

Mathematical Model for Simulation and Control of Drug Release from Hydrophilic Matrices

ABSTRACT SUMMARY

This work describes a predictive formulation model, HyperStart®, oral solid dose formulation service, that provides pharmaceutical scientists with a starting formula for hydrophilic matrix tablets. HyperStart uses mathematical relationships derived from extensive experimental data to provide start-up formulations based on drug loading, drug solubility, filler level and type and release profile desired.

INTRODUCTION

Hypromellose (hydroxypropyl methylcellulose; HPMC) is the most commonly used polymer in the formulation of extended release hydrophilic matrix systems.¹⁻³ The design of new extended release drug delivery systems (based on HPMC) to provide a particular, predetermined release profile is challenging and requires a good deal of experimentation and time.⁴⁻⁶ In an industrial set up, it is desirable to develop an acceptable formulation using the minimum amount of time and raw materials. The objective of this study was to generate mathematical models based on design of experiments (DoE) for the prediction of a drug release profile based on a start up formulation composition. Systematic experimentation was performed with selected model drugs and variables such as polymer type and quantity, and the choice of filler. Based on the observed values of the response (e.g. drug release profile), it was possible to design a model which could then be used as a predictive tool to generate new formulation recommendations.

EXPERIMENTAL METHODS

Experimental Design

A model design of experiment for this study was generated using the Fusion Pro software (S-Matrix, California, USA). Five model drugs with a range of solubilities were used in the formulation of hydrophilic extended release matrices (Table 1). The other formulation variables and their ranges for investigation are shown in Table 2. A total of 37 experiments were performed with 3 replicate pairs to assess experimental error.

Tablet Formulations

Tablet formulations containing HPMC substitution type 2208 (METHOCEL™, premium cellulose ethers, Dow Chemical Company) as the rate controlling polymer were prepared by direct compression. Microcrystalline cellulose (MCC, Avicel PH 102, FMC) and spray dried lactose (SDL, Fastflo, Foremost) were selected as the insoluble and soluble fillers, respectively. Partially pregelatinized maize starch (Starch 1500®, Colorcon) was used alone as a filler or in combination with either MCC or SDL. Magnesium stearate (Peter Greven) and

fumed silica (Aerosil 200, Degussa) were constant (0.5% w/w). All ingredients (except lubricant) were mixed in a Turbula mixer (Type T2A, Pleuger) for 10 minutes. Magnesium stearate was then added and blended for an additional 2 minutes. Depending on the target weight of the tablet and the bulk density of the powder blends, 6, 7, 8, or 9 mm diameter standard concave tooling was used to compress tablets using a compression force of 10 kN on an instrumented 10 station rotary press (Piccola, Riva).

Table 1. Five Model Drugs Used in the Formulation of Hydrophilic ER Matrices

Drug	Solubility in Water ^{7&8}	Solubility Classification
Chlorpheniramine Maleate	1 in 4	Freely soluble
Anhydrous Caffeine	1 in 46	Sparingly soluble
Theophylline	1 in 120	Slightly soluble
Propyl parabens	1 in 2,500	Very slightly soluble
Indomethacin	1 in 10,000	Practically insoluble

Sample Analysis

Dissolution testing was performed using a Sotax dissolution bath and Apparatus II (paddles) at 100 rpm with sinkers, except samples containing indomethacin, which were tested using Apparatus IV (flow-through cell). The dissolution media used was purified water at 37± 0.5°C. Drug concentration was measured using a dual beam spectrophotometer (Perkin Elmer) equipped with an automated sampling device for all drugs.

