measurements of the coating thickness and the size and shape of the pellets used would have been required, which is rather demanding. Moreover, for geometries other than spherical and ellipsoidal ones, the relationship between the pressure build-up and the tensile stress on the coating is not straightforward. The use of dose-release data has the disadvantage that the fitted parameters are averaged over the whole population, which in some cases may mean that they have no physical meaning. However, the assumption of a spherical shape is less inaccurate when applied to several hundred pellets that are not perfectly spherical but differ in, hopefully, compensating ways, than when considering only one pellet. Almost all the model parameters were obtained experimentally or from values reported in the literature, and the only two fitted parameters were the drug effective diffusion coefficient and the tensile strength. The fact that the two fitted parameters control different parts of the release curve means that they are not correlated to each other and they can be fitted simultaneously. The tensile strength determines the lag time, and the effective diffusion coefficient determines the release rate. The more important of the two parameters is the tensile strength, as this determines the duration of the lag phase. Both the effective diffusion coefficient and the tensile stress would have physical meaning if they had been deduced from single-pellet release data, but do they still have a physical meaning when deduced from dose-release data? The effective diffusion coefficient will probably not. However, importantly, the tensile strength obtained from dose-release data obtained from pellets with different coating thicknesses were basically the same. Moreover, when the model was used to predict the lag time of pellets immersed in release medium with different osmotic pressures, the agreement between the predicted value and the experimental results was very good. This means that the tensile strength obtained from dose-release data was representative of the system under study.

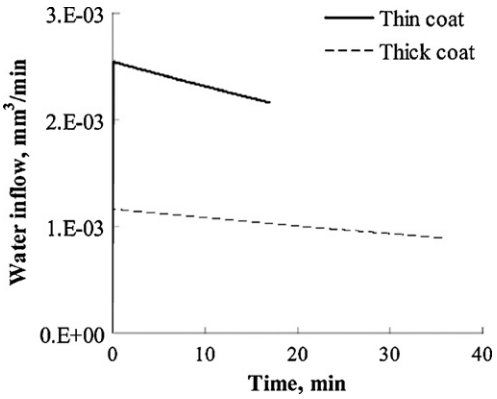

Fig. 12. Water in-flow simulated with the model for pellets with coatings of different thicknesses.

Importantly, the model can be used to investigate how the drug formulation performs during the lag phase. For example, the water inflow calculated for the pellets having different film thickness is given in Fig. 12. The model can also be used to study the effect of the pellet radius and coating thickness on the lag time (see Fig. 13).

3. Modelling of polymer dissolution and swelling and dissolving matrix formulations

3.1. Dissolution of amorphous glassy polymers

The dissolution process of an amorphous polymer in a solvent involves three important mechanisms, namely solvent diffusion,

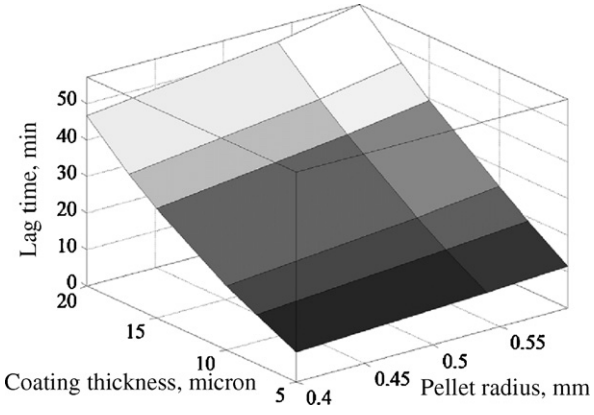

Fig. 13. Prediction of lag time for pellets with different radii and coating thicknesses.

chain disentanglement and solvent-induced polymer plastization. Due to the latter a gel-layer is formed, creating two distinct interfaces between the glassy polymer and the gel-layer (solid-gel interface) and the gel-layer and the solvent (gel–solvent interface). One of the earliest contributors to outline this process was Ueberreiter (1968). The mechanism proposed was an initial solvent penetration pushing the swollen polymer into the direction of the solvent followed by the formation of a dilute upper layer which is further pushed into the solvent. The solvent penetration increases the size of the gel-layer until a quasisteady state is reached where the transport of polymer molecules into the solution balances gel formation, preventing a further increase in the gel-layer. The structure of the polymer was summarized according to Fig. 14:

The layers pictured in Fig. 14 constitute a common qualitative foundation for the construction of mathematical models describing amorphous glassy polymer dissolution. Many existing models differ only in the lumping of layers and complexity of transport and kinetics assumptions involved in the dissolution process. Models for amorphous polymer dissolution have previously been classified into four categories (Narasimhan, 2001; Miller-Chou and Koenig, 2003):

(i) Models based on phenomenology and Fickian equations (Tu and Ouano, 1977; Devotta et al., 1994; Ranade and Mashelkar, 1995; Vrentas and Vrentas, 1998; Chirico et al., 2007).
(ii) Models in which external mass transfer limits dissolution (Lee and Peppas, 1987; Lee and Lee, 1991).
(iii) Models based on stress-relaxation (Brochard and de Gennes, 1983; Herman and Edwards, 1990).
(iv) Anomalous transport models and scaling laws for chain disentanglement (Papanu et al., 1989; Peppas et al., 1994; Narasimhan and Peppas, 1996).

Tu and Ouano (1977) developed one of the first models describing the kinematics of polymer dissolution. The model was based on two Fickian diffusion processes in the gel-layer and the liquid-layer, respectively, combined with an equation for the moving gel–solvent interface. Importantly, a parameter describing the dissociation rate of the polymer molecules from the gel–solvent interface was included, and thus, the dissolution process could be dissociation controlled if diffusion is faster than dissociation and diffusion controlled in the opposite case. The model also utilized the now more common assumption of a constant critical (equilibrium) polymer/solvent concentration at the gel–solvent interface (Lee and Peppas, 1987; Papanu et al., 1989; Lee and Lee, 1991; Peppas et al., 1994; Narasimhan and Peppas, 1996; Chirico et al., 2007), which is a defined property for a given polymer. Further, a continuity condition at the solid–gel interface at a threshold water concentration was assumed.

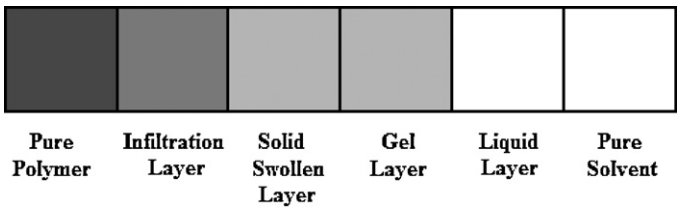

Fig. 14. . Schematic picture of amorphous polymer structure during dissolution.

Diffusion in the polymer according to Tu and Ouano (1977), Eq. (24):

$$\frac{\partial c_{2,v}}{\partial t} = D_{sol}\frac{\partial}{\partial x}\left[f_{sol}(c_{2,v})c_{2,v}\frac{\partial c_{2,v}}{\partial x}\right] \tag{24}$$

Diffusion of dissolved polymer in the liquid solution according to Tu and Ouano (1977), Eq. (25):

$$\frac{\partial c_{2,v}}{\partial t} + \frac{\partial x_{gs}}{\partial t}\frac{\partial c_{2,v}}{\partial x} = D_{pol}\frac{\partial}{\partial x}\left[f_{pol}(c_{2,v})\frac{\partial c_{2,v}}{\partial x}\right] \tag{25}$$

Velocity of the gel–solvent interface according to Tu and Ouano (1977), Eq. (26):

$$\frac{\partial x_{gs}}{\partial t} = D_{pol}f_{pol}(c_{2,v})\frac{\partial c_{2,v}}{\partial x}\bigg|_{x=x_{gs}^{-}(t)} - D_{sol}\frac{\partial c_{2,v}}{\partial x}\bigg|_{x=x_{gs}^{+}(t)} \tag{26}$$

Continuity condition at the solid–gel interface, according to Tu and Ouano (1977), Eq. (27):

$$\left[f_{sol}(c_{2,v})\frac{\partial c_{2,v}}{\partial x}\right]_{x=x_{sg}^{-}(t)} = \left[f_{sol}(c_{2,v})\frac{\partial c_{2,v}}{\partial x}\right]_{x=x_{sg}^{+}(t)} \tag{27}$$

The model was verified against front position data for the dissolution of a polystyrene (PS) film in methyl ethyl ketone (MEK). It was concluded that the kinematics of polymer dissolution depend highly on the concentration dependence of the diffusion coefficient of solvent in the polymer.

Lee and Peppas (1987) developed a model for prediction of polymer dissolution. A Fickian's equation was used to describe the solvent transport in the polymer. The movement of the solid–gel interface was limited by the diffusion flux at a threshold solvent concentration controlled by the thermodynamic characteristics of the transport phenomenon. Further, the movement of the gel–solvent interface was based on the solvent diffusion flux and mass transfer limited polymer dissolution at a critical polymer concentration. However; by assuming a steady state assumption, i.e. that the solvent concentration can be expressed as a linear function of distance after a certain time the model was simplified and an approximate expression for the gel-layer thickness as a function of time could be derived.

