Model-based computer-aided design for controlled release of pesticides

Núria Muro-Suñé and Rafiqul Gani*
CAPEC
Department of Chemical Engineering, Technical University of Denmark, DK-2800 Lyngby, Denmark
Gordon Bell and Ian Shirley
SYNGENTA
Jealotts Hill Research Station-Bracknell
Bracknell, Berkshire RG42 6E4, UK

Abstract

In the field of controlled release technology for pesticides or active ingredients (AI), models that can predict its delivery during application are important for purposes of design and marketing of the pesticide product. Appropriate models for the controlled release of pesticides, if available, can be used to study and analyze some of the important issues related to the design/application of the pesticide. This paper highlights the needs for predictive models and proposes the use of a computer aided modelling framework through which a collection of reliable and predictive constitutive (property) models can be combined with various types of release models. Use of a group-contribution based property model for one of the constitutive variables (AI solubility in polymers) and a free-volume theory based model for another (diffusion coefficient), has been proposed and the corresponding extended models have been developed and implemented into a computer-aided system. The total model consisting of the property models embedded into the release models are then employed to study the release of different combinations of AIs and polymer-based microcapsules.

Keywords: Controlled release, Microcapsule, Solubility, Diffusivity, Pesticide, Polymer

* Author to whom correspondence should be addressed : rag@kt.dtu.dk
1. Introduction

There are many applications in agriculture, where protection from pests is required for extended periods of time. If control is required for periods of a year or more, then the conventional methods of delivering the pesticide compound (for instance, spraying a solution of the pesticide over the crop) may not be good enough because the pesticide might not be delivered at the specific desired site and also because it does not last long enough to accomplish the protection of the crop. Considerable improvement can be achieved by using controlled release systems for the pesticide delivery to the environment. Through the sustained release of the pesticide from these devices, the amount of pesticide used, as well as, the number of times it needs to be applied on the crop, is reduced. As the pesticide is usually encapsulated within a polymer membrane, there is also a reduction with respect to environmental hazards and human toxicity.

Controlled release technology presents several advantages over the conventional applications of pesticides (to be called AIs in all text below) as illustrated in Figure 1. A comparison of the AI concentration in the environment over time obtained from a conventional AI application (—) with the concentration from a controlled delivery system (— -) is presented in this figure. It can be observed that with a conventional application a very high concentration is obtained initially, which can even be greater than the allowed toxicity level. This concentration decreases rapidly and is soon below the minimum effective level. On the other hand, the benefits of having a sustained pesticide delivery are immediately observed in the other concentration plot (— -), due to the quick achievement of the desired concentration that is then maintained over time. This is obviously a more desirable scenario.
A great number of models have been derived (for example, Peppas (1984), Comyn (1985) and Scher et al. (1977), to name a few) for describing the controlled release of active ingredients (pesticides, drugs, etc.) from various types of devices. Most of these models are based on Fick’s laws of diffusion. In recent years the technology for controlled release systems has developed greatly and with it the mathematical models required to study the newly produced systems have also improved [Siepmann et al. (2001)].

In the majority of cases the new models (such as, Frenning et al. (2003) and Koizumi et al. (2001)) are extensions or modifications of the previous models where some phenomena (such as, degradation of the polymer membrane, swelling, leaching, etc.) that were not considered previously have been taken into account. One modelling issue, the use of appropriate constitutive (or property) models for some of the controlled release model parameters (which are actually physical properties of the chemical system), does not appear to have been considered. Appropriate selection and use of models for constitutive variables is important because they describe the behaviour of the AI and the polymer with
respect to solubility and diffusivity, which play important roles in defining the release characteristics of
the AI. These constitutive variables are very important properties because they differ for different
combinations of AIs and polymers. The controlled release (CR) models that have been found through a
search of the open literature use at least one of these properties (solubility and/or diffusivity) as fixed
parameters. Consequently, in our opinion, they cannot be considered predictive with respect to either
the AI or the polymer used for the microcapsule. Therefore, in order to have a fully predictive CR-
model, it is necessary to account for the properties as well as the physical parameters of the
microcapsule, such as size, volume, thickness and number. This can be achieved through a modelling
framework that can combine different types of release models with the appropriate constitutive models
for the required properties for a large collection of AIs, polymers and AI application scenarios.

The objective of this work has been to evaluate and further develop the needed constitutive models for
use within CR-models so that the controlled release of AIs can be predicted for various application
scenarios and to make them available through a computer aided system for model-based
design/analysis studies. As the controlled release devices consist basically of an AI that is encapsulated
or incorporated within a polymer membrane, the most important properties in the CR-models are the
ones that relate to the AI and the polymer. These are, the solubility of the AI in the polymer and its
diffusivity through the polymer membrane, which have a significant influence in the release of an AI
from a controlled release device and for this reason, the use of predictive constitutive models for AI-
polymer systems becomes important. The CR-models can also, of course, be used for study of the
physical parameters of the microcapsule (not discussed in this paper).

With reference to the above stated objectives, this paper highlights how the application range of any
selected CR-model can be made predictive by embedding the needed constitutive models, and how the
“new” model can be used rapidly and reliably in design/analysis studies involving AI formulations and
their delivery. This implies that the CR-models should be able to predict the properties that are critical to the controlled release mechanism through specially developed property (constitutive) models, and the need for a modelling framework through which any number of CR-models can be quickly evaluated and employed for specific AI-polymer systems. As the design of the AI products involves a “generate and test” paradigm, the inclusion of these models as part of a computer aided systematic approach would be a valuable addition to the tools for polymer as well as product design and analysis. In this systematic approach we perform a model analysis after the CR-model derivation and generate the solution strategies so that the derived CR-model can be modified and extended for different applications.

2. Modelling Framework

Figure 2 illustrates the main features of the modelling framework where different CR-models are coupled together with their corresponding constitutive models for a specific controlled release product design/analysis problem. In principle any CR-model can be included and combined with an appropriate property model through this modelling framework. The framework also needs a database, as different property models come with their corresponding model parameters. The database can also be used to store useful information related to the devices that the CR-model may need. The objective is to very quickly generate the controlled release profile for the specific design/analysis problem under investigation. The modelling tools within ICAS-MoT [Sales-Cruz and Gani, 2003], provides the basis for development of this modelling framework.
The field of controlled release technology offers a wide variety of devices, such as microcapsules that are considered in this paper, all having a similar final goal. A microcapsule is a reservoir system where the AI is enclosed (in the core of radius $r_i$, and with concentration $C_d$) within a polymer membrane (providing an outer microcapsule radius $r_o$), as shown in Figure 3. The AI is released to the surroundings where the concentration is $C_r$. Several commercial products can be found in the market of microencapsulated AIs (pesticides) such as TopNotch and Fultime, with different properties and functionalities [Scher et al. (1998)].
In this section, two basic models (that is, release models without the added constitutive models) are discussed and analyzed in sections 2.1 and 2.2. The extension of the basic model with appropriate constitutive models, including extension of the selected model parameters and their validation are presented in section 2.3. In principle, any basic model can be introduced and combined with these specially developed (with respect to typical AI-polymer combinations) constitutive models.