Table 2. Variables in the Experimental Design

Variable	Type	Range/Level(s)	Variable Symbol
Polymer Type (METHOCEL)	Categorical	K100M CR	A
		K100LV CR	A (L2)
		K4M CR	A (L3)
Polymer Llevel (% w/w)	Numeric	25 Polymer 45	B
Drug Loading	Numeric	5 Drug 60	C
Filler Solubility	Categorical	Insoluble, Soluble	D
Filler Level (Lactose, % w/w)	Numeric	0 Filler 70	E
Starch 1500 Level (% w/w)	Numeric	0 Starch 30	F
Tablet Weight (mg)	Numeric	100, 200, 300	G

Data Analysis

Drug release data between 5% and 60% (of drug released) was fitted to the power law Equation 1, described below:

$$Q = K_1 t^n \quad \text{Equation 1}$$

Where Q is the fractional amount released at time t, K₁ is the kinetic constant and n is the release exponent. The values of Q, K and n were correlated to the design variables by Fusion Pro software to generate a predictive mathematical model. Both a simple linear and quadratic model was generated by regression analysis and F-statistics to identify statistically significant terms. Corrective algorithms were incorporated for some formulation variables.

RESULTS AND DISCUSSION

Figure 1 shows the drug release profile for all the experimental runs in the DoE. The results indicate that a broad range of release profile types can be obtained depending on the drug solubility and choice of the variable (Table 2). The results also indicated that the value of release exponent was strongly dependant on

the drug solubility (n ranging from 0.4 to 1.5). Polymer type and filler solubility also affected the value of release exponent. Figure 2 shows the influence of drug solubility and polymer viscosity on release exponent. The value of kinetic constant, K_1 was also affected by formulation variables. Figure 3 shows the influence of polymer viscosity and polymer level on kinetic constant, K_1 .

The results from the Fusion Pro analysis demonstrated the relationships between various formulation variables and the drug release profile. General observations were; a) drug solubility and drug: polymer ratios were the most important factors, b) the drug release rate was faster with soluble drugs compared to low solubility drugs and c) the drug release rate was faster with a soluble filler. These relationships were mathematically correlated to the drug release profiles to generate a predictive model. A simple linear model of the following form with statistically significant terms adequately described the drug release profile (Equation 2). Corrective algorithms were incorporated for some formulation variables (e.g. polymer level and drug loading) where good correlation was not observed with drug release profile ($r^2 < 0.85$). A correction factor was also included for tablet weight values outside the design space of the DoE.

$$\text{Response, } Q = a_1A(L2) + a_2A(L3) + a_3B + a_4C + a_5D + a_6E + a_7F + a_8G + b \quad \text{Equation 2}$$

Where Q is the fractional amount released at time t and $A(L2)$, $A(L3)$, B , C , D , E , F and G are the independent variables in the experimental design as shown in Table 2 and a_1 to a_8 are the coefficients for the variables and b is constant. The predicted drug release profile was calculated by substituting the derived values of the coefficients in equation 2.

Model validation was performed by comparing predicted drug release with experimental data. Figure 4 shows the model validation for a formulation containing a soluble drug, HPMC K100M and a soluble filler. The predicted drug release profile was similar to experimental results (f_2 value ~ 74) indicating the validity of the developed model. Although the tablet size had an effect on the release profiles, it was more predictable than some formulation variables. The presence of Starch 1500 in the formulations caused a decrease in the release rate for all drugs studied here. This has been related to the contribution of Starch 1500 in the gel layer formation and its synergistic effects with HPMC.