Diffusion in the polymer according to Lee and Peppas (1987), Eq. (28):

$$\frac{\partial c_{1,v}}{\partial t} = \frac{\partial}{\partial x}\left[D_1^v\frac{\partial c_{1,v}}{\partial x}\right] \tag{28}$$

Velocity of the solid–gel interface according to Lee and Peppas (1987), Eq. (29):

$$D_1^v\frac{\partial c_{1,v}}{\partial x} = c_{1,v}\frac{\partial x_{sg}}{\partial t} \tag{29}$$

Velocity of the gel–solvent interface according to Lee and Peppas (1987), Eq. (30):

$$D_1^v\frac{\partial c_{1,v}}{\partial x} - k_{2,m}c_{2,v,gs} = (c_{1,v} + c_{2,v})\frac{\partial x_{gs}}{\partial t} \tag{30}$$

Approximate gel-layer thickness according to Lee and Peppas (1987), Eq. (31):

$$\delta_g \approx \sqrt{\frac{2(2-c_{1,v,sg})(c_{1,v,sg}-c_{2,v,gs})D_1^v t}{(1-c_{1,v,sg})L_{init}^2}} \tag{31}$$

The model was verified against gel-layer thickness literature data for PS in MEK, poly methyl methacrylate (PMMA) in MEK and two mixed tablets of mixed polymers. The first tablet consisted of 50 wt% phenylpropanolamine–HCl, 25 wt% poly vinyl alcohol (PVA), 25 wt% poly N-vinyl-2-pyrrolidone whereas the second tablet consisted of 40 wt% mannitol, 10 wt% PVA and 50% of a hydrophilic low molecular weight drug. The analyzed systems all showed the same behaviour in gel-layer thickness as predicted by the model.

Papanu et al. (1989) developed models describing polymer dissolution by accounting for both Fickian and Case II diffusion mechanisms. Reptation theory was used to scale the disentanglement rate with the polymer molecular weight and solvent concentration, where the latter could be obtained by using thermodynamics of swollen networks. Two different expressions for the movement of the gel–solvent interface for slow and fast external mass transfer were also assumed. In the Case II model the movement of the solid–gel interface was limited by a critical stress level for crazing and the actual stress which is a function of the osmotic pressure which in turn, according to the Flory–Huggins theory, is a function of the solvent concentration.

Diffusion in the polymer according to Papanu et al. (1989), Eq. (32):

$$\frac{\partial c_{1,v}}{\partial \bar{t}} = (1-c_{1,v})F(c_{1,v})\frac{\partial^2 c_{1,v}}{\partial x^2} + \left(\frac{\partial c_{1,v}}{\partial x}\right)^2 \times \left[(1-c_{1,v})\frac{dF}{dc_{1,v}} - F(c_{1,v})\right] \tag{32}$$

Velocity of the gel–solvent interface according to Papanu et al. (1989), Eqs. (33) and (34):

Mass transfer limited analysis:

$$\frac{d\eta_{gs,x}}{d\bar{t}} = \left.\frac{\partial c_{1,v}}{\partial \eta}\right|_{\eta_{gs,x}^-} + \left.\frac{\partial(1-c_{1,v})}{\partial \eta}\right|_{\eta_{gs,x}^+} \tag{33}$$

Dissolution limited analysis:

$$\frac{d\eta_{gs,x}}{d\bar{t}} = \left.\frac{\partial c_{1,v}}{\partial \eta}\right|_{\eta_{gs,x}} - \bar{r} \tag{34}$$

Case II penetration at the solid–gel interface according to Papanu et al. (1989), Eq. (35):

$$\frac{dx_{sg}}{d\bar{t}} = -f_{front}(\sigma - \sigma_{craz}) \tag{35}$$

The model was verified against dissolution data for PMMA in methyl isobutyl ketone (MIBK), using the Case II model. It was concluded that the model can predict dissolution rates if the critical stress for crazing is function of molecular weight. However; the dependence of penetration rate at low molecular weights needs to be investigated further.

Peppas et al. (1994) proposed a mathematical model describing polymer dissolution based on an anomalous transport model together with a disentanglement mechanism. In this model a "dissolution clock" was used to define a polymer disentanglement time i.e. a characteristic time for a point in the gel-layer at the threshold gel concentration to disentangle and dissolve, thus controlling the movement of the gel–solvent interface. The polymer disentanglement time was used to develop scaling laws for the gel-layer thickness and the dissolution rate. A dissolution number was also defined as the ratio between the polymer disentanglement time and the solvent diffusion time and was found to be proportional to the square of the gel-layer thickness. Narasimhan and Peppas (1996) later extended this model to account for relaxational mechanisms (solid–gel interface) and divided the concentration field into three different regimes with three different transport processes, using distinct changes in the solvent diffusion coefficient. A semi-empirical expression for the kinetics at the solid–gel interface, as earlier proposed by Astarita and Sarti (1978), was used.

Diffusion in the polymer according to Narasimhan and Peppas (1996), Eqs. (36) and (37):

$$\frac{\partial c_{1,v}}{\partial t} = \frac{\partial}{\partial x}\left[D_{12}\frac{\partial c_{1,v}}{\partial x}\right] + \frac{\partial}{\partial x}\left[\frac{D_{12}\hat{V}_1}{RT(1-c_{1,v})(1-2\chi c_{1,v})}\frac{\partial \sigma_{xx}}{\partial x}\right] \tag{36}$$

$$\frac{\partial \sigma_{xx}}{\partial t} = -\frac{\sigma_{xx}}{(\mu/E)} + \frac{E}{(1-c_{1,v})^2}\frac{\partial c_{1,v}}{\partial t} \tag{37}$$

Diffusion of dissolved polymer in the liquid solution according to Narasimhan and Peppas (1996), Eq. (38):

$$\frac{\partial c_{2,v}}{\partial t} = \frac{\partial}{\partial x}\left[D_{pol}\frac{\partial c_{2,v}}{\partial x}\right] - \frac{\partial x_{gs}}{\partial t}\frac{\partial c_{2,v}}{\partial t} \tag{38}$$

Velocity of the gel–solvent interface according to Narasimhan and Peppas (1996), Eq. (39):

$$\frac{\partial x_{gs}}{\partial t} = v_{1,x} - \frac{D_{pol}}{c_{1,v}^-}\left(\frac{\partial c_{2,v}}{\partial x}\right)^+ \tag{39}$$

Velocity of the solid–gel interface according to Narasimhan and Peppas (1996), Eq. (40):

$$\frac{\partial x_{sg}}{\partial t} = f_{prop}\left(c_{1,v}\big|_{x=x_{sg}} - c_{1,v,sg}\right)^{f_{kin}} \tag{40}$$

The original model (Peppas et al., 1994) was verified against front position data for PS in MEK and PMMA in MEK. For PS in MEK the model was able to predict the dissolution behaviour for a wide range of molecular weights of PS. Interestingly, there was no visible gel-layer for the case of PMMA in MEK, but instead small cracks at the interface. Thus, it was concluded that PMMA dissolves by crack propagation. This result is similar to that of Papanu et al. (1989) for dissolution of PMMA in MIBK. Regarding the extended model (Narasimhan and Peppas, 1996), simulations were performed with relevant thermodynamical and structural parameters for dissolution of PS in MEK, but the model was never verified against experimental data.

Brochard and de Gennes (1983) developed a model for the kinetics of polymer dissolution. The model described the dissolution of a semi-dilute droplet of polymer immersed in pure solvent by using a transport equation based on the osmotic pressure of the polymer solution, a viscoelastic equation for the stress based on a memory function and the osmotic pressure and scaling laws restricted to semi-dilute solutions. It was found that at times much shorter than the polymer reptation time the dissolution was limited by swelling described by a cooperative diffusion coefficient. However; at finite times of the order of the reptation time the dissolution was controlled by the viscous yield of the polymer network, assuming that the osmotic pressure was equal to the stress, i.e. swelling equilibrium. Thus, it was concluded that there exists an optimal droplet size for fast dissolution defined by a characteristic length. Droplets larger than the characteristic length implied swelling controlled dissolution whereas droplets below the characteristic length implied reptation controlled dissolution. Herman and Edwards (1990) later extended the model proposed by Brochard and de Gennes (1983) by considering in detail the

stress that accompanies the swelling of the polymer. More specifically two contributions to the chemical potential, i.e. mixing due to osmotic pressure gradients and an orientational contribution induced by the swelling process are examined. It was concluded that when the orientational contribution is much larger than the osmotic mixing terms the system undergoes a phase separation into a gel-phase and a dilute solution phase, where the presence of a gel-phase may lower the dissolution rate.