2.1 Basic Model A

The process of AI release from a polymer microcapsule can be described in most cases by Fickian diffusion, with the appropriate initial and boundary conditions. The CR-model considered here (Comyn, 1985) to illustrate the modelling framework can be used for microcapsules where the concentration of AI in the core is lower than the saturation level. Diffusion of the AI takes place through a very thin film, so Fick’s law can be considered in one dimension only.

2.1.1. Model description

The CR-model consists of a macroscopic part that accounts for the number of microcapsules of different sizes and a microscopic part that accounts for the actual release of the AI from the microcapsule. The number of microcapsules and their size differences are considered through a normal distribution function (Eq. 1).

\[
F(r; \mu; \sigma) = \int_{-\infty}^{r'} \frac{1}{\sqrt{2\pi}\sigma} \exp\left(-\frac{(r - \mu)^2}{2\sigma^2}\right) dr
\]  

(1)
Equation 1 represents the normal distribution function for the microcapsule radius \( r \) in order to get a representation of the various sizes of microcapsules found in solution. This distribution is applied with a specified mean distribution value \( \mu \) and a specific standard deviation \( \sigma \).

In the microcapsules, diffusion occurs through a thin film (of thickness \( h \)), thus the equation of diffusion can be considered in one dimension only with respect to space. The controlled release is modelled with the equations for non-constant activity source \([\text{Eqs. } 2 \text{ and } 3, \text{ Comyn (1985)}]\), that are derived from Fick’s law of diffusion and provide the concentration dependence with time. The CR-model is applicable to systems where the AI is available in solution below the solubility limit (i.e. when the concentration is lower than that of saturation). The concentrations of the AI in the donor compartment and in the release medium are given by Eqs. 2 and 3 (detailed derivations of these equations from Fick’s law can be obtained from the corresponding author.)

\[
\frac{dC_d}{dt} = -\frac{DA}{hV_d} K_{m/d} C_{d,initial} \exp\left(-\frac{DAK_{m/d}}{V_r h} \left(\frac{V_d}{K_{m/d} + V_r} + \frac{V_r}{V_d}\right) t\right) \\
\frac{dC_r}{dt} = \frac{DA}{V_r h} K_{m/d} C_{d,initial} \exp\left(-\frac{DAK_{m/d}}{V_r h} \left(\frac{V_d}{K_{m/d} + V_r} + \frac{V_r}{V_d}\right) t\right)
\] (2) (3)

Equation 2 represents the rate at which the concentration changes with respect to time \( t \) in the donor compartment \( (C_d, \text{g/m}^3) \), that is the “core” (see Figure 3), while Eq. 3 represents the variation of the concentration in the receiver or release medium \( (C_r, \text{g/m}^3) \) with respect to time. In the total model, the size (defined by radius) distribution from Eq. 1 is used to calculate the microcapsule volume and surface areas that need to be specified in order to solve Eqs. 2 and 3. The concentration \( C_d \) is affected
by two properties related to the AI and the polymer, thereby affecting also the performance and release of the AI:

- the diffusion coefficient ($D$, m$^2$/s) of the AI within the polymer.
- the partition coefficients between the polymer membrane and the donor ($K_{m/d}$) and between the release medium and the polymer membrane ($K_{m/r}$).

The geometric parameters of the microcapsule also have an effect on the release: these are the surface area through which diffusion takes place ($A$, m$^2$), the volume of the microcapsule or donor volume ($V_d$, m$^3$), and the thickness of the microcapsule wall ($h$, m). Finally, the initial concentration in the core ($C_{d,initial}$, g/ m$^3$) and the volume of the release medium ($V_r$, m$^3$), also known as bulk volume, are also considered.

### 2.1.2 Model analysis and solution strategy

The CR-model is analysed in terms of number and types of variables and equations. The CR-model represented by Eqs. 1-3 corresponds to a DAE (differential-algebraic equations) system where the different types of variables are listed in Table 1.

### Table 1. Classification of the variables of the model

<table>
<thead>
<tr>
<th>Input/Design Variables</th>
<th>Calculated variables</th>
<th>Parameters (Constitutive variables)</th>
<th>Independent variable</th>
<th>Dependent/State variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>$r_{min}, r_{max}, r_{step}$, $\sigma, \mu$</td>
<td>$r_{\text{mean}}, V_i, A_i$, $%\text{particles}<em>i, N</em>{p,i}$, $M_{\text{initial}}, \Delta M_i, \Delta M_{\text{total}}, %\text{release}$</td>
<td>$K_{m/d}, K_{m/r}$, $D$</td>
<td>$T$</td>
<td>$C_d$</td>
</tr>
</tbody>
</table>

| $C_{d,initial}, V_d$ | $V_r, h$ | |

| $C_r$ |
The CR-model analysis shows that the model equations can be solved for the dependent state variables, given their initial values at time \( t_0 \), the values for the design variables, and the parameters or constitutive variables (or models representing them). Also the equation set can be decomposed into two sub-models:

Sub-model I: Solve Eq. 1, to generate the size distribution data for a specified number of microcapsules.

Sub-model II: Solve Eqs. 2-3, plus associated constitutive equations for each microcapsule size.

Solution strategy for Sub-model I:
For given values of maximum and minimum microcapsule radius (\( r_{\text{max}} \) and \( r_{\text{min}} \) respectively), together with a radius increment (\( r_{\text{step}} \)), the number of microcapsule sizes (\( n_f \)) for which the normal distribution (Eq. 1) needs to be evaluated is calculated through Eq. 4.

\[
  n_f = \frac{r_{\text{max}} - r_{\text{min}}}{r_{\text{step}}} 
\]  

(4)

The distribution function (Eq. 1) is now solved \( n_f \) times to generate a profile of percentage of particles (or number of particles, \( N_{p,i} \)). From these values a total donor volume (\( V_{d,\text{calc}} \)) is calculated according to Eq. 5.

\[
  V_{d,\text{calc}} = \sum_i N_{p,i} V_i 
\]  

(5)

As the total donor volume (\( V_d \)) is usually known (see Table 1), the number of particles of each size (\( N_{p,i} \)) is revised according to the specified donor volume, with Eq. 6.
\[ N_{p,i} = N_{p,i}^* \frac{V_d}{V_{d,\text{calc}}} \] (6)

**Solution strategy for Sub-model II:**

Using the size distribution data for the microcapsules, and initial values for the dependent variables, Eqs. 2-3 plus associated constitutive equations are solved for each microcapsule size. The additional constitutive equations are derived for the variables listed as “calculated” in Table 1. For each microcapsule size, an average radius is calculated (\( r_{\text{mean},i} \), Eq. 7), which provides the area (\( A_i \), Eq. 8) and the volume (\( V_i \), Eq. 9) of each microcapsule.

\[ r_i = r_{\text{mean},i} = \frac{r_{\text{min},i} + r_{\text{max},i}}{2} \ ; \ i = 1, n_f \] (7)

\[ A_i = 4\pi r_i^2 \quad ; \quad i = 1, n_f \] (8)

\[ V_i = \frac{4}{3} \pi r_i^3 \quad ; \quad i = 1, n_f \] (9)