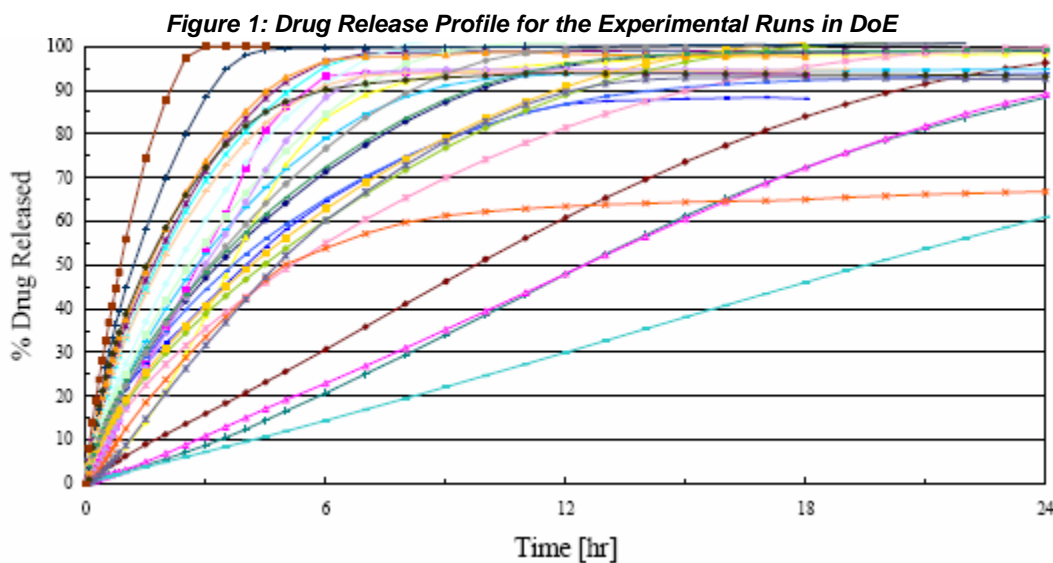


Figure 2: Influence of Drug Solubility and Polymer Viscosity on Release Exponent

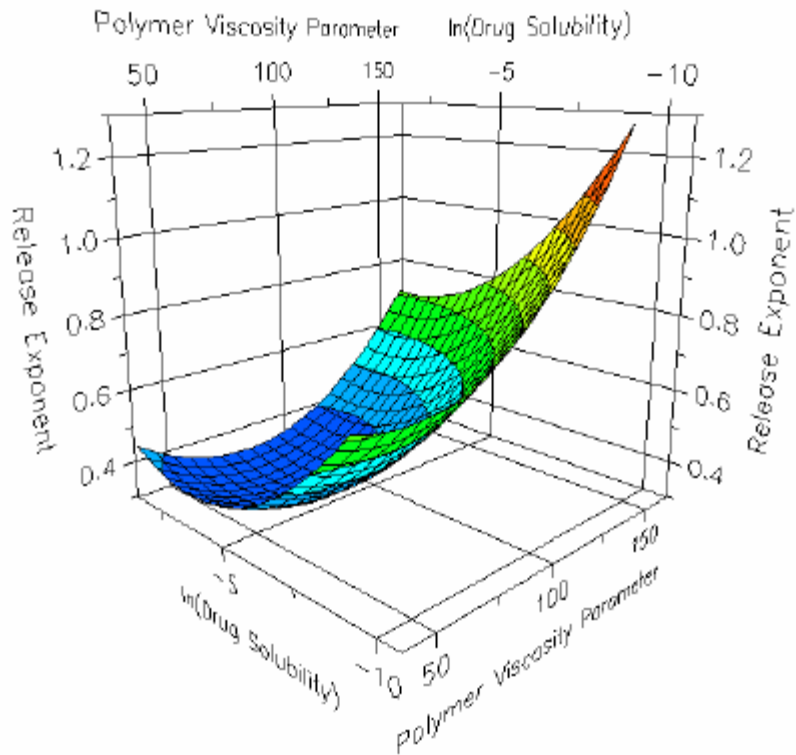


Figure 3: Influence of Polymer Viscosity and Polymer Level on Kinetic Constant, K_1