Polymer transport equation according to Brochard and de Gennes (1983), Eqs. (41) and (42):

$$\frac{\partial \Pi}{\partial t} = U_{coop}(\Pi)\frac{\partial}{\partial x}\left[K_{coop}(\Pi)\frac{\partial}{\partial x}(\Pi - \sigma)\right] \tag{41}$$

$$D_{coop} = U_{coop}K_{coop} \tag{42}$$

Viscoelastic equation according to Brochard and de Gennes (1983), Eq. (43):

$$\sigma(x,t) = -\lambda^{-1}\int_{-\infty}^{t} G(t-t')\frac{\partial \Pi}{\partial t'}(x,t')dt' \tag{43}$$

Characteristic drop length according to Brochard and de Gennes (1983), Eq. (44):

$$l = \left[D_{coop}t_{rep}\right]^{0.5} \tag{44}$$

The models proposed by Brochard and de Gennes (1983) and Herman and Edwards (1990) were used for theoretical discussions, but were not compared to experimental data for verification.

Based on the findings of Brochard and de Gennes (1983) and Herman and Edwards (1990), Devotta et al. (1994) developed a model to investigate the dissolution time for a polymer particle in a hydrodynamic field. The model was based on a spherically symmetric Fickian's transport equation for the solvent in the polymer, including a convective contribution from the swelling rate. The movement of the gel–solvent interface was based on the swelling due to solvent ingress and the dissolution of polymer chains at the surface. The solid–gel interface was neglected, assuming rapid glass transition kinetics. Polymer dissolution was limited by either the disengagement rate or the mass transfer through the liquid-layer, where the latter could be estimated from a Sherwood correlation based on the terminal velocity of the particle.

Diffusion in the polymer according to Devotta et al. (1994), Eq. (45):

$$\frac{\partial c_{1,v}}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D_{sol}\frac{\partial c_{1,v}}{\partial r}\right) - \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 c_{1,v}D_{sol}\frac{\partial c_{1,v}}{\partial r}\right) \tag{45}$$

Velocity of the gel–solvent interface according to Devotta et al. (1994), Eq. (46):

$$\frac{\partial r_{gs}}{\partial t} = \left(D_{sol}\frac{\partial c_{1,v}}{\partial r}\right)_{r=r_{gs}^{-}} - \left(\frac{D_{pol}}{c_{2,v,gs}}\frac{\partial c_{2,v}}{\partial r}\right)_{r=r_{gs}^{+}} \tag{46}$$

The model was verified by fitting the gel–solvent interfacial concentration and the polymer disengagement rate against experimental data for dissolving PS particles in cyclohexane. It was concluded that the model was able to define a lower limit to which a polymer particle should be reduced to dissolve optimally and that this size (to some extent) can be increased by an increased stirring rate. Further reduction of a particle does not affect the dissolution time.

3.2. Dissolution of semi-crystalline polymers

Unfortunately the attempts to model semi-crystalline polymer dissolution have been quite few although there has been a lot of experimental work dedicated to the subject. However, Mallapragada and Peppas (1996) were able to propose a dissolution mechanism based on experimental observations. The mechanism was based on the idea that the crystals formed by folding of the polymer chains were assumed to unfold in the presence of solvent, thereby joining the amorphous portion around them. The idea was later refined into a mathematical model describing crystal unfolding and chain disentanglement during semi-crystalline polymer dissolution (Mallapragada and Peppas, 1997a). In this model the polymer was assumed to be in the rubbery state, i.e. the rubbery transition kinetics is very fast compared to the dissolution kinetics. Thus, the three components in the system were the solvent, the amorphous portion of the polymer and the crystalline portion of the polymer. The rate of change of the crystalline portion was assumed to follow a first order reaction with respect to the solvent concentration where the rate constant was obtained from free energy considerations. The transport of amorphous polymer was described by a Fickian's transport equation and the movement of the gel–solvent interface was governed by the solvent diffusion flux and the dissolution rate. Further, dissolution of the amorphous portion was only allowed if there were no crystals present at the gel–solvent interface.

Diffusion in the polymer according to Mallapragada and Peppas (1997a), Eq. (47):

$$\frac{\partial c_{2,v,a}}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial c_{2,v,a}}{\partial x}\right) + k_{crys}c_{1,v}H(c_{2,v,c}) \tag{47}$$

Velocity of the gel–solvent interface according to Mallapragada and Peppas (1997a), Eq. (48):

$$\frac{\partial x_{gs}}{\partial t} = -\left(D\frac{\partial c_{1,v}}{\partial x}\right)_{x=x_{gs}} - k_{2,dis}c_{2,v,a}\delta_{dir}(c_{2,v,c}) \tag{48}$$

Rate of change of the crystalline portion according to Mallapragada and Peppas (1997a), Eq. (49):

$$\frac{\partial c_{2,v,c}}{\partial t} = -k_{crys}c_{1,v}H(c_{2,v,c}) \tag{49}$$

The model was verified against dissolution data for PVA in water, by assuming a uniform crystal size, and it was concluded that the dissolution process exhibited Case II behaviour due to the presence of crystals. However; to investigate the effects of crystal size distribution on dissolution, Hassan et al. (2000) used a similar model to describe the dissolution kinetics of freeze/thawed PVA hydrogels. It was predicted that large crystals are extremely important in the overall stability of PVA gels due to their slow dissolution kinetics.

Many models describing polymer dissolution are limited to polymer films or slabs and restricted to one spatial dimension. These simplifications may sometimes be justified depending on the purpose of the study. However; within the field of controlled drug delivery it is necessary to study whole dissolving tablets in order to obtain proper mechanistic understanding of the dissolution process. In response to this Kaunisto et al. (2010) developed a mechanistic finite element method (FEM) model describing polymer dissolution from a rotating disc. The model was based on axially symmetric tablet geometry, see Fig. 15, assuming a Fickian diffusion mechanism in the axial and radial directions, respectively.

The volumetric fluxes of solvent and polymer were assumed equal and there was no volume change upon mixing. Regarding the solid–gel interface two different approaches were used. The first approach consisted of a continuous transport of solvent throughout the polymer by using a "Fujita-like" free volume theory for the diffusion coefficient (Fujita, 1961), where the solid–gel interface was defined by a threshold solvent concentration above which there is no crystallinity. The second approach was based on that if the kinetics of crystallite unfolding and glass transition are

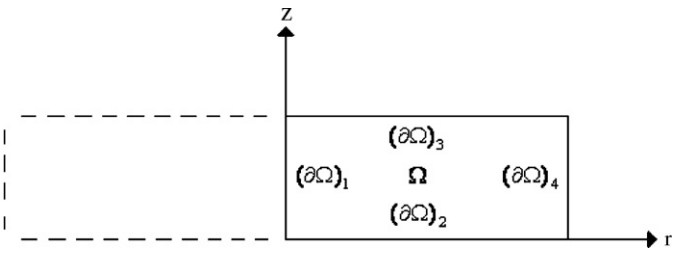

Fig. 15. Tablet geometry with associated boundaries. The rotating disc is at $z=0$ (mm).

assumed relatively fast compared with the mass transfer into the solid core, then a discontinuity in the diffusion coefficient at the threshold solvent concentration can be used at the solid–gel interface. Further, the gel–solvent interface was controlled by using a boundary governed Arbitrary Lagrangian Eulerian (ALE) method. By assuming that hydrodynamic force equilibrium is established at the gel–solvent interface, the net interface velocity was obtained from the solvent diffusion flux and the polymer erosion flux at a critical solvent concentration where the polymer is free to diffuse into the bulk solution. Accordingly, erosion was assumed to start when the force equilibrium was established, i.e. after a lag time. The tablet was assumed to swell and erode in the normal direction with respect to the gel–solvent interface. In addition, Winslow smoothing equations were also solved to determine the mesh positions in the deformed tablet and a mesh flux corrected time derivative for the solvent accumulation was used.