From the initial concentration in each microcapsule (\( C_{d,\text{initial}} \), which is assumed equal for all the microcapsules), the total initial mass (\( M_{\text{initial}} \)) is calculated, as:

\[ M_{\text{initial}} = \sum_i C_{d,\text{initial}} V_i N_{p,i} \] (10)

The mass change (\( \Delta M_i \)), the total mass change (\( \Delta M_{\text{total}} \)) and the release percentage (\( \%\text{release} \)) are obtained through the following equations respectively.

\[ \Delta M_i = C_{d,i} V_i N_{p,i} \] (11)

\[ \Delta M_{\text{total}} = \sum_i \Delta M_i \] (12)

\[ \%\text{release} = 100 \left( \frac{M_{\text{initial}} - \Delta M_{\text{total}}}{M_{\text{initial}}} \right) \] (13)
Note that Eqs. 2-3, 7-9 and 11 are solved for each microcapsule size, while Eqs. 10, 12 and 13 are solved once for the total set of microcapsules. That is, the CR-model consists of $2n_f$ ODE’s (Ordinary Differential Equations), plus $4n_f + 3$ algebraic equations (AE’s), not counting the constitutive model equations. Note that Eqs. 2-3 can also be converted to their analytical AE forms and the resulting AE-system solved as a function of time.

2.1.3 Model solution

In this section the CR-model presented above is tested with experimental data in order to assess its performance and suitability. The test example is selected so that the values of the model parameters and input (design) variables required for the CR-model equation solution, are available from experiment. Shao et al. (1993) have studied the release of a disperse dye solution from a microcapsule and provide all the needed experimental data. The microcapsule used by Shao et al. is prepared by complex coacervation (i.e., phase separation in colloidal systems) and the dye solution is encapsulated with a gelatin and gum acacia membrane.

The CR-model equations (Eqs. 2 and 3) are solved by setting values for the diffusion coefficient ($D$), the wall thickness ($h$) and the two partition coefficients ($K_{m/d}$, $K_{m/r}$) obtained from Shao et al. (1993). The available value for the diffusion coefficient is the apparent diffusion coefficient ($D_{app}$), which includes the partitioning effect ($D_{app} = D/K$), therefore in our simulations the partition coefficients are considered to be equal and with a value of one ($K_{m/d} = K_{m/r} = 1$), in order to avoid accounting for them more than once. The calculated values obtained from the simulation with the microcapsule release model are plotted together with the experimental values from the literature in Figure 4. Note that the sources for the CR-model and the data are not the same and this simple test is made only to confirm that release data obtained independently can be represented by the CR-model. It can be observed that
the model reproduces the release of the dye solution from the microcapsules reasonably well, even though the simulated values are somewhat lower than the experimental data. This small disagreement can be due to differences in the donor volume arising from the distribution of microcapsules sizes, which affects the amounts of AI released.

\[ -\ln \left( \frac{(C_d - C_r)}{(C_d - C_{r,\text{init}})} \right) \]

**Figure 4.** Comparison of model results with literature data [Shao et al. (1993)]; where \( C_{r,\text{initial}} \) is the concentration of the receiver at time zero (g/m\(^3\)) and \( C_{r,f} \) is the concentration of the receiver at 24h (g/m\(^3\)).

### 2.2 Basic Model B

For many microcapsule devices, the release can be accurately modelled with CR-models similar to that of basic model A when the release rate of the AI is of the first-order type (as shown above and in the case studies in section 3) and all the needed model parameters are available. A more complex model is therefore, in principle, not required for these specific applications. Even so, CR-models can be further refined in order to predict more accurately the initial periods of delivery as part of the total release behaviour. In this initial period, before an eventual steady-state is achieved, it is necessary to account...
for the history of the system. That is, the so-called burst and lag time effects. These phenomena depend mainly on the diffusivity of the solute in the polymer, the thickness of the membrane and the storage as well as usage conditions.

The burst and lag time effects occur when, for example, the devices are stored for a period, giving time for the AI to diffuse into the polymer membrane and saturate it. Then, when the system is used the initial delivery rate from the microcapsule becomes greater than that of the steady state, producing thereby the burst effect. On the other hand, if there is no lapse between fabrication and use of the device, the active ingredient does not have time to partition into the membrane and there is a delay before the steady state gradient is reached, this is the lag time effect.

The general equations to model these effects (Eqs. 14 and 15, for burst and lag time effect respectively) are taken from Kydonieus (1980) and the variation of the mass in the receiver as a function of time is derived, where it can be observed that the two phenomena are equivalent but with opposite signs.

\[
\frac{J}{J_{\text{max}}} = 1 + 2 \exp \left( \frac{-DK_{m/d} r^2 t}{h^2} \right) \Rightarrow M_r(t) = J_{\text{max}} A \left[ t + \frac{2}{\alpha'}(1 - \exp(-\alpha' t)) \right] 
\]  

(14)

\[
\frac{J}{J_{\text{max}}} = 1 - 2 \exp \left( \frac{-DK_{m/d} r^2 t}{h^2} \right) \Rightarrow M_r(t) = J_{\text{max}} A \left[ t - \frac{2}{\alpha'}(1 - \exp(-\alpha' t)) \right] 
\]  

(15)

where,

\[
\alpha' = \frac{D \pi^2}{h^2} K_{m/d}
\]

\[
J_{\text{max}} = \frac{DC_{d,\text{initial}}}{h} K_{m/d}
\]
Note that Eqs. 14 and 15 are only applicable for the initial period and not for the rest of the delivery in the cases treated in this work. Therefore, Eqs. 14 and 15 have been modified (see Eqs. 16 and 17) in order to give a first-order release rate after the initial burst or lag time periods.

\[
M_r(t) = \frac{V_r C_{d,initial}'}{(K_{m/r} / K_{m/d} + V_r / V_d)} (1 - \exp(-\alpha t)) + J_{\max} A \frac{2}{\alpha'} (1 - \exp(-\alpha't))
\]

\[
M_r(t) = \frac{V_r C_{d,initial}'}{(K_{m/r} / K_{m/d} + V_r / V_d)} (1 - \exp(-\alpha t)) - J_{\max} A \frac{2}{\alpha'} (1 - \exp(-\alpha't))
\]

where,

\[
\alpha = \frac{DA}{V_r h} \frac{K_{m/d} V_r}{K_{m/r} + V_r / V_d}
\]

\[
C_{d,initial}' = \frac{M_{d,initial}'}{V_d}
\]

\[
M_{d,initial}' = M_{d,initial} - M_{burst/\text{lag},c}
\]

\[
M_{\text{burst},\infty} = \frac{2}{\alpha'} J_{\max} A
\]

\[
M_{\text{lag},\infty} = -\frac{2}{\alpha} J_{\max} A
\]

It is important to note that the initial concentration used (\(C_{d,initial}'\)) in Eqs. 16 and 17 is not the total concentration but a modified one, where the mass released by either burst or lag effect is subtracted (or added respectively) in order to comply with the mass balances.

