Application of the "Sequential Layer" Model to Drug-Release Profiles

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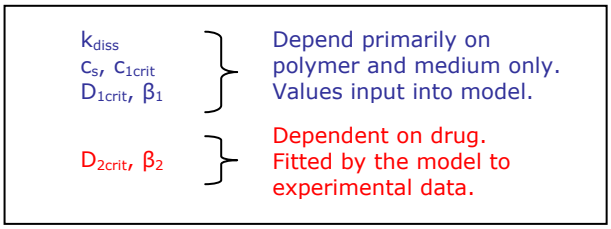
Introduction

Polymeric matrices are commonly used in oral controlled drug-delivery systems. The most widely used hydrophilic polymers are hypromellose (HPMC) structural variants.

Many mathematical models have been developed to describe drug release from HPMC-based tablets, from simple empirical and semi-empirical models to more complex mechanistic models that consider diffusion, swelling, and dissolution processes.[1] The Siepmann-Peppas "sequential layer" model is a more fundamental mathematical model for the prediction of sustained drug release.[2]

The model considers many of the factors and physical phenomena relevant to modeling the sustained release of drugs from tablets under typical *in vitro* conditions. Values for the parameters used by the model have been published for only a few drugs.[2-5] In this study, parameters that are drug-independent are entered into the model, and the two parameters describing concentration-dependent diffusivity of the drug are fitted by the model to experimental data (Figure 1).

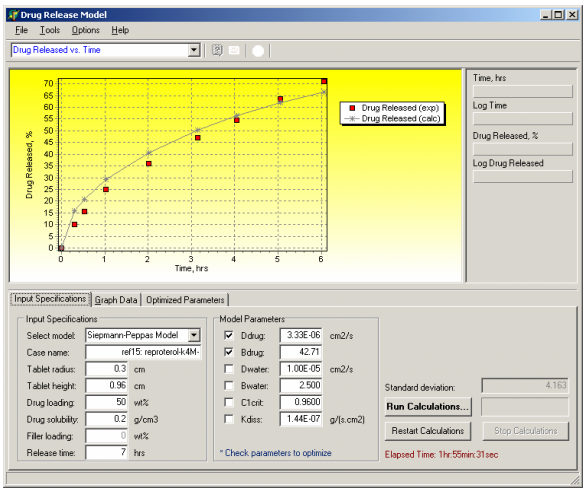
Figure 1. Parameters used by the model.



Dow Implementation

The sequential layer model was implemented using Fortran (see "Implementation of the 'Sequential Layer' Controlled-Release Model," Form No. 198-02121). The user interface was developed using Delphi (Figure 2). The user can either input model parameters or choose them to be fitted using a particle swarm optimizer (e.g., diffusivities, erosion rate, etc.). The interface gives a graphical representation of experimental results and model predictions and provides standard deviation to determine goodness of fit. Results can be exported to Excel.

Figure 2. Graphic user interface.



Values for drug-independent parameters are those reported by Siepmann *et al.*[1-5] To determine the drug-dependent model parameters, experimental data were fitted using a Dow implementation of particle swarm optimization.[6] Figure 3 is a flowchart for the implementation. A typical optimization required 40 iterations with a population size of 20.

Results and Discussion

A systematic shift in results obtained with the Dow implementation of the sequential layer model was observed compared to the results published by Siepmann *et al.*[3,4] when setting all seven model parameters to previously published values.

The observed discrepancies in the results can have several explanations (see "Implementation of the 'Sequential Layer' Controlled-Release Model," Form No. 198-02121 for details). For example, the Dow implementation of the sequential layer model was compared with experimental data for a theophylline-METHOCEL* K15M system published by Siepmann and Peppas[3] and the output from their implementation of the model (see Figure 4). Although the model predictions published by Siepmann and Peppas were in very good

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agreement with the experimental data (not shown), our initial results were not.

Figure 3. Flow for Dow implementation of a particle swarm optimizer.