Diffusion in the polymer and mixing rule according to Kaunisto et al. (2010), Eqs. (50)–(55):

$$\frac{\partial(\rho c_{1,w})}{\partial t} + \frac{1}{r}\frac{\partial(r j_{1,r})}{\partial r} + \frac{\partial j_{1,z}}{\partial z} = 0 \tag{50}$$

$$j_{1,r} = -\rho D_{12}\frac{\partial c_{1,w}}{\partial r} + c_{1,w}(j_{1,r} + j_{2,r}) \tag{51}$$

$$j_{1,z} = -\rho D_{12}\frac{\partial c_{1,w}}{\partial z} + c_{1,w}(j_{1,z} + j_{2,z}) \tag{52}$$

$$\frac{j_{1,r}}{\rho_1} = -\frac{j_{2,r}}{\rho_2} \tag{53}$$

$$\frac{j_{1,z}}{\rho_1} = -\frac{j_{2,z}}{\rho_2} \tag{54}$$

$$\frac{1}{\rho} = \frac{c_{1,w}}{\rho_1} + \frac{1-c_{1,w}}{\rho_2} \tag{55}$$

Solid–gel interface description i.e. diffusion model according to Kaunisto et al. (2010), Eqs. (56)–(57):

Model 1:

$$D_{12} = D_{12,gs}\exp\left(-\beta\left(1 - \frac{\rho c_{1,w}}{\rho_{gs} c_{1,w,gs}}\right)\right) \tag{56}$$

Model 2:

$$D_{12} = (D_{12,gel} - D_{12,core}) * H(c_{1,w} - c_{1,w,sg}, \Delta c_{1,w}) + D_{12,core} \tag{57}$$

Velocity of the gel–solvent boundary according to Kaunisto et al. (2010), Eqs. (58)–(59):

$$\left.\frac{\partial r_{ALE}}{\partial t}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} = \left.\frac{(j_{1,r}+j_{2,r})}{\rho}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} + \left.\frac{n_r(n_r\rho D_{12}(\partial c_{1,w}/\partial r) + n_z\rho D_{12}(\partial c_{1,w}/\partial z))}{\rho(1-c_{1,w})}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} - n_r k_{2,m} H(t - t_{lag}, \Delta t)\big|_{(\partial\Omega)_3+(\partial\Omega)_4} \tag{58}$$

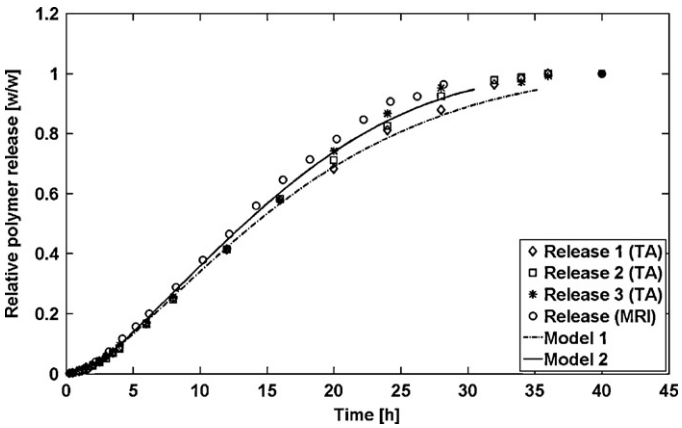

Fig. 16. Simulated and experimental polymer release profiles at 100 RPM, using Model 1 and Model 2. Experimental data seem to justify the existence of a lag time. Model 1 underestimates the release at later times, while the fit for Model 2 is good.

$$\left.\frac{\partial z_{ALE}}{\partial t}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} = \left.\frac{(j_{1,z}+j_{2,z})}{\rho}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} + \left.\frac{n_z(n_r\rho D_{12}(\partial c_{1,w}/\partial r) + n_z\rho D_{12}(\partial c_{1,w}/\partial z))}{\rho(1-c_{1,w})}\right|_{(\partial\Omega)_3+(\partial\Omega)_4} - n_z k_{2,m} H(t - t_{lag}, \Delta t)\big|_{(\partial\Omega)_3+(\partial\Omega)_4} \tag{59}$$

The model was applied to the dissolution of a polyethylene oxide (PEO) tablet in water. Figs. 16–18 show polymer release profile, polymer front position and solvent concentration profiles in the tablet at 100 RPM. Importantly, the model was calibrated not only against polymer release and front position data, but also against magnetic resonance microimaging (MRI) data providing concentration profiles in the gel-layer of the tablet. Only axial concentration profile data were used in the calibration, but a comparison with experimental data in both axial and radial directions was made. To study the influence of hydrodynamic shearing the model was also re-calibrated at an increased rotation speed of 200 RPM. It was concluded that a Fickian's diffusion mechanism together with a sharp discontinuity in the diffusion coefficient is sufficient to describe the solvent transport in the polymer and that the model assumption of a force equilibrium at the gel–solvent interface is plausible. However;

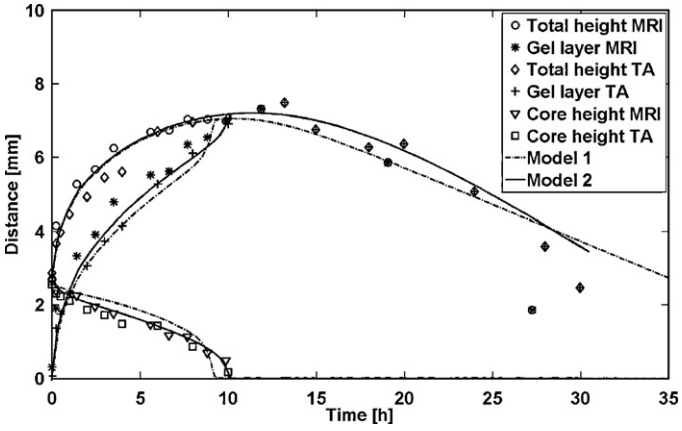

Fig. 17. Simulated and experimental axial front position at 100 RPM, using Model 1 and Model 2. The total height, core height and gel layer thickness are shown. Both models fail to describe the swelling accurately at later times, but the overall agreement is better for Model 2.

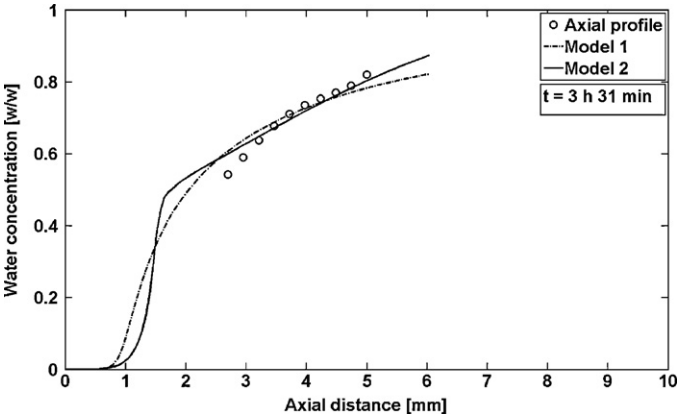

Fig. 18. Simulated and experimental axial water concentration profiles at $r = 0$ (mm) and 100 RPM, using Model 1 and Model 2. Model 1 underestimates the critical water concentration at the boundary, while Model 2 shows better overall agreement.

the predicted radial concentration profiles showed a systematic deviation from experimental data, which was explained by possible tablet compression effects or the possible spatial dependency on the critical solvent concentration at the gel–solvent interface due to increased shearing forces in the radial direction. Moreover it was concluded that discriminating experiments, i.e. experimental data from inside the tablet are necessary to accurately calibrate the model, since different model parameters are sensitive to different types of experimental data. Especially, the diffusion coefficient in the polymer core was found to be rather insensitive to all experimental data, requiring additional concentration data inside the polymer core to be properly determined.

3.3. Diffusion models in polymers

Different models describing diffusion in polymer solutions, gels and solids have earlier been reviewed (Masaro and Zhu, 1999). Depending on the physical mechanism the diffusion models were divided into three main categories:

(i) Models based on obstruction effects.
(ii) Hydrodynamic models.
(iii) Models based on free volume theory.

3.3.1. Models based on obstruction effects

In the models based on obstruction effects the polymer chains are regarded as motionless relative to the diffusing solvent or solute. This approximation is based on the assumption that the self-diffusion coefficient of the polymer is much smaller than that of the diffusant. In this case the presence of polymer segments lead to an increased mean path length for the diffusing molecules between two points in the system, thus lowering the diffusion coefficient.

The first model based on obstruction effects was the Maxwell–Fricke model (Waggoner et al., 1993). The self-diffusion coefficient could be estimated from the following expression, Eq. (60):

$$\frac{D_1(1-c_{2,v})}{D_{pure}} = \frac{1-c_{2,v}-c_{2,v,b}}{1+(c_{2,v}+c_{2,v,b}/\kappa)} \tag{60}$$

Eq. (60) relates the diffusion coefficient to the diffusion coefficient in pure solvent, also taking into account the shape of the solvent (rods or spheres). The expression seemed valid in dilute polymer solutions, and was shown to overestimate the diffusion coefficient at higher polymer concentrations. However, other studies later confirmed that the expression applies also to concentrated systems (Akanni and Evans, 1987; Westrin and Axelsson, 1991).

Another model was proposed by Mackie and Meares (1955) when analyzing the mobility in an ion-exchange resin membrane, Eq. (61):

$$\frac{D_1}{D_{pure}} = \frac{(1-c_{2,v})^2}{(1+c_{2,v})^2} \tag{61}$$

Eq. (61) can be derived from the tortuosity imposed by the motionless polymer molecules, by assuming a cubic lattice model. The model works well for small diffusants of various sizes in cellulose networks, but fails to describe diffusion of large molecules in polymer solutions or at high polymer concentrations (Masaro and Zhu, 1999).