To illustrate the need and application of the burst and lag time effects, the AI-polymer system considered in case study 1 (for more details on the AI-polymer system and microcapsule data see
section 3.1) is used. This system was reported by Lukaszczyk et al. (1997). In Figure 5 (a) the improvement in the representation of the initial delivery period by using the lag time effect model combined with a first-order release is shown. In this case the burst effect model is also plotted even though it is not occurring, only for illustration purposes. In Figure 5 (b) the need for the modification of the original equations is highlighted by including a first-order release rate process after the initial period. The predicted release also confirms that the release behaviour can be reproduced without the need of more complicated models.

2.3. Extension of Basic Model

Analyzing the microcapsule CR-models presented in the previous section and others reported in the open literature, we observe that there are two parameters that are critical for the applicability of the model to a wide range of polymer-based microcapsules and AIs. These two parameters are the partition coefficient (related to the solubility of the AI in the polymer) and the diffusion coefficient. The

![Graphs showing predicted release of AI as a function of time compared with experimental data.](image-url)
objective here is to present the constitutive models through which the applicability of the basic CR-models in general and those presented above in particular can be extended with respect to the AI-polymer systems. Note that while the constitutive models considered below have been already developed, they have been adapted in this work for the properties of the AI-polymer systems. Therefore, not only the suitability of these models needed to be verified but also, their applicability needed to be extended in terms of new model parameters.

2.3.1. Constitutive model for prediction of partition coefficients

The first attempt has been to select and implement a model for the prediction of the thermodynamic partition coefficients \( K_{p/solv} \) through infinite dilution activity coefficient calculations (Eq. 18).

\[
K_{p/solv} = \frac{\Omega_{1,solv}^*}{\Omega_{1,p}^*}
\]

The challenge here is to use a simple model that is predictive and can then be extended to account for a wide range of complex molecules. The selected model is the “GC-Flory Equation of State” by Bogdanic et al. (1994), which is a simple activity coefficient model based on a group contribution approach, with an existing parameter table that provides accurate and predictive results for solvent-polymer systems. This model is based on a modified form of the Flory equation of state [Flory et al. (1964)], which has been converted into a group-contribution form by Chen et al. (1990). The original Chen et al. (1990) model was revised and simplified together with a new parameter table provided by Bogdanic et al. (1994). This revised model is used in this work as the starting point. The model equations are given in Appendix A.

The GC-Flory EoS is a predictive model in the sense that only the molecular structure (represented by groups), the temperature and the composition of the system need to be provided in order to estimate the
activity coefficient, as illustrated in Figure 6. One advantage of the GC-Flory EOS over some of the other GC-models [Entropic-FV, Kontogeorgis et al. (1993) and UNIFAC-FV, Oishi and Prausnitz (1978)] is that they need accurate data of density for the solvent as well as the polymer at the system temperature. The parameters of the GC-Flory EOS (constitutive model) are both pure component ($C_i$) and group interaction parameters ($\epsilon_{mn}$ and $\epsilon_{mm}$).

![Figure 6. Procedure of activity coefficient calculation through GC-Flory EoS model.](image)

### Testing of GC-Flory EoS

In order to illustrate the possibility of having a completely predictive model for the controlled release of AIs, some test calculations related to the prediction of the partition coefficient are presented. In Table 2 the experimental values [Hao et al. (1992)] of activity coefficients at infinite dilution ($\Omega_{1,p}^\infty$) of two chemicals in a polymer (Poly(n-butyl methacrylate), PBMA) are compared with the ones calculated with the GC-Flory EoS. It can be noted that good agreement has been obtained even though the model parameters were not regressed or tuned with these data. After this initial test, the next validation test involved the calculation of partition coefficients of complex molecules (similar to AIs) in selected polymers. Table 3 highlights some of these results involving three complex molecules in Poly(ethylene-co-vinyl acetate), EVA (drugs are used in this example as the pesticide molecules being studied cannot be disclosed for reasons of confidentiality). These examples are selected so that the
available parameter table of the GC-Flory EoS model could be used and the predicted property values are compared with experimental data reported by Pitt et al. (1988).

Although there are some differences between the experimental and calculated values we have to keep in mind that this has been pure prediction that is, without any adjustment of the original parameters regressed with non-polymer data. We would like to note though, the qualitative goodness of the results. This means that through a modelling framework for generating new groups and parameters, the application range of this constitutive model and its quantitative accuracy can be further extended.

Table 2. Comparison of experimental and calculated activity coefficients at infinite dilution, in weight-basis ($\Omega^{\infty}_{1,p}$)

<table>
<thead>
<tr>
<th>Comp. 1</th>
<th>Comp. 2</th>
<th>T (°K)</th>
<th>$\Omega^{\infty}_{1,p}$</th>
<th>$\Omega^{\infty}_{1,p}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-pentane</td>
<td>PBMA (91000)</td>
<td>343.2</td>
<td>11.0</td>
<td>11.65</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>PBMA (73500)</td>
<td>393.2</td>
<td>3.18</td>
<td>3.38</td>
</tr>
</tbody>
</table>

Table 3. Comparison of experimental and calculated drug partition coefficients between polymer and water ($K^A_{p/w}$), at 298 °K

<table>
<thead>
<tr>
<th>Drug</th>
<th>Polymer</th>
<th>Log $K^A_{p/w}$</th>
<th>Log $K^A_{p/w}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione</td>
<td>EVA</td>
<td>2.61</td>
<td>2.182</td>
</tr>
<tr>
<td>Testosterone</td>
<td>EVA</td>
<td>2.66</td>
<td>2.217</td>
</tr>
<tr>
<td>Progesterone</td>
<td>EVA</td>
<td>3.01</td>
<td>3.210</td>
</tr>
</tbody>
</table>
Extension of GC-Flory EoS

Having the capabilities of the GC-Flory EoS model tested and verified, the next step has been to use the modelling framework to systematically extend the group parameter table so that a large range of AIs and polymers can be handled, as the available parameter table [Bogdanic et al. (1994)] does not have the groups to describe the complex AI molecules as well as the parameters to estimate the needed properties. An extension of the model has been performed [Muro et al. (2005)] and the procedure employed for parameter estimation is highlighted in Figure 7. The data required for estimation of the group parameters includes low molecular weight pure component thermal expansivities ($\alpha$) and enthalpies of vaporization ($\Delta H_{\text{vap}}$) together with the corresponding VLE data. As illustrated in Figure 7, for a new group $n$, the volume and surface area parameters ($R_n$, $Q_n$) are given together with the pure component thermal expansivity, $\alpha(T)$, of the solvent as a function of temperature. With these data, the GC-Flory model is used to generate the heat of vaporization ($\Delta H_{\text{vap}}$) of the solvent as a function of temperature and the activity coefficients ($\Omega_i$), for guessed values of the model parameters (the $C$-parameters and the interactions, $\varepsilon_{nn}$ and $\varepsilon_{nm}$). The calculated values are then checked against experimental values and the procedure is repeated until a minimum of the objective function is obtained.
More details on the methodology for parameter estimation together with the extended group parameter table have been presented elsewhere [Muro et al. (2005)]. The following new groups have been added: aC-O, aC-OH and Cl-(C=C). The important point about introducing new groups is to find solvent-solute mixtures that are smaller than the AI and polymer, respectively, but have the same groups needed to represent the AI and the polymer.

