The Influence of Formulation Variables on Drug Release Kinetics from Hypromellose Extended Release Matrices

ABSTRACT SUMMARY

The influence of formulation variables on the release kinetics from METHOCEL™, premium cellulose ethers, extended release matrices were quantified using a statistical Design of Experiments. Drug solubility had a strong influence on the release exponent and lag time. The kinetic constant was affected by filler level and drug loading.

INTRODUCTION

The basic principles describing drug release from hypromellose (HPMC) matrices have been studied extensively. Theoretical models have been developed to accurately predict drug release kinetics based on fundamental polymer properties.[1] Combinations of HPMC with other excipients and the influence of processing variables continue to be studied to quantify interrelationships that affect drug release.[2&3] The purpose of this work was to investigate the effect of (model) drug solubility, drug loading, filler level, filler solubility, and HPMC viscosity, on release kinetics using a statistically designed set of experiments.

EXPERIMENTAL METHODS

A model robust screening study was generated using Fusion Pro software (S-Matrix, California, USA). The variable types and ranges for investigation are shown in Table 1.

Table 1. Experimental Design

Variable	Type	Range
Drug Loading (% w/w)	Mixture	5 Drug 60
Filler Solubility	Categorical	Insoluble, Soluble
Filler Level (% w/w)	Mixture	0 Filler 70
PPGS Level (% w/w)	Mixture	0 Starch 30
Polymer Type (HPMC, METHOCEL)	Categorical	K100LV CR K4M CR K100M CR
Polymer Level (% w/w)	Mixture	25 Polymer 45
Tablet Weight (mg)	Discrete Numeric	100, 200, 300

37 experiments were performed with 3 replicate pairs to assess experimental error.

TABLET PREPARATION

Hydrophilic extended release (ER) formulations of drugs with varying solubility (Table 2) and containing hypromellose substitution type 2208 (METHOCEL™ K, International Flavors and Fragrances Inc.) 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 manufacture tablets at 10 kN on an instrumented 10 station rotary press (Piccola, Riva).

Table 2. Drug Solubility

Active Pharmaceutical Ingredient	**Solubility in Water[4&5]**
Chlorpheniramine Maleate	1 in 4
Anhydrous Caffeine (Scientific Instrument and Technology Corp.)	1 in 46
Theophylline (BASF)	1 in 120
Propyl Parabens (Chemlink Specialties Ltd)	1 in 2,500
Indomethacin (Fabbrica Italiana Sintetici S.p.A.)	1 in 10,000

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 4 (flow-through cell).

The dissolution media 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.

DATA ANALYSIS

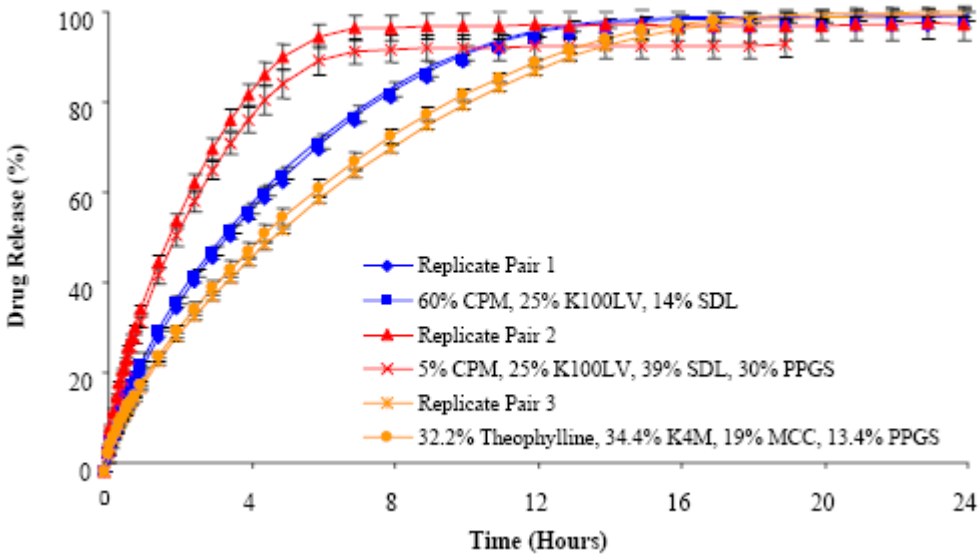
Drug release data between 5 and 60% drug released was fit to Equation 1 where Q is the fractional amount released at time t, $K1$ is the kinetic constant, n is the release exponent, and l is the lag time. Equation 1 was preferred over Equation 2 based on lower values for the Schwartz information criteria and is in agreement with the results published by other authors.[2] Values of n ~0.5, 0.5 < n < 1.0, and 1.0 indicate Fickian diffusion, non-Fickian transport, and Case II transport, respectively. Additionally, n > 1.0 indicates Super Case II transport.[6]