In order to describe large diffusants Ogston et al. (1973) developed an approach where the polymer is considered as barriers formed by a random distribution of long molecular fibers. The following expression was obtained, Eq. (62):

$$\frac{D_1}{D_{pure}} = \exp\left[-\frac{r_h+r_e}{r_e}c_{2,v}^{1/2}\right] \tag{62}$$

Eq. (62) takes into account both the hydrodynamic size of the diffusing molecule and the effective cylindrical radius of the fibre. Unfortunately, later studies showed that this model did not show satisfactorily results for large molecules in general, but remains valid for dilute or semi-dilute polymer solutions (Masaro and Zhu, 1999).

3.3.2. Hydrodynamic models

In the hydrodynamic models all hydrodynamic interactions between the components in the system are taken into account. These interactions include contributions from frictional forces between solute, solvent and the polymer. The approach allows the description of diffusion in more concentrated systems where the polymer chains start to overlap, which is difficult with the obstruction models.

Cukier (1984) developed an equation based on hydrodynamic interactions to describe the diffusion of Brownian spheres in semi-dilute polymer solutions, Eq. (63):

$$\frac{D_1}{D_{pure}} = \exp(-\alpha_{screp} r_h) \tag{63}$$

In Eq. (63) the semi-dilute solution was considered a uniform polymer–solvent mixture represented by randomly distributed spheres immersed in an incompressible Navier–Stokes fluid and was considered motionless relative to the diffusing solvent. Therefore the diffusant was assumed to undergo screening effects due to the overlapping polymer chains. The model is limited to diffusion of small diffusants in semi-dilute networks and slightly cross-linked gels (Masaro and Zhu, 1999). Altenberger and Tirrell (1984) also proposed a mathematically equivalent expression for small diffusants in dilute or semi-dilute regimes although derived differently. The generalized expression was (here adapted to molar fraction form), Eq. (64):

$$\frac{D_1}{D_{pure}} = \exp(\alpha_{padp} c_{2,n,o}^{1/2}) \tag{64}$$

In order to describe self-diffusion over a wide range of concentrations a phenomenological model very similar to that of Cukier and Altenberger was developed by Phillies (Masaro and Zhu, 1999). The expression was in the form of a stretched exponential (here adapted to molar fraction form), Eq. (65):

$$\frac{D_1}{D_{pure}} = \exp(\alpha_{scap} c_{2,n}^{\upsilon_{scap}}) \tag{65}$$

An important difference between the between the models of Cukier and Altenberger and that of Phillies is that in Phillies' model the polymer chains are regarded as mobile. They are described by

spheres joined by rods that are able to rotate. However; the physical significance of this consideration becomes somewhat vague as the scaling parameters in Phillies' model are determined from experimental data. The model should therefore probably be considered semi-empirical.

The concept of reptation was first introduced by de Gennes (1971) when describing the self-diffusion of a polymer chain inside a three-dimensional entangled gel network. In reptation theory the polymer is considered to be confined in a tube built up from fixed obstacles, i.e. the surrounding gel chains. Movement is constrained to the extremities of the diffusing polymer chain, allowing only tubular motion into new sections of tube and no lateral motion. The time required to escape a tube, i.e. for complete tube renewal is thus referred to as the reptation time. It was shown that the diffusion coefficient scales with the molecular mass, according to Eq. (66):

$$D_2 \propto M^{-2} \tag{66}$$

Eq. (41) can be compared with the scaling law for polymer self-diffusion in unentangled or diluted solution as described by the Rouse model (Masaro and Zhu, 1999), Eq. (67):

$$D_2 \propto M^{-1} \tag{67}$$

de Gennes also extended his model to take the effect of the matrix on the self-diffusion coefficient of the diffusant into account (de Gennes, 1976). This resulted in a new model referred to as the reptation plus scaling concept (here adapted to molar fraction form), Eq. (68):

$$D_2 \propto M^{-2} c_{2,n}^{(2-\gamma)(1-3\gamma)} \tag{68}$$

There are several applications for de Gennes' diffusion models in the literature and they work well for diffusion in concentrated polymer solutions and gels. However the models do not account for the exponential dependence on polymer concentration which has been frequently observed (Masaro and Zhu, 1999). Further, the models may fail when describing polymer diffusion in melts as there is no temperature dependence on the diffusion coefficient taken into account.

3.3.3. Models based on free volume theory

In the free volume theories, originally sprung from Eyring's rate theory for liquids, the volume of a system is considered to be composed of two parts: the actual volume occupied by the molecules and the free volume due to thermal fluctuations. From this viewpoint diffusion can be described as jumps, where the diffusant jumps from its original position to an adjacent free volume. The statistical probability for such a jump to be successful depends on the probability of finding a free volume of adequate size and the probability of overcoming attractive forces. Since the magnitude of thermal fluctuations is related to the actual temperature of the system, so is the free volume, and therefore it can be described as the volume of a system at given temperature minus the volume at 0 K.

Fujita (1961) proposed a diffusion model based on the free volume concept by assuming that the expression of the probability for finding a large enough hole in a liquid, earlier proposed by Cohen and Turnbull (Masaro and Zhu, 1999), also was valid in the case of a binary system. The expression for the self-diffusion coefficient was, Eq. (69):

$$D_1 = \alpha_{prop} RT \exp\left(-\frac{\alpha_{padp}}{V_V}\right) \tag{69}$$

Eq. (69) was later expanded by Yasuda et al. (1968), by assuming that the contributions to the total free volume can be described by the contributions from both the polymer and the solvent, i.e. by weighing the individual free volumes with the respective volume fractions, Eq. (70):

$$\frac{D_1}{D_{pure}} = \exp\left[\frac{\alpha_{padp}}{V_{VSOL}}\left(1 - \frac{1}{1 - c_{2,v}}\right)\right] \tag{70}$$

Another important contribution to the development of the free volume theory was made by Vrentas and Duda (Masaro and Zhu, 1999). They were able to extend the theory to describe a wide range of concentrations and temperatures. However, the extension resulted in a complex model with many parameters, where for many systems very few are available in the literature, making a proper utilization of the model difficult. In some studies the model was reported to show no difference as compared to the original model by Fujita. On the other hand, the original model is still valuable as it has shown successful correlations between model and data in the case of the diffusion of small molecules in semi-crystalline polymers. The model seems to be applicable in dilute and semi-dilute polymer solutions and gels, mostly organic systems (Masaro and Zhu, 1999).

3.4. Drug release from swelling and dissolving polymer matrix formulations

In an earlier review by Siepmann and Peppas (2001) different empirical, semi-empirical and mechanistic models for describing drug release from hydroxypropyl methylcellulose (HPMC) has been summarized. In this work, however, the focus will be directed towards mechanistic models for drug release from swelling and dissolving matrix formulations in general.

Before getting into detail, it is appropriate to describe more simple models. In 1961 Higuchi developed a model describing drug release from solid drugs suspended in ointment bases (Higuchi, 1961). The initial model was valid only for homogenous planar systems, but was later extended to consider spherical geometry and a heterogeneous porous structure (Higuchi, 1963). The basic Higuchi equation is, Eq. (71):

$$\frac{m_{drug}}{A_{surf}} = \sqrt{\frac{D_{drug}}{\tau^2}(2c_{init} - c_{sat})c_{sat}t} \tag{71}$$

In Eq. (71) it is assumed that the drug loading is much higher than the solubility and that a pseudo-steady state assumption can be applied to the drug concentration profile within the matrix. Further, the expression requires fine drug particles, negligible swelling and dissolution of the polymer matrix, constant drug diffusivity and perfect sink conditions. From Higuchi's model it is evident that the drug release should vary with the square root of time if the release process is diffusion controlled. Unfortunately, this reasoning is not valid in vice versa, since there could possibly be a sum of different drug release mechanisms that ultimately results in an observed square root of time behaviour. It is therefore reasonable to characterize the release process from a more empirical perspective, as was made by Ritger and Peppas (1987) and Korsmeyer et al. (1983), i.e. Eq. (1). However, this approach was further developed by Peppas and Sahlin (1989) to account for both Fickian and case II mechanisms, Eq. (72):

$$\frac{m_t}{m_\infty} = k_{fick} t^{\omega} + k_{\text{case II}} t^{2\omega} \tag{72}$$

Regarding simple mechanistic models Lee (1980) developed analytical solutions for the dispersed solute release from planar and spherical polymers considering both dissolving and non-dissolving polymers. Matrix swelling, concentration dependency of the solute diffusivity and external mass transfer were neglected. Another model developed by Harland et al. (1988a) considered drug release from non-swelling polymeric microspheres. An analytical solution

for the case of drug loadings higher than the solubility assuming constant drug diffusivity was derived. Harland et al. (1988b) also considered cylindrical tablet dissolution, including swelling, by using a one-dimensional model. The model was able to predict both Fickian and non-Fickian diffusion. Importantly, it was concluded that front synchronization of the solid–gel and the gel–solvent interfaces at later times in the dissolution process leads to zero-order release. Another one-dimensional model describing drug release from swellable polymers was developed by Brazel and Peppas (2000). The transport of drug was described by a Fickian's diffusion equation whereas the equation for water transport included both diffusion and a convective contribution from the polymer relaxation rate. Moreover, a swelling number (solvent motion/drug diffusion) and a diffusional Deborah number (relaxation time/diffusion of solvent) was defined in the gel–layer and at the gel–solvent interface, respectively, and the predicted water uptake and drug release profiles were investigated for different values on these numbers. Assuming negligible swelling the model was also verified against water uptake data and drug release data from poly 2-hydroxyethyl methacrylate (PHEMA) and (PVA) hydrogels, using diffusion coefficients from the literature.

