Implementation of the "Sequential Layer" Controlled-Release Model

Irina Graf, Sweta Somasi, Jozef Bicerano, Tim Cabelka

The Dow Chemical Company, Midland, MI 48674

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Introduction

Polymeric matrices containing hypromellose (HPMC) are widely used as oral sustained-release drug-delivery systems. An accurate, predictive model of drug release would rapidly provide an initial formulation, permit an inexpensive investigation of multiple size and shape options, and provide insight into real-world formulation development challenges. As a result, both development expenses and time to market would be reduced.

A broad spectrum of mathematical models has been developed to describe drug release from HPMC-based tablets, from simple empirical and semi-empirical models to more complex mechanistic theories that consider diffusion, swelling, and dissolution processes simultaneously.[1] The "sequential layer" model developed by Siepmann, Peppas, *et al.*, is a more fundamental mathematical model for controlled drug release.[1-5]

To our knowledge there is no commercially available software that uses the Siepmann-Peppas model to predict drug release. Therefore, we undertook to implement it into a user-friendly tool. It was also of interest to us to implement this model as a starting point in gaining a better understanding of drug-release kinetics. The fit to experimental data for two polymer-drug combinations is compared to that previously given in the literature. Possible explanations for the systematic differences in the predicted profiles are given.

Model Description

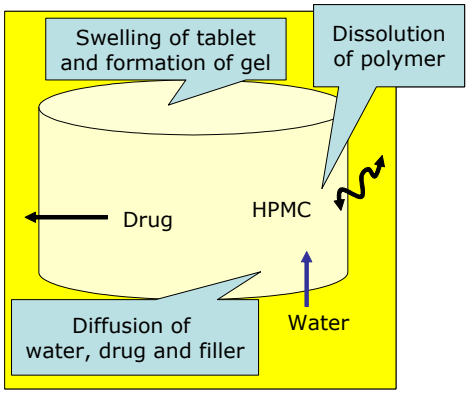
There are several simultaneous processes considered in the Siepmann-Peppas "sequential layer" model (Figure 1):

- Diffusion of water into the tablet.
- Swelling of the tablet as water enters.
- Formation of gel.
- Diffusion of drug and filler out of the tablet.
- Dissolution of the polymer matrix.

Key attributes of the model include:

- Tablet geometry is cylindrical.
- Water and drug diffusion coefficients vary as functions of water concentration.
- Polymer dissolution is incorporated.
- Change in tablet volume is considered.

Figure 1. Model requirements.



Key equations include:

$$\frac{\partial c_w}{\partial t} = \nabla(-D_1 \nabla c_w)$$

$$\frac{\partial c_d}{\partial t} = \nabla(-D_2 \nabla c_w)$$

$$D_i = D_{i,\text{crit}} \exp\left[-\beta_i\left(1-\frac{c_w}{c_{1\text{crit}}}\right)\right]$$

$$\frac{\partial m_p}{\partial t} = -k_{diss} A_t$$

where:
m_p = mass of polymer at time t
k_{diss} = dissolution rate constant
A_t = time-dependent surface area of the tablet

The primary advantage of the Siepmann-Peppas model is that it is mathematically simple, yet physically reasonable. We were able to test the model with different molecular weight grades of METHOCEL* K hypromellose (USP substitution type 2208), different dissolution media (0.1N HCl, 7.4 phosphate buffer), different drugs (theophylline, acetaminophen, propranolol hydrochloride, chlorpheniramine maleate, diclofenac sodium), and different drug loadings (1-70%).

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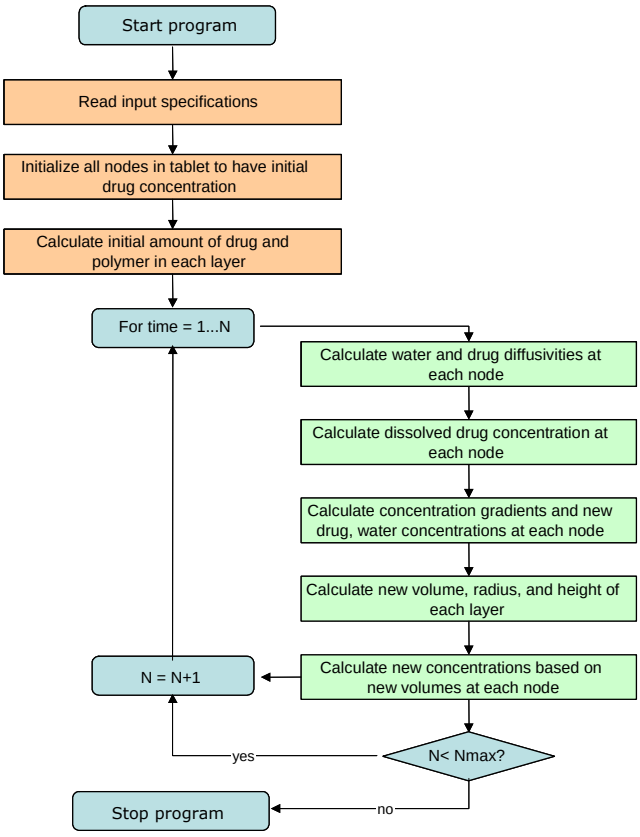
However, the model does have some limitations, such as:

- No explicit formation of gel.
- Fillers cannot be added to the current framework.
- Hydrodynamic effects of media ignored.
- Ideal conditions (thermodynamic mixing, perfect sink conditions, *etc*.) assumed.
- Instantaneous dissolution assumed, dissolution kinetics ignored. (An alternative approach is given in Ref. 6.)