### 2.3.2 Model for the diffusion coefficient

The selected constitutive model in this work is based on the free-volume theory of diffusion [Vrentas & Duda (1977)]. Extensive work has been presented about the free-volume theory as well as attempts to obtain a purely predictive model [Zielinski & Duda (1992)] for solvents in polymers. The objective of this work is to apply and test the same theory for the diffusion of the more complex AI molecules in polymers. The details on how to use the theory in a predictive manner have been presented elsewhere [Zielinski & Duda (1992)] and only the model equations needed for property estimation are given in Appendix B.

As the original model did not have the necessary parameters for the AIs being considered in this work, they had to be first estimated according to the procedure suggested by Zielinski & Duda (1992). In this case, the parameter defined as the ratio of molar volumes of solvent and polymer jumping units ($\xi$), needs a special mention. In the case where the solvent is “small” this parameter is easily obtained through Eq. B.6, given that the volume of the solvent jumping unit ($V_{1j}$) corresponds to its molar...
volume at 0 K ($V_1^0$) and the volume of the polymer jumping unit can be calculated through available correlations (Eqs. B.7-B.8). On the other hand, when the molecule is “large” (as is the case of most AI compounds), Eq. B.6 is not valid and thus the estimation of this parameter is not straightforward. In these cases, two alternatives are possible depending on: (a) if experimental data is available or (b) if no experimental data is available. Application of the first alternative is illustrated for Permethrin (a pesticide AI) for which experimental data of diffusion coefficient in Polypropylene as a function of temperature is available (provided by Syngenta).

The results are presented in Figure 8 and they are considered satisfactory given the small amount of diffusion data available. From this estimation of the $\xi$ parameter the volume of the Permethrin jumping unit can be back-calculated. This is in fact a property of the AI, which is independent of the polymer and can therefore be used to calculate the $\xi$ parameter for this same pesticide in any other polymer. That is, once this $\xi$ parameter has been estimated, it can be used to predict the diffusion coefficient for this AI in all other polymers without the need for additional experimental data. This feature has been illustrated for case study 2 (see section 3.2.).

For the second alternative where no experimental data is available, an extension of the free-volume theory for large molecules [Vrentas et al. (1996)] is used. The theory is based on accounting for the effects of the molecular shape (asymmetry) of the compound and this feature is illustrated through case study 1 (see section 3.1), where molecular modelling has been used to generate the necessary information for the estimation of the $\xi$ parameter.
3. Case studies

As some pesticide and drug molecules are similar in molecular structure and as more data could be found for drug-polymer systems than for pesticide-polymer systems, two case studies are presented, one involving a drug-polymer system and another involving a pesticide-polymer system. The case study with the drug-polymer system also tests the predictive nature of the constitutive models used. The property prediction package within ICAS [Gani, (2002)] has been used to predict some of the necessary properties of AIs and solvents, and, the ICAS-MoT [Sales-Cruz and Gani, (2003)] has been used to provide the modelling objects.

3.1. Case study 1

This case study involves the application of the free-volume theory in a purely predictive manner for the estimation of the diffusion coefficient without use of any experimental diffusivity data and the predicted values are analyzed through the CR-models incorporated into the framework and described in

Figure 8. Diffusion coefficient of Permethrin in Polypropylene. Comparison of estimated (- - -) and experimental data (Δ).
section 2. Note that for this system, experimental data of the release behaviour with respect to time is available in the literature [Lukaszczyk et al. (1997)].

The case study concerns the drug Codeine [CAS Number 76-57-3] that is encapsulated, together with a carrier (an ion exchange resin), within microcapsules made of polyurea. The polymer wall is formed by water promoted polyreaction of the monomer Methylene diphenyl diisocyanate (MDI, [CAS Number 101-68-8]), that can give a cross-linked polymer.

The composition of the microcapsules is taken from the literature [Lukaszczyk et al. (1997)] together with the conditions at which the release experiments have been performed. These data together with the rest of the data that is required in the CR-model is summarized in Table 4 ((a) and (b)) for four different scenarios that have been investigated. Each scenario has a different membrane thickness (defined through a different monomer-MDI to resinate ratio). As some of the data needed by the model was not available, their values have been assumed (marked in italics in Table 4(a)). For example, the dimensions (and the size distribution) of the capsules were not available and therefore, values have been assumed (using as basis dimensions of commercial microcapsules) which were then used to calculate the wall thickness of each of the experiments. With respect to the needed properties of the system, summarized in Table 4 (b), the diffusivity has been predicted with the developed constitutive model while the value for the partition coefficient \( (K_{mr}) \) is adapted from data of Kubo et al. (2001). As for the membrane-donor coefficient \( (K_{md}) \), its value is assumed (based on values for similar systems). The value of the partition coefficients accounts for the respective solubility of the encapsulated compound with the polymer and the release medium, and the donor medium, respectively. Since these do not change from one experiment to another, they are kept constant.
Table 4(a). Summary of the input data required for the mathematical release model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI/resinate</td>
<td>0.1</td>
<td>0.25</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>h (m)</td>
<td>2.86·10^-9</td>
<td>6.72·10^-9</td>
<td>12.23·10^-9</td>
<td>20.85·10^-9</td>
</tr>
<tr>
<td>Max. radius (m)</td>
<td>329·10^-6</td>
<td>329·10^-6</td>
<td>329·10^-6</td>
<td>329·10^-6</td>
</tr>
<tr>
<td>Min. radius (m)</td>
<td>29·10^-6</td>
<td>29·10^-6</td>
<td>29·10^-6</td>
<td>29·10^-6</td>
</tr>
<tr>
<td>Mean radius (m)</td>
<td>129·10^-6</td>
<td>129·10^-6</td>
<td>129·10^-6</td>
<td>129·10^-6</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>3·10^-8</td>
<td>3·10^-8</td>
<td>3·10^-8</td>
<td>3·10^-8</td>
</tr>
<tr>
<td>Radius Step</td>
<td>1·10^-8</td>
<td>1·10^-8</td>
<td>1·10^-8</td>
<td>1·10^-8</td>
</tr>
<tr>
<td>V_b (m³)</td>
<td>400·10^-6</td>
<td>400·10^-6</td>
<td>400·10^-6</td>
<td>400·10^-6</td>
</tr>
<tr>
<td>t (s)</td>
<td>12600</td>
<td>12600</td>
<td>12600</td>
<td>12600</td>
</tr>
<tr>
<td>C_d,initial (g/m³)</td>
<td>358.44·10^3</td>
<td>324.72·10^3</td>
<td>280.697·10^3</td>
<td>220.825·10^3</td>
</tr>
<tr>
<td>V_d (m³)</td>
<td>0.485·10^-6</td>
<td>0.536·10^-6</td>
<td>0.620·10^-6</td>
<td>0.788·10^-6</td>
</tr>
</tbody>
</table>

Table 4(b). Properties required by the controlled release model

<table>
<thead>
<tr>
<th>Variable</th>
<th>All scenarios</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>D (m²/s)</td>
<td>1.027·10^-19</td>
<td>Estimated</td>
</tr>
<tr>
<td>K_mr</td>
<td>2.67</td>
<td>Adapted</td>
</tr>
<tr>
<td>K_m/d</td>
<td>0.11</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