Considering swelling, but neglecting polymer dissolution Peppas et al. (1980) developed a one-dimensional model for diffusive transport of water and drug in a polymeric tablet, based on Fick's second law. The transport equations were solved analytically with constant diffusion coefficients and the model was verified by fitting diffusion coefficients against experimental concentration profile data for water, drug and polymer in the gel phase of a HPMC matrix. Kiil and Dam-Johansen (2003) also developed a model for drug release from a swelling cylindrical tablet. In this model only radial transport was considered and polymer dissolution was neglected. The solid–gel interface was modelled by using an analogous expression to that originally proposed by Astarita and Sarti (1978). The movement of the gel–solvent interface was assumed to obey an empirical expression based on the ratio of the fully swollen to the initially unswollen matrix and the position of the solid–gel interface. The model was fitted to experimental drug release and front position data from a high viscosity HPMC matrix and it was concluded that more experimental data are needed to calibrate the model.

Taking both swelling and polymer dissolution into account Ju et al. (1995a,b) developed a model describing water transport and drug release from a cylindrical tablet, based on scaling laws. Mass transport was assumed to occur only in the radial direction and drug dissolution was assumed to be much faster than drug diffusion. The mass balances for water and drug contained a convection, diffusion and dilution term to account for swelling, diffusive transport and the expansion of the polymer network, respectively, where the convective term was approximated as the swelling rate based on the overall tablet radius. The model was evaluated against drug release and polymer dissolution data from HPMC tablets.

Narasimhan and Peppas (1997) developed a one-dimensional model describing drug release from a glassy polymer. Polymer dissolution according to the reptation theory was incorporated into the model, based on earlier work on a pure polymer/solvent system (Peppas et al., 1994; Narasimhan and Peppas, 1996). Fickian transport equations for water and drug were valid in the gel-layer and convective terms were neglected. The movement of the solid–gel and the gel–solvent interfaces were obtained from mass balances over each interface. At the gel–solvent interface the polymer and drug molecules were assumed to diffuse through a liquid solution boundary-layer analogous to earlier work (Narasimhan and Peppas, 1996). Further, a mathematical solution at steady state was derived, and the resulting equation was verified against gel-layer thickness and drug release data for PVA and mannitol based tablets. The resulting equation was a special case of the Peppas–Sahlin expression, Eq. (72), with $\omega = 0.5$.

Diffusion of water and drug in the polymer according to Narasimhan and Peppas (1997), Eqs. (73) and (74):

$$\frac{\partial c_{1,v}}{\partial t} = \frac{\partial}{\partial x}\left(D_{sol}\frac{\partial c_{1,v}}{\partial x}\right) \tag{73}$$

$$\frac{\partial c_{drug,v}}{\partial t} = \frac{\partial}{\partial x}\left(D_{drug}\frac{\partial c_{drug,v}}{\partial x}\right) \tag{74}$$

Diffusion of dissolved polymer in the liquid solution according to Narasimhan and Peppas (1997), Eq. (75):

$$\frac{\partial c_{2,v}}{\partial t} = \frac{\partial}{\partial x}\left[D_{pol}\frac{\partial c_{2,v}}{\partial x}\right] - \frac{\partial x_{gs}}{\partial t}\frac{\partial c_{2,v}}{\partial t} \tag{75}$$

Velocity of the solid–gel interface according to Narasimhan and Peppas (1997), Eq. (76):

$$(c_{1,v} + c_{drug,v})\frac{\partial x_{sg}}{\partial t} = -\left(D_{sol}\frac{\partial c_{1,v}}{\partial x}\right) - \left(D_{drug}\frac{\partial c_{drug,v}}{\partial x}\right) \tag{76}$$

Velocity of the gel–solvent interface according to Narasimhan and Peppas (1997), Eq. (77):

$$\frac{\partial x_{gs}}{\partial t} = \frac{D_{sol}c_{1,v,gs}}{c_{1,v,gs} + c_{drug,v,gs}}\frac{\partial c_{1,v}}{\partial x} + \frac{D_{drug}c_{drug,v,gs}}{c_{1,v,gs} + c_{drug,v,gs}}\frac{\partial c_{drug,v}}{\partial x} - \frac{D_{pol}}{c_{1,v,gs} + c_{drug,v,gs}}\frac{\partial c_{2,v}}{\partial x} \tag{77}$$

Mallapragada and Peppas (1997b) developed a one-dimensional model describing drug release from semi-crystalline polymers, based on earlier work on a pure semi-crystalline polymer/solvent system (Mallapragada and Peppas, 1997a). Fickian transport equations for the drug and the amorphous polymer as well as a first order crystal-unfolding mechanism was included. Dissolution of semi-crystalline PVA in water was used as a model system for which drug release was predicted. It was concluded that drug release is controlled by the dissolution rate of the polymer crystals and that higher initial degrees of crystallinity or larger crystal sizes lead to a slower and non-Fickian drug release process.

So far all the models presented have been one-dimensional in space and transport in several directions has been neglected. However, Siepmann et al. (1999a) developed a model describing drug release from HPMC-based cylindrical matrix tablets taking transport in axial and radial directions into account. The model was based on an axially symmetric transport equation with Fickian's diffusion of water and drug. Importantly, the drug was assumed to dissolve instantaneously in the water, implying that the model is restricted to freely water-soluble drugs at low initial drug loadings. Further, swelling of the matrix was included and was assumed to be isotropic throughout the tablet, but polymer dissolution was neglected.

Diffusion of water and drug in the polymer according to Siepmann et al. (1999a), Eqs. (78) and (79):

$$\frac{\partial c_1}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_{sol}\frac{\partial c_1}{\partial r}\right) + \frac{\partial}{\partial z}\left(rD_{sol}\frac{\partial c_1}{\partial z}\right)\right\} \tag{78}$$

$$\frac{\partial c_{drug}}{\partial t} = \frac{1}{r}\left\{\frac{\partial}{\partial r}\left(rD_{drug}\frac{\partial c_{drug}}{\partial r}\right) + \frac{\partial}{\partial z}\left(rD_{drug}\frac{\partial c_{drug}}{\partial z}\right)\right\} \tag{79}$$

The model was verified against experimental drug release and water uptake data and it was concluded that the model could be used predict the required size and aspect ratio of a tablet to achieve a desired drug release profile. This analysis was also performed by Siepmann et al. (2000) with a revised version of the original

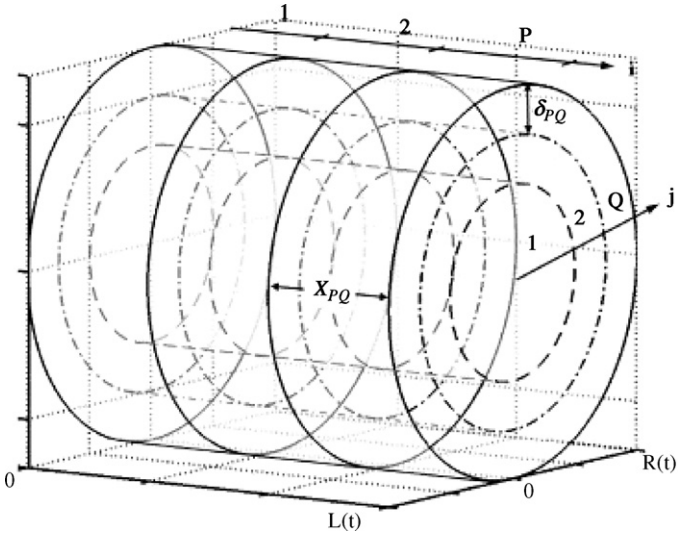

Fig. 19. The finite volume discretization, exemplified for 9 finite volumes (3 × 3). The axial dimension (index *i*) is discretized in *P* slices and each slice is discretized in *Q* (index *j*) annular rings (larger indices indicate locations closer to the bulk phase). (Nomenclature note: In this work *i* and *j* are represented by *p* and *q*, respectively).

model, where also polymer dissolution was taken into account (Siepmann et al., 1999b). In this case the model was only verified against drug release data. The model was also further expanded by Siepmann and Peppas (2000), to be able to account for high initial drug loadings and inhomogeneous swelling. This model was based on "sequential layers" where each layer was assumed to swell homogeneously upon contact with water. Drug dissolution was assumed to be fast compared to drug diffusion and if drug in a layer exceeded the saturation concentration, the excess was considered non-dissolved and thus not available for diffusion. This new model was also used by Siepmann et al. (2002) to study the effects of the initial dimensions of the tablet and was verified against experimental drug release and polymer dissolution data. Importantly, it was concluded that the geometry of the tablet has a non-trivial impact on the drug release profile and has to be accurately taken into account when designing a tablet formulation.