Dow Implementation

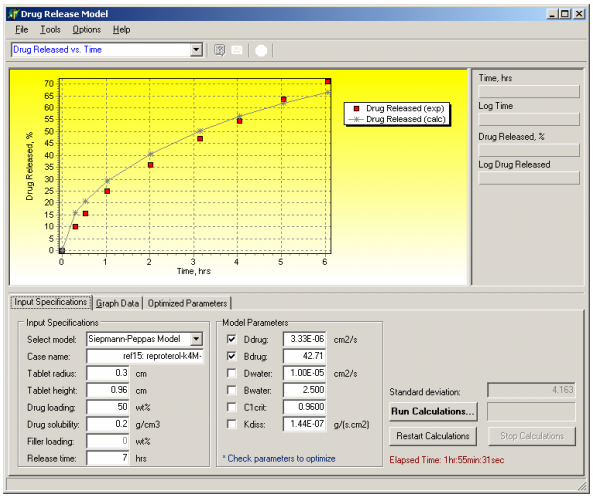
Figure 2 is a flow chart of the Dow implementation of the model. Following initialization of the input parameters, the system of partial differential equations given above is solved using finite difference methods. The tablet volume is recomputed, and the system remeshed. The concentrations of drug, polymer, and water are normalized after the volume update to keep the mass inside the tablet boundaries constant during the same time step. Then the time step is incremented. The typical calculation time is in the range of 1 minute for simulation of a dissolution of 12 h.

Figure 2. Flow chart for implementation of the Siepmann-Peppas model.



A Dow implementation of the Siepmann-Peppas model was developed using Fortran language. The user interface (Figure 3) was developed using Delphi language (Borland Delphi V7 environment). With the user interface, the user can either input model parameters or choose them to be fitted using the particle swarm optimizer (e.g., diffusivities, erosion rate, etc.). The interface gives a graphical representation of experimental results and model predictions and provides the standard deviation to determine goodness of fit. Results can be exported to Excel.

Figure 3. Graphic user interface.



Results and Discussion

The Dow implementation of the model was tested for METHOCEL K15M Premium matrices and compared to Siepmann-Peppas published results. In our study, we used experimental data published by Siepmann *et al.*,[3] and model parameter values (*e.g.*, $D_{2,crit.}$, β_2) that were given in their reports.[2-5] For values used, see "Application of the 'Sequential Layer' Model to Drug-Release Profiles," Form No. 198-02120.

Predicted water concentration profiles at time steps 0.05, 1, and 8 h for a theophylline/METHOCEL K15M system were as expected (Figure 4).

Predicted tablet dimensions (radius and half-height) for theophylline/METHOCEL K15M Premium system during drug release were also as expected (Figure 5).

Figure 4. Predicted water concentration profiles.

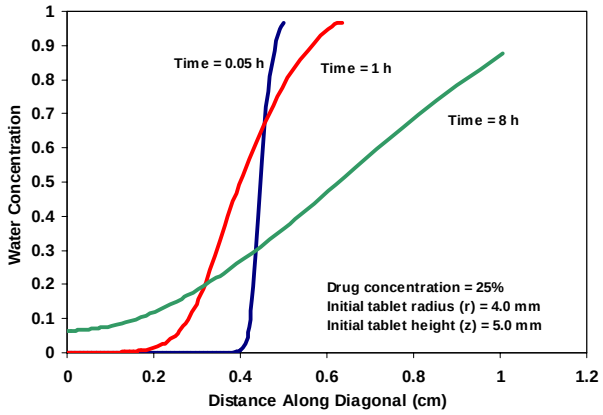
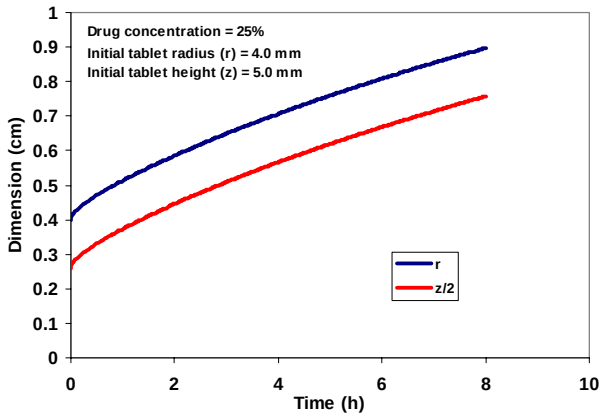


Figure 5. Predicted change in size with time.