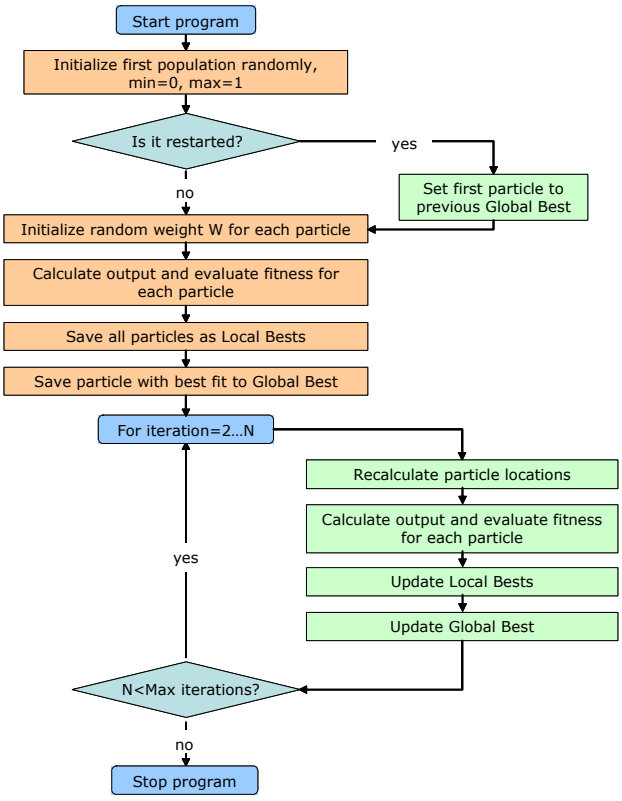


Figure 4. Drug-release profiles for theophylline-METHOCEL K15M Premium.

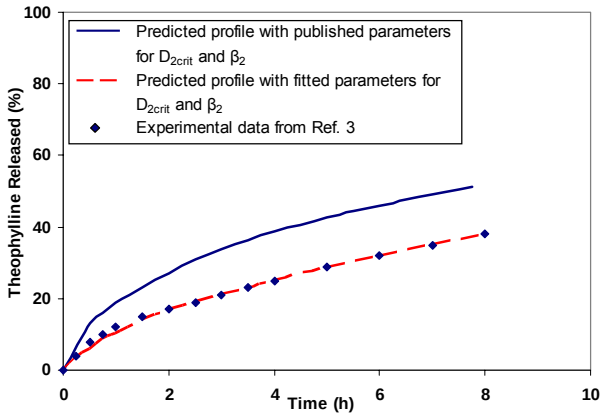


Figure 4 shows the predicted drug release obtained using Dow implementation of the sequential layer model using only previously published values and where the parameters D_{2crit} and β_2 were re-determined by fitting the experimental data using the particle swarm optimizer. The values for model parameters used in Figure 4 are given in Table 1. In this case, changing only the values for D_{2crit} and β_2 dramatically improved the goodness of the fit.

Table 1. Model parameters used for predicted theophylline release.

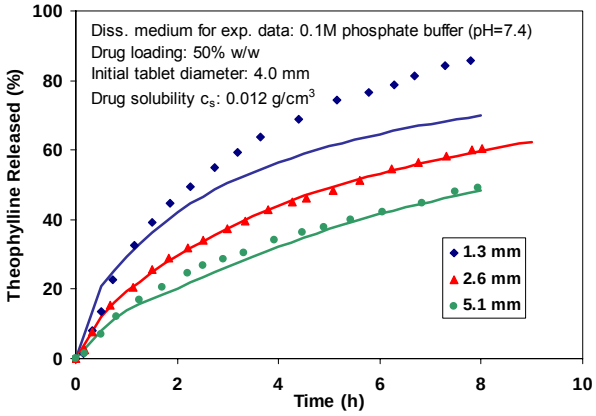
Parameter	A	B
c_{1crit}	0.968	0.968
k_{diss} (g/cm^{2}s)	1.07×10^{-7}	1.07×10^{-7}
D_{1crit} (cm^2/s)	5.6×10^{-6}	5.6×10^{-6}
β_1	2.5	2.5
D_{2crit} (cm^2/s)	11×10^{-6}	1.6×10^{-6}
β_2	22.4	3.579

A: Literature values
B: Values used following fitting with particle swarm optimizer
Matrix polymer: METHOCEL K15M Premium
Dissolution medium for experimental data: 0.1M phosphate buffer (pH=7.4)
Drug loading: 60% w/w, tablet diameter: 6.0 mm, tablet weight: 500 mg
Drug solubility c_s: 0.012 g/cm^3

The Dow implementation was also tested against the theophylline-METHOCEL K15M Premium data given in Ref. 4, where the effect of initial tablet height on drug release was investigated. Once again, simply entering available literature values for all of the model parameters did not produce good fits to the experimental data for all three tablet heights (data not shown). However, if D_{2crit} and β_2 were fitted to the experimental data with the optimizer, good fits were obtained.