The value of the diffusion coefficient of Codeine in polyurea is estimated, as mentioned above, in a completely predictive manner through the extended predictive model. In order to perform the free volume theory based calculations, some parameters related to the polymer viscosity with respect to temperature (the WLF parameters – see appendix B, Eqs. B.5 to B.7) are required. For the polymer of interest, that is, polyurea, these parameters (or experimental data to estimate them) are not available. Therefore, the parameters corresponding to a polymer that is assumed to have a similar behaviour, a polyurethane, are used [Mark (1996)]. The value for the diffusion coefficient is estimated at the temperature for which the release experiments are reported, that is 309.15 K. The estimated parameters for the free volume theory based model (Eq. B.1 plus associated equations for the parameters) are summarized in Table 5, and the estimated value for the diffusion coefficient is given in Table 4 (b).
Table 5. Free volume theory estimated parameters (pure prediction) for Codeine in Polyurea (modelled as Polyurethane).

<table>
<thead>
<tr>
<th>Compound</th>
<th>(V(0, K) \times 10^6) (m(^3)/mol)</th>
<th>(K_{11}/\gamma \times 10^9) (m(^3)/g K)</th>
<th>(K_{2i-Tg_i}) (K)</th>
<th>(D_0) (m(^2)/s)</th>
<th>(\xi_{theory})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>214.5</td>
<td>1.362</td>
<td>-132.75</td>
<td>5.142 \times 10^{-8}</td>
<td>2.26</td>
</tr>
<tr>
<td>Polyurea (Polyurethane)</td>
<td>148.8</td>
<td>0.323</td>
<td>-181.4</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Finally the release of Codeine from the polyurea microcapsules is calculated using the CR-model (Eqs. 1-3) for the four scenarios listed in Table 4 (a) and the simulated release behaviours are compared with experimental data in Figure 9. The performance of the release model with the predicted diffusion coefficient is very good in all the cases, except for the scenario with the smallest thickness (Scenario 1). This can be attributed to different degrees of cross-linking of the polymer that would affect the value of the diffusion coefficient. In the mentioned case (Scenario 1) the amount of monomer forming the wall is smaller than in the others, the degree of cross-linking being reduced and thus increasing the value of the diffusion coefficient. This is shown in Figure 10 where a higher value for the diffusion coefficient is used (\(D = 1.59 \times 10^{-19}\) m\(^2\)/s) and the release data are accurately described.
Figure 9. Comparison of experimental and estimated Codeine release values as a function of time (\(K_{m/d}=0.11\)). Experimental data: (\(\square\)) Scenario 1, (\(\triangle\)) Scenario 2, (\(\times\)) Scenario 3, (\(o\)) Scenario 4. Predicted release: — Scenario 1, ------ Scenario 2, — — Scenario 3, — Scenario 4.

Figure 10. Comparison of experimental and estimated Codeine release values as a function of time (\(K_{m/d}=0.11\)). Experimental data: (\(\square\)) Scenario 1, (\(\triangle\)) Scenario 2, (\(\times\)) Scenario 3, (\(o\)) Scenario 4. Predicted release: — Scenario 1, ------ Scenario 2, — — Scenario 3, — Scenario 4. Plus: — -- — Scenario 1 with \(D = 1.59 \times 10^{-19}\) m\(^2\)/s.

3.2. Case study 2

In this case study the release of a well-known AI, a pesticide called Permethrin [CAS Number 52645-53-1], from a microcapsule device is presented in order to illustrate the overall application of the developed modelling framework. The encapsulation of this pyrethroid insecticide has a number of advantages, such as the reduction of fish toxicity and a more durable biological effectivity [Dahl (1987)]. The insectically effective amount of Permethrin is 2.24–28.02 mg/m\(^2\), whereas the maximum concentration of Permethrin (related to toxicity) is 18.5 mg of active ingredient/litre. The encapsulation of Permethrin is done by interfacial condensation, resulting in microcapsules of 10 to 45 µm, as the average size and with a polyester wall of 1 to 3 µm of thickness.
As shown in Eq. 18, to estimate the AI-polymer partition coefficient, it is necessary to estimate the infinite dilution activity coefficients for the AI-solvent as well as the AI-polymer systems. The extended GC-Flory model has been used to estimate the infinite dilution activity coefficients of Permethrin-polymer. The polymer in this case is a specific polyester, poly(ethyl methacrylate), PEMA.

For the infinite dilution activity coefficient of AI-solvent, experimental data, if available, can be used. Otherwise, a predictive model such as the UNIFAC model [Fredenslund et al. (1977), Kang et al. (2002)] can be used. For this case study experimental data [Tomlin (2003)] was available and therefore used. From these, the partition coefficients needed in the CR-model were calculated and given in Table 6. For the prediction of the diffusion coefficient, the free-volume theory based model has been used. In this case study, this model is used in a completely predictive manner as the value for the diffusion coefficient of Permethrin in PEMA has been calculated (given in Table 6) with ξ parameter estimated earlier (see section 2.3.2).

Table 6. Inputs for the microcapsule controlled release model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Data type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius (m)</td>
<td>5·10⁻⁶ - 2.25·10⁻⁵</td>
<td>experimental</td>
</tr>
<tr>
<td>Wall thickness (m)</td>
<td>2·10⁻⁶</td>
<td>experimental</td>
</tr>
<tr>
<td>K_{m/d}</td>
<td>2.941</td>
<td>calculated</td>
</tr>
<tr>
<td>K_{m/r}</td>
<td>4.902·10⁸</td>
<td>calculated</td>
</tr>
<tr>
<td>D (m²/s)</td>
<td>1.02·10⁻¹⁵</td>
<td>calculated</td>
</tr>
</tbody>
</table>

Having all the needed CR-model parameters (see Table 6), the release of the AI from the microcapsule can be predicted and analyzed through the modelling framework. The calculated results are shown in Figure 11, where the total number of particles (Nₚ, total) is 8.95·10⁷, nₙ is 175, which resulted in a total of 1053 DAE’s (2*nₙ = 350 ODE’s plus 4*nₙ +3 = 703 AE’s). These results refer to the use of a normal
distribution function for the microcapsule sizes. Other distribution functions, if found more appropriate, can easily be implemented and tested through the modelling framework.

**Figure 11.** Results obtained using the microcapsule model, for release (left) and microcapsule size distribution (right).