Wu et al. (2005) developed a model describing drug release from a highly swellable and dissolving polymer matrix based on PEO of high molecular weight. The model consisted of two axially symmetric transport equations for water and drug within the polymer matrix, respectively, assuming Fickian's transport mechanisms in both directions, Eqs. (78) and (79). Tablet swelling was assumed to be homogenous and convective contributions from stresses and diffusion-induced convection were neglected. By assuming that the tablet retains a cylindrical shape and that the swelling in the radial and axial directions are independent (neglecting edge effects), the velocity of the radial and axial part of the gel–solvent interface could be derived. The solid–gel interface was not included in the model but could be approximately defined by the concentration dependence of the water diffusion coefficient. The model was fitted to water uptake and polymer dissolution data in order to obtain water diffusion and polymer dissolution parameters. Obtained parameter values were used to predict the dimensional change of the tablet which was compared with experimental data in the radial direction. Further, the model was also fitted to drug release data, and the influence of tablet aspect ratio on the drug release profile was investigated.

Velocity of the gel–solvent interface according to Wu et al. (2005) (the polymer dissolution rate coefficient has been re-written in terms of the mass transfer coefficient and the polymer equilibrium concentration), Eqs. (80) and (81):

$$z_{gs}(1-c_{1,v,gs})\frac{\partial r_{gs}}{\partial t} = \frac{1}{\rho_1}\int_0^{z_{gs}} D_{sol}\left.\frac{c_1}{\partial r}\right|_{r=r_{gs}} dz + \frac{1}{\rho_{drug}}\int_0^{z_{gs}} D_{drug}\left.\frac{c_{drug}}{\partial r}\right|_{r=r_{gs}} dz - z_{gs}\frac{k_{2,m}c_{2,gs}}{\rho_2} \tag{80}$$

$$r_{gs}^2(1-c_{1,v,gs})\frac{\partial z_{gs}}{\partial t} = \frac{1}{\rho_1}\int_0^{r_{gs}} D_{sol}\left.\frac{c_1}{\partial z}\right|_{z=z_{gs}} 2r\,dr + \frac{1}{\rho_{drug}}\int_0^{r_{gs}} D_{drug}\left.\frac{c_{drug}}{\partial z}\right|_{z=z_{gs}} 2r\,dr - r_{gs}^2\frac{k_{2,m}c_{2,gs}}{\rho_2} \tag{81}$$

Petroviç et al. (2009) used the modelling approach suggested by Wu et al. (2005) to study the release of diclofenac sodium from swelling and dissolving PEO of low molecular weight. Transport parameters for water were determined by fitting the model to water uptake data after which the model was fitted to drug release data with different drug loading. Importantly, the model was able to quantify a sudden decrease in the drug diffusion coefficient for a certain initial drug loading. This behaviour was attributed to a possible percolation threshold for the matrix which is to be avoided for optimal release.

In order to increase the mechanistic understanding of polymer matrix formulations Borgquist et al. (2006) developed a model for describing swelling, dissolution and drug release from a cylindrical tablet on a rotating disc, during the entire dissolution process. The model consisted of two axially symmetric transport equations for water and drug within the polymer matrix, respectively, assuming a Fickian's transport mechanism in radial and axial directions. Contributions from diffusion, swelling (diffusion-induced convection) and dissolution were taken into account. The tablet was discretized into axial and annular slices, see Fig. 19, and mass balances over the slices were formulated by using finite differences.

Diffusion and convection in the polymer according to Borgquist et al. (2006), Eqs. (82) and (83):

$$\frac{V_{pq}}{c_{2,v,pq}}\frac{\partial c_{1,v,pq}}{\partial t} - A_{pq}^{es,out}c_{1,v,p,q+1}\sum_{k=1}^{q}\frac{\partial \delta_{an,pq}}{\partial t} + A_{pq}^{es,in}c_{1,v,pq}\sum_{k=1}^{q-1}\frac{\partial \delta_{an,pq}}{\partial t} - A_{pq}^{cs}c_{1,v,p+1,q}\sum_{k=1}^{p}\frac{\partial Z_{kq}}{\partial t} + A_{pq}^{cs}c_{1,v,pq}\sum_{k=1}^{p-1}\frac{\partial Z_{kq}}{\partial t} = -c_{1,v,pq}A_{pq}^{B}\Phi_{pq} + A_{pq}^{es,out}N_{p,q+1\to q}^{Dw} - A_{pq}^{es,in}N_{p,q\to q-1}^{Dw} + A_{pq}^{es,in}N_{p+1\to p,q}^{Dw} - A_{pq}^{es,in}N_{p\to p-1,q}^{Dw} \tag{82}$$

$$V_{pq}\left[\frac{\rho_{drug}}{\rho_{drug}-c_{drug,sat}c_{drug,ON,pq}}\right]^2 c_{1,v,pq}\frac{\partial c_{drug,ON,pq}}{\partial t} + V_{pq}\frac{\rho_{drug}}{\rho_{drug}-c_{drug,sat}c_{drug,ON,pq}}\frac{c_{drug,ON,pq}}{c_{2,v,pq}}\frac{\partial c_{1,v,pq}}{\partial t} - A_{pq}^{es,out}c_{drug,N,p,q+1}\sum_{k=1}^{q}\frac{\partial \delta_{an,pq}}{\partial t} + A_{pq}^{es,in}c_{drug,N,pq}\sum_{k=1}^{q-1}\frac{\partial \delta_{an,pq}}{\partial t}$$

$$-A_{pq}^{cs}c_{drug,N,p+1,q}\sum_{k=1}^{p}\frac{\partial Z_{kq}}{\partial t}+A_{pq}^{cs}c_{drug,N,pq}\sum_{k=1}^{p-1}\frac{\partial Z_{kq}}{\partial t}$$
$$=-\frac{\rho_{drug}}{\rho_{drug}-c_{drug,sat}c_{drug,ON,pq}}c_{drug,ON,pq}c_{1,v,pq}A_{pq}^{B}\Phi_{pq}$$
$$+A_{pq}^{es,out}N_{p,q+1\to q}^{AD}-A_{pq}^{es,in}N_{p,q\to q-1}^{AD}+A_{pq}^{es,in}N_{p+1\to p,q}^{AD}-A_{pq}^{es,in}N_{p\to p-1,q}^{AD} \quad (83)$$

In the model it was assumed that hydrodynamic force equilibrium is established at the gel–solvent interface, implying a critical polymer concentration at which the polymer molecules are removed by hydrodynamic forces. Accordingly, polymer erosion was assumed to start when force equilibrium was established, i.e. after a lag time. Swelling of the tablet was assumed to occur in the radial and axial directions in proportion to the relative fluxes in each direction with respect to the total flux. Further, the movement of the solid–gel interface was assumed to be limited by mass transfer into the solid core at a critical penetrant concentration. Regarding the drug transport it was assumed that the drug is immobilized in the solid core, and diffusion was restricted to the portion of dissolved drug in the solvent phase.

Axial and radial swelling and polymer dissolution according to Borgquist et al. (2006), Eqs. (84)–(86):

$$\frac{\partial Z_{pq}}{\partial t}=\frac{s_{pq}^{w}}{A_{pq}^{cs}}\frac{\partial V_{pq}}{\partial t}\bigg|^{w}+\frac{s_{pq}^{w}}{A_{pq}^{cs}}\frac{\partial V_{pq}}{\partial t}\bigg|_{gs} \quad (84)$$

$$\frac{\partial \delta_{an,pq}}{\partial t}=\frac{1-s_{pq}^{w}}{A_{pq}^{es,out}}\frac{\partial V_{pq}}{\partial t}\bigg|^{w}-\frac{\delta_{an,pq}}{R_{an,pq}}\frac{\partial R_{an,p,q-1}}{\partial t}+\frac{1-s_{pq}^{w}}{A_{pq}^{es,out}}\frac{\partial V_{pq}}{\partial t}\bigg|_{gs} \quad (85)$$

$$\frac{\partial m_{pq}}{\partial t}=-k_{2,m}A_{pq}^{B}\rho_2 c_{2,v}\big|_{gs} \quad (86)$$

Velocity of the solid–gel interface according to Borgquist et al. (2006), Eq. (87):

$$N_{p+1\to p,q}^{wD}=-k_{1,m}(c_{1,v,pq}-c_{1,v,p+1,q}) \quad (87)$$

The model was tested for the case of a drug loaded (methyl paraben or saligenin) PEO tablet. By assuming that small drug loadings do not affect the dissolution behaviour compared to pure polymer dissolution, parameters based on experimental polymer dissolution and tablet front position data from a pure polymer dissolution study were used together with a fitted value for the drug diffusion coefficient. It was concluded that the model was able to describe the release profiles and front positions of both slightly soluble and soluble drugs. Further the sensitivity of the drug diffusion coefficient, drug solubility and drug loading was examined. Interestingly, the model was able to keep track of the solid–drug front, i.e. the points in the tablet beyond which the drug is completely dissolved. With a low solubility or high drug loading the solid–drug interface was positioned closer to the gel–solvent boundary, where the drug release profile will be similar to that of the polymer dissolution. In the opposite case the solid–drug front will be closer to the solid core and the drug release will be significantly faster than polymer dissolution. Results from the simulations are shown in Fig. 20.