While the model predictions published by Siepmann *et al.* were in good agreement with experimental data,[3] our implementation agreed only qualitatively with the observed trends, as shown in Figure 6 for the slightly soluble drug theophylline with METHOCEL K15M Premium in phosphate buffer (pH 7.4). Initial tablet radius was 4.0 mm, tablet height as given in the legend. Drug loading was 50%. The curves are model predictions from Dow implementation; the symbols are experimental data (see Ref. 4).

We conducted a similar simulation for the soluble drug chlorpheniramine maleate in a METHOCEL K15M Premium matrix (Figure 7), also extensively studied.[3] A systematic shift in results was observed here as well, compared to the previously published model predictions. The experimental data is from Ref. 3. The drug system was chlorpheniramine maleate (50% drug loading) and METHOCEL K15M Premium in 0.1 M HCl media. Initial tablet radius and height are given in the legend. All input parameters were from previously cited publications of Siepmann and co-workers. Siepmann *et al.*[3] report a much better fit for these data.

Figure 6. Predicted and experimental theophylline release.

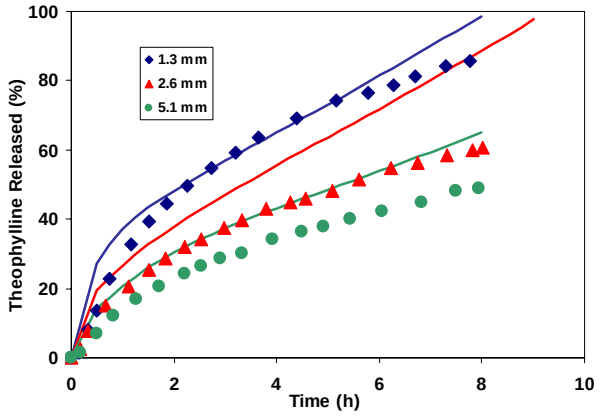
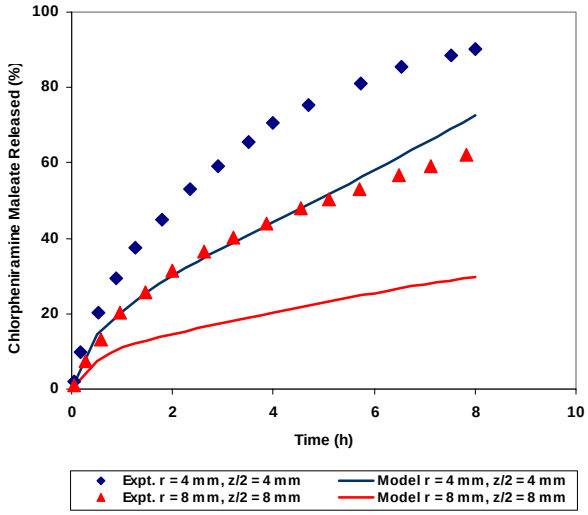


Figure 7. Predicted and experimental chlorpheniramine maleate release.



There are several possible reasons for differences between published and Dow results:

- Some of the parameter values (water diffusivity, for example) were published only for the original "uniform swelling" model of Siepmann *et al*.[5]
- Previously published dissolution profiles frequently fit multiple parameters simultaneously. In this work, all input parameters were "set."
- The density values used for drug, polymer, and water components during model calculations are not explicitly stated in the publications. In the figures shown, we assumed a tablet density of 1.0 g/cm^3 for calculating tablet mass.

- The details of an important step required in the model are not explicitly described in the published reports. This step normalizes the concentrations of drug, polymer, and water after the volume update to keep their mass inside the tablet boundaries constant during the same time increment. Given the boundary conditions of the outside surface of the tablet, there is no exact way of solving this step, but there are several ways of "approximating" it. Depending on the approximation technique chosen, there will be differences in the solution to the coupled partial differential equations.

Conclusions

The sequential layer model developed by Siepmann, Peppas, *et al.*, is a promising approach to modeling the controlled release of drugs from hydrophilic matrices. Using previously published values for the input parameters, the Dow implementation of the sequential layer model exhibited a systematic shift in the predicted drug-release profiles compared to the published results. This illustrates that predicted drug-release profiles are sensitive to parameters such as experimentally determined drug and water diffusion coefficients, to assumptions about the densities of the materials, and to the techniques used to normalize concentrations following each remeshing step.

We will continue to refine the model as a means of improving our understanding of these important oral sustained-release systems. Implementation of the sequential layer model serves as a key step in building increasingly more sophisticated mathematical models capable of predicting drug release from the more complex formulations typically commercialized.

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