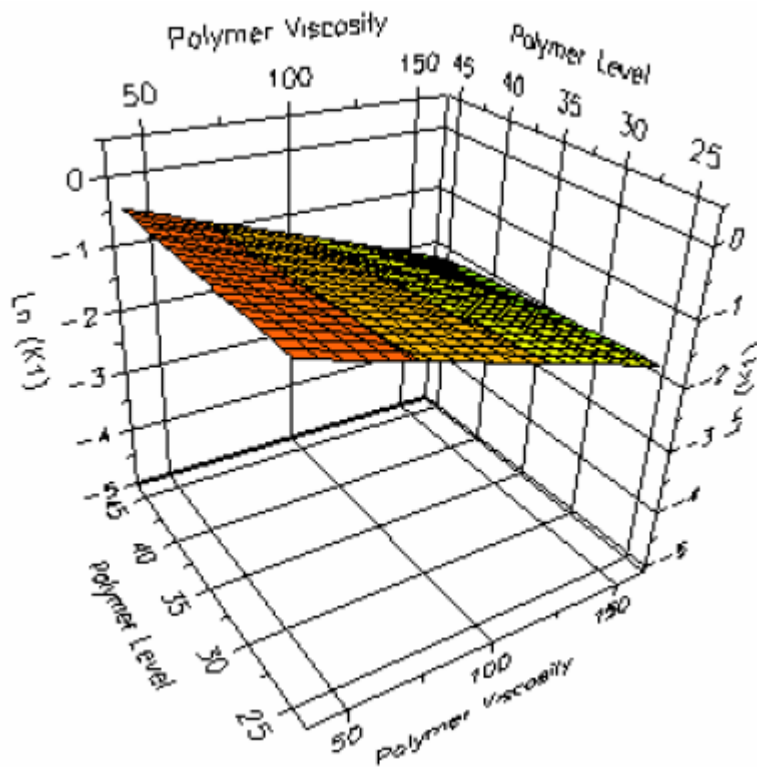
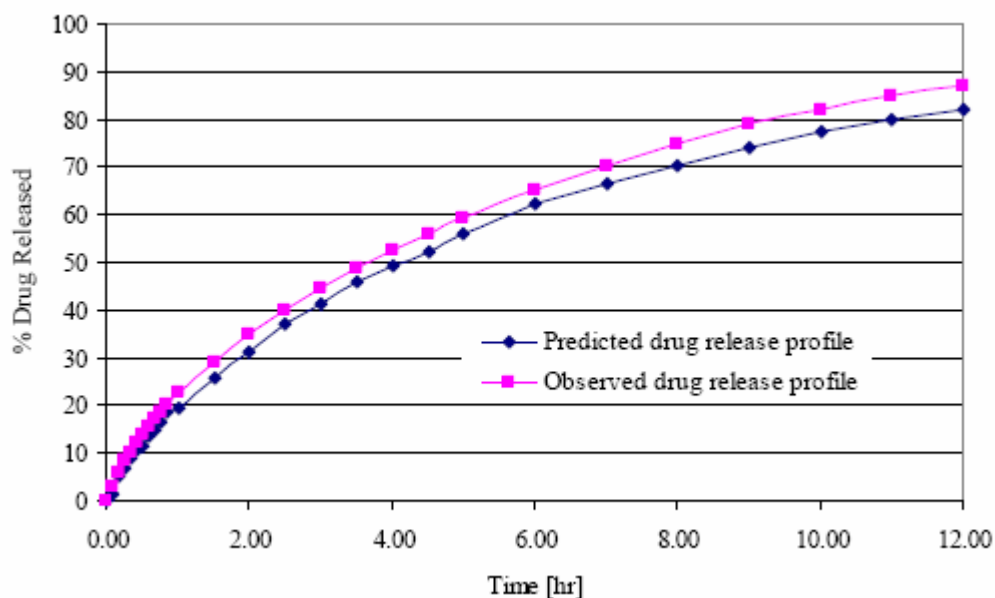


Figure 4: Predicted and Observed Drug Release Profile for a Soluble Drug (Chlorpheniramine maleate), HPMC, K100M and Soluble Filler (Lactose)



CONCLUSIONS

The influence of various formulation variables such as drug solubility and loading, type of HPMC, type and level of filler, on the drug release profile from extended release matrices were quantified. The interactions between these formulation variables were analyzed and quantified by mathematical means to generate a model called HyperStart for the prediction of start up formulations. The practical benefit of such a predictive model is the possibility to simulate the effect of the design parameters of HPMC based drug delivery systems on the release profiles. In an ideal case, the required composition (type and amount of drug, polymer and additives) and geometry of the new extended release system, designed to achieve a certain drug release profile, can be predicted theoretically.

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