### 4. Conclusions

A computer aided modelling framework through which CR-models can be tested, validated and extended has been presented, highlighting the specific basic CR-models and their extension through the addition of the necessary constitutive models. The important constitutive properties in this work are solubility and diffusivity. An activity coefficient model has been tested, validated and adapted for the prediction of solubilities of AIs in polymers for use in various types of CR-models. Also, a model based on the free-volume theory has been tested, validated and adapted for the prediction of diffusion coefficients of AIs in polymers. In both cases, parameter estimation features have been incorporated into the modelling framework so that new groups or components and their parameters, when necessary,
can be easily and systematically obtained. As highlighted through the case studies, the integration of the CR-models, the constitutive models and a database within a computer-aided (modelling) framework provides useful tools for design and analysis studies of formulated pesticide products. That is, through this modelling framework, it will be possible to generate formulated pesticide product alternatives and microcapsule alternatives and test them very quickly before performing the final step of experimental analysis. These results also illustrate the successful application of a systematic computer aided approach to solve non-traditional CAPE problems. It should be noted, however, that the consitutive models have been adapted and extended so the final CR-model predicts reliable release behaviour. It is a bonus if the constiutive models also predict the corresponding properties accurately. In this case, much work is needed to establish the changes of diffusivity as a function of the application scenario (a topic for further research).

Acknowledgment

The authors would like to thank Syngenta for the funding provided for this project, as well as the advice and the interest received.

List of Symbols

\begin{itemize}
  \item $A$ Surface area through which diffusion takes place (m$^2$)
  \item $C$ Temperature dependent molecular external degrees of freedom parameter
  \item $C_{10,n}$, $C_{T,n}$, $C_0$ Degree of freedom parameters
  \item $C_d$ Concentration of the donor as a function of time (g/m$^3$)
  \item $C_i$ Number of external degrees of freedom associated with component i
  \item $C_r$ Concentration of the receiver as a function of time (g/m$^3$)
  \item $C_{1j}^{\text{WLF}}$ WLF parameter of component j
  \item $C_{2j}^{\text{WLF}}$ WLF parameter of component j (K)
\end{itemize}
D  Polymer-solvent binary mutual diffusion coefficient (m^2/s)
D_1  Self-diffusion coefficient of the solvent (m^2/s)
D_o  Constant pre-exponential factor (m^2/s)
D_{app}  Apparent diffusion coefficient (m^2/s)
E  Energy (per mol) that a molecule needs to overcome attractive forces which constrain it to its neighbours (cal/mol)
h  Thickness of the microcapsule wall (m)
J  Flux (g/m^2s)
J_{max}  Steady-state flux (g/m^2s)
K_{ij}  Free-volume parameter of component j (m^3/g K)
K_{2j}  Free-volume parameter of component j (K)
K_{m/d}  Partition coefficient of the AI between the donor and the polymer membrane
K_{m/r}  Partition coefficient of the AI between the polymer membrane and the release medium
K_{p/solv}  Partition coefficient between polymer and solvent
M  Mass (g)
M_j  Molecular weight of component j (g/mol)
M_{2j}  Molecular weight of the polymer jumping unit (g/mol)
n_f  Number of points to evaluate the function
n  Total number of moles of the system (kmol)
n_i  Number of moles of component i (kmol)
N_p  Number of particles
P  Pressure of the system (Pa)
q_i  Surface area of component i
Q_n  Surface area of group n (normalized Van der Waals surface area, UNIFAC)
r  Microcapsule radius (m)
r'  Integration limit for microcapsule radius, see Eq. (1)
R  Gas constant
R_n  Hard-core volume of group n (normalized Van der Waals volume, UNIFAC)
t  Time (s)
T  Temperature of the system (K)
T_0  Reference temperature (298.15 K)
T_{g,j}  Glass transition temperature of component j (K)
V  Volume (m^3)
V_d  Donor volume (m^3)
V_r  Receiver volume (m^3)
v  Molar volume of the system (m^3/kmol), in GC-Flory EoS
v_i  Molar volume of component i, in GC-Flory EoS
v_i^*  Molar hard-core volume of component i (m^3/kmol), in GC-Flory EoS
\bar{v}  Reduced volume of the system
\bar{v}_i  Reduced volume of pure component i
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_j^*$</td>
<td>Specific critical hole free volume required for a jump (m$^3$/g), for component j, in free volume theory</td>
</tr>
<tr>
<td>$V_1^0$</td>
<td>Molar volume of a solvent at 0 K (m$^3$/mol)</td>
</tr>
<tr>
<td>$V_{ij}$</td>
<td>Molar volume of a solvent jumping unit (m$^3$/mol)</td>
</tr>
<tr>
<td>$V_{2j}$</td>
<td>Molar volume of a polymer jumping unit (m$^3$/mol)</td>
</tr>
<tr>
<td>$w_i$</td>
<td>Weight fraction of component i</td>
</tr>
<tr>
<td>$x_i$</td>
<td>Molar fraction of component i</td>
</tr>
<tr>
<td>$z$</td>
<td>Coordination number (z=10)</td>
</tr>
</tbody>
</table>

**Greek letters**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Thermal expansivity (K$^{-1}$)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Polymer specific proportionality constant</td>
</tr>
<tr>
<td>$\chi$</td>
<td>Flory-Huggins polymer-solvent interaction parameter</td>
</tr>
<tr>
<td>$\Delta H_{\text{vap}}$</td>
<td>Enthalpy of vaporization (J/kmol)</td>
</tr>
<tr>
<td>$\Delta M$</td>
<td>Mass change (g)</td>
</tr>
<tr>
<td>$\Delta \epsilon_{ij}$</td>
<td>Interaction energy parameter (J/kmol of contact sites)</td>
</tr>
<tr>
<td>$\Delta \epsilon_{nm}$</td>
<td>Interaction energies between unlike groups n and m (J/kmol of interaction sites)</td>
</tr>
<tr>
<td>$\epsilon_{nn}$</td>
<td>Interaction energies between like groups (J/kmol of interaction sites)</td>
</tr>
<tr>
<td>$\epsilon_{ij}(\bar{V}<em>j), \epsilon</em>{ij}(\bar{V}_i)$</td>
<td>Energy interaction parameters</td>
</tr>
<tr>
<td>$\phi_j$</td>
<td>Volume fraction of component j</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Overlap factor accounting for shared free volume</td>
</tr>
<tr>
<td>$\theta_i$</td>
<td>Surface area fraction of component i</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Microcapsule mean radius (m)</td>
</tr>
<tr>
<td>$v_n^{(i)}$</td>
<td>Number of groups n in component i</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>$\varphi_i$</td>
<td>Segment volume fraction of component i</td>
</tr>
<tr>
<td>$\Omega_i$</td>
<td>Activity coefficient (weight basis) of component i</td>
</tr>
<tr>
<td>$\Omega_i^{\infty}$</td>
<td>Infinite dilution activity coefficient (weight basis) of component i</td>
</tr>
<tr>
<td>$\Omega_i^{\text{attr}}$</td>
<td>Attractive contribution to the activity coefficient</td>
</tr>
<tr>
<td>$\Omega_i^{\text{comb}}$</td>
<td>Combinatorial contribution to the activity coefficient</td>
</tr>
<tr>
<td>$\Omega_i^{\text{fv}}$</td>
<td>Free-volume contribution to the activity coefficient</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Ratio of molar volumes for the solvent and the polymer jumping units</td>
</tr>
</tbody>
</table>

**Subscripts**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>calc</td>
<td>Calculated (value)</td>
</tr>
</tbody>
</table>
d Donor
exp Experimental (value)
i, j Component i and j respectively
initial Initial value
m, n Group of type m, n
max Maximum
mean Mean value
min Minimum
p Polymer
r Release medium
solv Solvent
step Step size (increment)
total Total value