In Figure 5, the optimizer was used to generate D_{2crit} and β_2 at tablet height 2.6 mm, and these values were then used as inputs to the model to generate release profiles for tablets with heights of 1.3 mm and 5.1 mm. The fit for tablet height 5.1 mm is quite good, while the predicted profile for tablets with height 1.3 mm begins to deviate from experiment after about 2 hours.

Figure 5. Effect of initial tablet height on drug-release profiles for theophylline-METHOCEL K15M Premium.

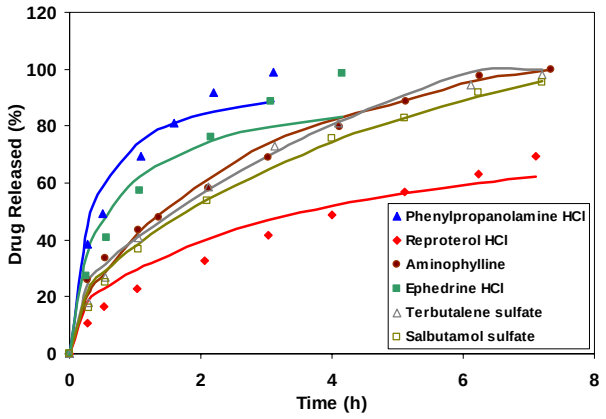


Dow implementation of the sequential layer model was also applied to experimental data for a series of structurally-related bronchodilators.[7] The drugs have similar solubility, but their calculated "cavity surface areas" vary from 3.5 to 6.7 nm^2. The

original authors had correlated the rate of drug release with the cavity surface area.

Figure 6 shows drug-release profiles calculated using the published parameters D_{1crit}, β_1, k_{diss}, and c_{1crit}. The drug-dependent parameters β_2 and D_{2crit} were determined by fitting the experimental data for individual drugs.

Figure 6. Drug-release profiles for a series of bronchodilators from matrix tablets containing METHOCEL K15M Premium.



While we were able to get a good fit for slower releasing drugs, the fit for faster releasing drugs (ephedrine HCl and phenylpropanolamine HCl) was poor. Interestingly, if we allowed D_{1crit} to increase, we were able to achieve a good fit for faster releasing drugs. However, when using the greater value for D_{1crit}, the fit for the slower releasing drugs then became poorer.

Conclusions

The Siepmann-Peppas sequential layer model is a promising model for controlled drug-release studies. The Dow implementation of the sequential layer model exhibited a shift in predicted drug-release profiles compared to the results published by Siepmann *et al*. By using most of the published parameter values and by fitting drug-dependent parameters, D_{2crit} and β_2, satisfactory fits were achieved.

The sequential layer model was tested with several experimental data sets found in the open literature. For one set of drugs, a satisfactory fit was achieved for the slower releasing drugs by using published parameters and by fitting the drug-dependent parameters D_{2crit} and β_2. To achieve a good fit for the faster releasing drugs of the set, it was necessary to adjust the D_{1crit} parameter, implying that at high drug loadings the structure of the drug may alter polymer hydration or tablet porosity. It has recently been reported that high drug loadings lead to faster diffusion of water molecules inside an HPMC gel layer.[8]

References

1. Siepmann, J.; Peppas, N.A. *Adv. Drug Deliv. Rev.* 48 (2001) 139-157.
2. Siepmann, J.; Kranz, H.; Bodmeier, R.; Peppas, N.A. *Pharm. Res.* 16 (1999) 1748-1756.
3. Siepmann, J.; Peppas, N.A. *Pharm. Res.* 17 (2000) 1290-1298.
4. Siepmann, J.; Streubel, A; Peppas, N.A. *Pharm. Res.* 19 (2002) 306-314.
5. Siepmann, J.; Podual, K.; Sriwongjanya, M.; Peppas, N.A.; Bodmeier, R. *J. Pharm. Sci.* 88 (1999) 65-72.
6. Kennedy, J.; Eberhart, R.C. *Swarm Intelligence*, Morgan Kaufmann Publishers, 2001.
7. Baveja, S.K.; Ranga Rao, K.V.; Singh, A.; Gombar, V.K. *Int. J. Pharm.* 41 (1988) 55-62.
8. Tritt-Goc, J.; Kowalchuk, J.; Pislewski, N. *J. Pharm. Pharmacol.* 55 (2003) 1487-1493.

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