$Q = K1\ (t\text{-}1)n$	Equation 1
$Q = K2tn$	Equation 2

RESULTS AND DISCUSSION

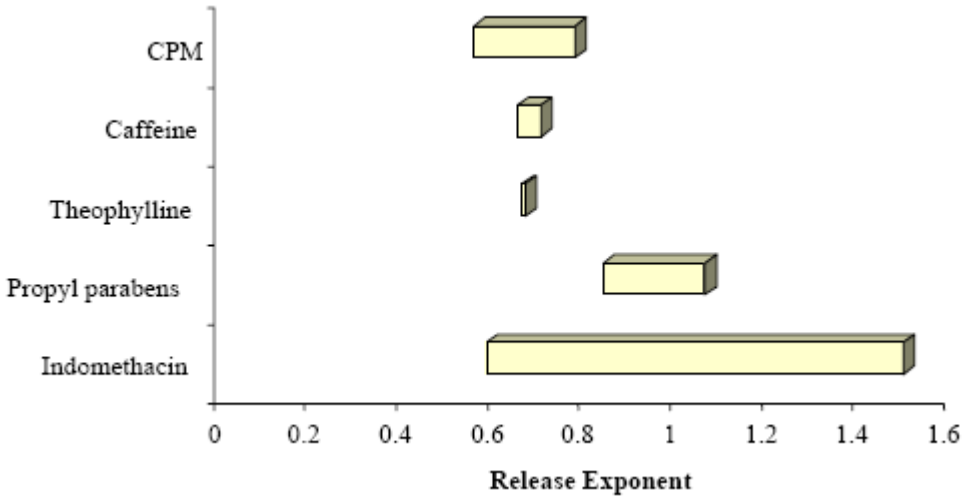
Figure 1 presents the drug release profiles for the three replicate pair formulations. The error within the replicate pairs is very small compared to the overall variation in the data set.

Figure 1. Reproducibility of Replicate Pairs



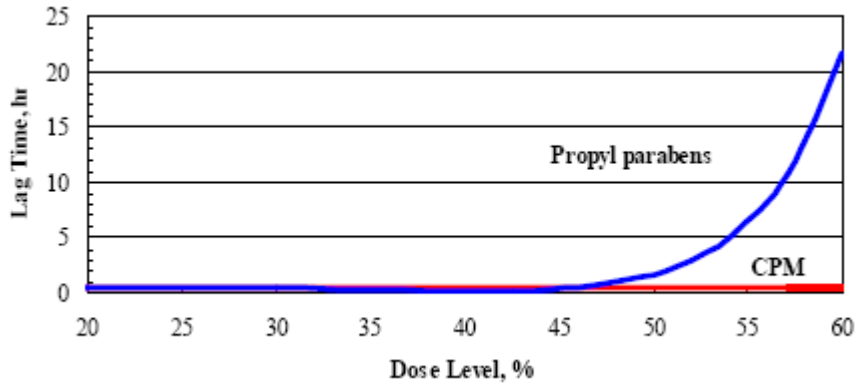
Results indicate that drug solubility has the greatest influence on the release exponent. The presence of insoluble actives (propyl parabens & indomethacin) causes the release exponent to increase. This result was expected because erosion control is generally associated with insoluble drugs. However, the observed release exponent for indomethacin ranged from ~0.6 to ~1.5 (Fickian to Super Case II) depending on the specific formulation parameters. Figure 2 demonstrates that a range of release exponents was observed for high solubility drugs. Filler concentration has a less significant influence on the release exponent with higher filler levels corresponding to lower values for the release exponent. The filler solubility and the polymer type have relatively weaker influences on the release exponent. The n value increases when MCC is used instead of lactose.

Figure 2. Release Exponents for Drug Release



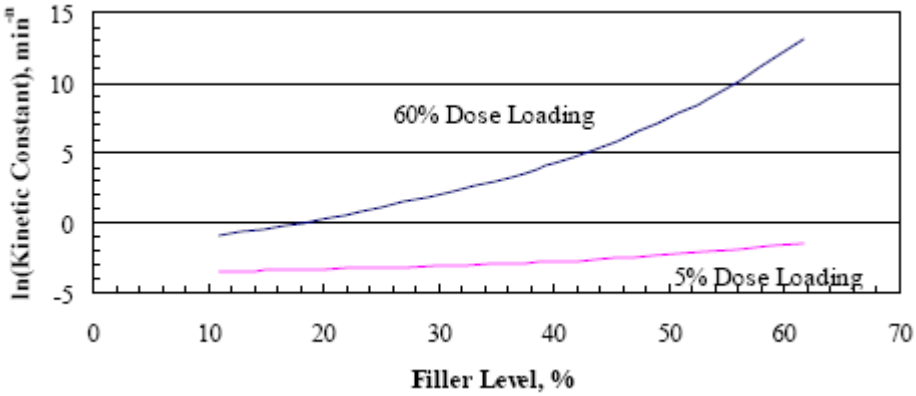
The lag time is strongly influenced by the drug solubility and concentration. A low solubility active at a higher level causes an increase in the lag time (Figure 3).

Figure 3. Effect of Drug Solubility on the Lag Time



The filler concentration has the strongest influence on the kinetic constant and causes the constant to increase (Figure 4) with increasing filler concentration. The effect is enhanced for higher drug loadings. This result was expected because the higher levels of filler and drug in the formulation correspond to lower concentrations of HPMC. The kinetic constant is similar for K100LV CR and K4M CR but decreases for K100M CR.

Figure 4. Effect of Filler Level on the Kinetic Constant



CONCLUSIONS

The influences of drug loading, drug solubility, HPMC grade, filler level, and filler solubility, on release kinetics from extended release matrix tablets were quantified. The results provided insight into how each formulation variable impacted the release exponent, kinetic constant, and lag time of the power law equation.

Comprehensive mathematical modeling of numerous interactive formulation variables combined with the predictive power of statistical software can also be used to generate formulation recommendations for a desired drug release profile. Future studies are intended to test the predictive power of this model and to expand the capabilities of existing Colorcon hydrophilic matrix formulation tools (HyperStart®, oral solid dose starting formulation service).

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