Finally, as in Section 3.1, there are also other models for drug release from matrix formulations that considers viscoelastic effects, i.e. Case II behaviour on solvent diffusion in the polymer (Grassi et al., 2007). One example is the model developed by Camera-Roda and Sarti (1990). In this model the solid–gel interface can be considered to be lumped into the constitutive relation for the solvent flux via relaxation flux contribution terms that account for the various molecular rearrangements that take place near and below the poly-

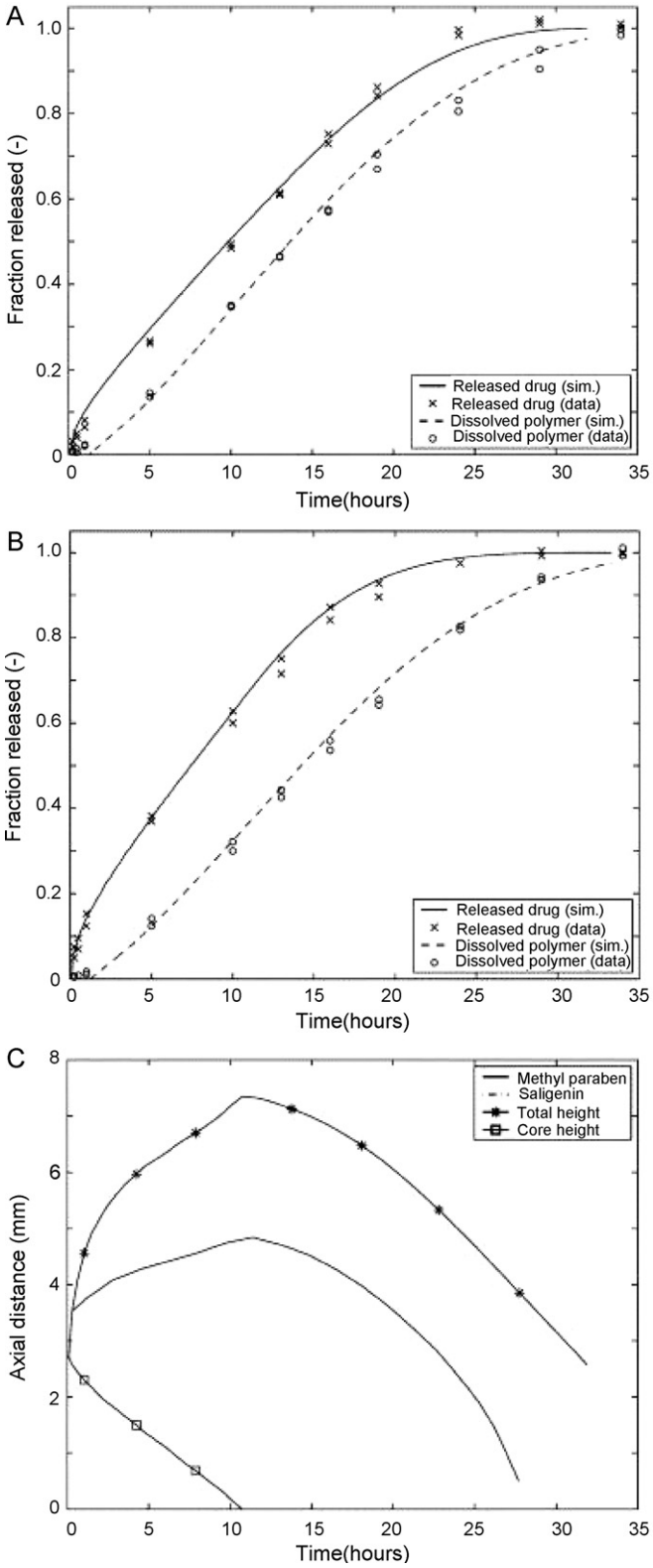

Fig. 20. Model validation against drug release and polymer dissolution data of (2) drug-loaded PEO tablets (molecular mass 2×10^6 Da) for a slightly soluble drug and a soluble drug. Initial loading: 2%, w/w. (A) Release of the slightly soluble drug Methyl paraben (solubility 2.5 kg m^{-3}), using a drug diffusion coefficient of 3×10^{-10} m^2 s^{-1}. (B) Release of the soluble drug Saligenin (solubility 74 kg m^{-3}), using a drug diffusion coefficient of 3×10^{-10} m^2 s^{-1}. (C) Predicted axial front position of the solid–drug interface of methyl paraben and saligenin, and the front positions of the total height (gel–solvent interface) and the core height (solid–gel interface). The front position of saligenin coincides with the solid–gel interface.

mer glass transition temperature at a given time scale. The model can also be generalized to take into account the effects of relaxation flux contributions on different time scales.

3.5. Model parameters and discriminating experiments

Today there are several different techniques available to characterize polymer dissolution (Narasimhan, 2001). Among important techniques that can be used to calibrate and validate mathematical models are polymer front position/gel-layer measurements, polymer/solvent concentration profile measurements, polymer release profile measurements and, if drug is present, drug release profile measurements. Inclusion of these data types in model calibrations is vital if reliable model predictions are to be expected.

As stated above it is vital that there are sufficient experimental data in a model calibration in order to obtain reliable model predictions. On the other hand, this also has consequences for the development of advanced mathematical models. In mechanistic modelling, it is not interesting to describe a process perfectly if it implies the use of redundant parameters that do not contribute to the understanding of the process. Therefore, it is important to restrict the number of model parameters so they can be calibrated by discriminating experiments. This, in turn, gives reliable parameters in terms of model prediction.

Regarding calibration and validation of the models presented in this work, it is remarkable how often only sparse amounts of experimental data are used to calibrate or validate the models, making it very difficult to deem their predictive qualities. For instance, when only release data and/or front position data are used, very little information about the parameters inside a polymer matrix can be obtained, ultimately resulting in several possible equally relevant explanations for species transport/kinetics inside the polymer. A concrete example is that fact that some of the parameters describing the gel–solvent and solid–gel interfaces have been found correlated or insensitive to available experimental data (Kiil and Dam-Johansen, 2003; Kaunisto et al., 2010). Therefore, experiments that can properly validate these assumptions are needed.

4. Conclusions and suggested future work

After the first modelling pioneering works, many works have been published and continuous to be published within modelling of drug release from coated formulation and from matrices. The complexity of the model has in many cases increased, and it was possible also due to a better understanding of the mechanism underlying the release and to the improvement of the simulation programs used to solve the mathematical problem. The better understanding of the mechanism of release and the validation of the models has often implied improvement in the experimental techniques and methods. In this section some possible improvements of the existing models are suggested.

When describing the diffusional drug release from pellets coated with a film whose porosity increases due to hydration and the leaching of the water-soluble polymer, the mechanistic modelling of the system would be more precise if D_e were correlated to the evolution of the coating structure, which in turn depends on the initial structure and on the mechanism of hydration and leaching of the water-soluble polymer. This would be possible if, among other things, accurate 3D measurements could be made on the structure of the coating as a function of time. The model could be further improved if the change in release mechanism from osmotic pumping to diffusion were to be considered for films that change from semi-permeable to permeable during the release due to the increase in the film porosity.

In the models applied to pellets coated with a semi-permeable film it was assumed that the coating was elastic during the whole lag phase, and that the elastic modulus was constant. The model could be further improved if plastic deformation and the effect of wetting on the mechanical properties of the film were to be considered. This would naturally require much more detailed experimental characterization of the mechanical properties of the film. Measurements on the swelling of single pellets, whose geometry and coating thickness have been well characterized, are highly desirable as the data obtained would provide important information on the mechanical properties of the coating films.

It is evident that there are many different approaches to model polymer dissolution, and the appropriate model may of course be problem dependent. If the aim of understanding polymer dissolution is to increase the mechanistic understanding of swelling and dissolving polymer matrix formulations in drug delivery the future focus should probably be directed towards improving mechanistic models describing whole swelling and dissolving tablets, as well as finding experimental techniques to confirm the model assumptions. It could also be useful to study the effects of pharmaceutical excipients more theoretically, by including them in the models and investigate their impact on drug release. Regarding transport assumptions in the polymer an alternative yet more complex approach is to consider multi-scale fluid transport theory (not mentioned in this work), to avoid lumping and to increase the physical meaning of the transport parameters inside the polymer (Singh et al., 2003). An attempt to extend this approach to include drug transport has also been made (Weinstein, 2006). However; the theory needs to be extended to cover also matrix erosion kinetics in order to be useful in the design of swelling and dissolving matrix systems.

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