Superscripts
attr Attractive
comb Combinatorial
fv Free-volume
∞ Infinite dilution
Appendix A. GC-Flory EoS model equations

The model equations are listed below without further explanations, these being out of the scope of this paper. For more details see Bogdanic et al. (1994). The activity coefficient (on weight basis) for component i is given by,

\[
\ln \Omega_i = \ln \Omega_i^\text{comb} + \ln \Omega_i^\text{f} + \ln \Omega_i^\text{attr}
\] (A.1)

Where, each of the terms on the right side of Eq. A.1 is given by,

\[
\ln \Omega_i^\text{comb} = \ln \frac{\phi_i}{w_i} + 1 - \frac{\phi_i}{x_i}
\] (A.2)

\[
\ln \Omega_i^\text{f} = 3(1 + C_i) \ln \frac{\hat{v}_i^{1/3} - 1}{\hat{v}_i^{1/3} - 1} - C_i \ln \frac{\hat{v}_i}{\bar{v}}
\] (A.3)

\[
\ln \Omega_i^\text{attr} = \frac{1}{2} \sum_j \left[ \frac{1}{RT} \left( \varepsilon_j(\bar{v}) - \varepsilon_j(\hat{v}) \right) + 1 - \ln \sum_j \theta_j \exp \left( \frac{-\Delta \varepsilon_{ij}}{RT} \right) \right] - \frac{\sum_j \theta_j \exp \left( \frac{-\Delta \varepsilon_{ij}}{RT} \right) \Delta \varepsilon_{ij}}{\sum_k \theta_k \exp \left( \frac{-\Delta \varepsilon_{kk}}{RT} \right)}
\] (A.4)

With the following definitions for each of the variables occurring in Eqs. A.2 – A.4,

\[
\phi_i = \frac{x_i v_i^*}{\sum_j x_j v_j}
\] (A.5)

\[
\theta_i = \frac{x_i q_i}{\sum_j x_j q_j}
\] (A.6)

\[
v_j^* = (1.448)(15.17) \sum_a n_a R_a
\] (A.7)

\[
v^* = \sum_j x_j v_j^*
\] (A.8)
\[ q_i = \sum_n v_n q_n \]  
(A.9)

\[ C = \sum_i x_i C_i \]  
(A.10)

where,

\[ C_i = \sum_n v_n \left[ C_{T_{0,n}} + C_{T,n} \left( \frac{1}{T} - \frac{1}{T_0} \right) + \sum_n \sum_m R_m r_m C_n^0 \right] \]  
(A.11)

\[ \varepsilon_{ji}^0 = \sum_m \theta_{m}^{(i)} \sum_n \theta_{n}^{(j)} \varepsilon_{nm} \]  
(A.12)

where,

\[ \theta_{n}^{(i)} = \frac{\nu_{n}^{(i)} Q_n}{q_i} \]  
(A.13)

\[ \varepsilon_{nm} = -\left[ \varepsilon_{mn} \varepsilon_{nn} \right]^{1/2} + \Delta \varepsilon_{nm} \]  
(A.14)

\[ \Delta \varepsilon_{ji} = \varepsilon_{ji} - \varepsilon_{ii} = \varepsilon_{ji}(\tilde{v}) - \varepsilon_{ii}(\tilde{v}) \]  
(A.15)

where,

\[ \varepsilon_{ji}(\tilde{v}) = \frac{\varepsilon_{ji}^0}{\tilde{v}} ; \varepsilon_{ii}(\tilde{v}) = \frac{\varepsilon_{ii}^0}{\tilde{v}} \]  
(A.16)

Finally, the last term on the right hand side of Eq. A4 is obtained from the following Equation of state,

\[ P = \frac{nRT}{\tilde{v}} \left( \tilde{v}^{1/3} + C \right) + \frac{E_{\text{attr}}(\tilde{v})}{\tilde{v}} \]  
(A.17)

where the energy parameter \( E_{\text{attr}} \) is defined as,
Appendix B. Free-volume theory based model for diffusion coefficient

A summary of the main equations for the free-volume theory based model for diffusion coefficient is presented below (for more details the reader is referred to Zielinski & Duda (1992)).

The polymer(2)-solvent(1) binary mutual diffusion coefficient (D) is expressed as,

\[
D = D_1 \left(1 - \phi_1\right)^\gamma \left(1 - 2\chi\phi_1\right)
\]

(B.1)

where \(D_1\) is the self-diffusion coefficient of the solvent, and is calculated as,

\[
D_1 = D_0 \exp\left(-\frac{E^{\text{attr}}}{RT}\right) \exp\left(-\frac{(w_1V_1^* + w_2\xi V_2^*)}{w_1 K_{11}\left(K_{21} - T_{g1} + T\right) + w_2 K_{22}\left(K_{22} - T_{g2} + T\right)}\right)
\]

(B.2)

for \(T_g < T \leq T_g + 150 \, ^\circ\text{K}\)

At high temperatures (\(T > T_g + 150 \, ^\circ\text{K}\)), diffusion is no longer free-volume limited and energy effects become dominant.

The parameters in Eq. B.2 can be calculated from the following equations,

\[
\frac{\gamma V^*_j}{K_{ij}} = 2.303C^{\text{WLF}}_i C^{\text{WLF}}_2
\]

(B.3)

\[
K_{2j} = C^{\text{WLF}}_{2j}
\]

(B.4)

\[
\xi = \frac{V_{1j}}{V_{2j}}
\]

(B.5)

If the solvent is “small”, the right hand side of Eq. B.5 is represented by,
\[ \xi = \frac{V^n_1}{V^*_{2j}} = \frac{M_1V^*}{M_jV^*_2} \quad \text{(B.6)} \]

\[ M_{2j} = \frac{\gamma}{\beta K_{12}} \quad \text{(B.7)} \]

\[ V_{2j} = 0.6224 * T_g (K) - 86.95 \quad \text{(B.8)} \]

Vrentas et al. (1996) proposed (Eq. B.9) a modification of Eq. (B.5) for calculation of the parameter \( \xi \), to be used with the free-volume theory based model for the diffusion and the self-diffusion coefficients (Eqs. (B.1) and (B.2)), respectively.

\[ \xi = \frac{V^n_{1j}}{V^*_{2j}} \quad \text{(B.9)} \]

The parameter \( \psi \), which previously was set equal to 1, must now different and calculated through Eq. (B.10), which includes the effect of the asymmetry of the molecule through the so-called aspect ratio (B/A).

\[ \psi = \frac{1}{1 + \frac{V^n_{1j}}{V^*_{2j}} (1 - A/B)} \quad \text{(B.10)} \]

The final expression for the \( \xi \) parameter is therefore obtained as,

\[ \xi = \frac{\xi_L}{1 + \xi_L (1 - A/B)} \quad \text{(B.11)} \]

With this modified model, the molecules still jump as single units but \( \xi \neq \xi_L \) because the average hole free volumes of the solvent and the polymer are different (due to the asymmetry of the molecule).
References


chitosan coated tablets. *J. of Controlled release* 70, 277-284


