Colorcon

Application of a modelling system in the formulation of extended release hydrophilic matrices

This article describes a predictive formulation service that provides pharmaceutical scientists with a starting formula for hydrophilic matrix tablets. This system (HyperStart) is based on mathematical models and relationships derived from extensive experimental data.

Marina Levina
Abhijit Gothoskar
Ali R. Rajabi-Siahboomi

The hydrophilic matrix system continues to be the most popular and widely used strategy to achieve extended drug release. Hypromellose (hydroxypropylmethylcellulose [HPMC]) is typically the polymer of choice for the rate-controlling carrier in these systems.

In its simplest form, a hydrophilic matrix is a compressed powder mixture of a drug with a water-swelling viscous polymer. A variety of other excipients may be included in the formulation to aid its tableting properties, as well as to modulate the release rate of the active. Key factors in the popularity of hypromellose matrices are:

- The ease of manufacture using traditional techniques, such as direct compression and granulation on conventional equipment.
- The ability to achieve reliable and consistent drug release when a robust matrix formulation has been developed.

A large array of drug delivery technologies is available to formulators, but hydrophilic matrices remain the most commonly used oral extended release (ER) systems. These devices are easy to manufacture, robust, flexible and reliable. Various water-soluble or water-swellable polymers with high molecular weight have been used in hydrophilic matrices, such as HPMC, hydroxypropylcellulose (HPC) and polyethylene oxide (PEO). HPMC, however, is by far the most popular polymer in matrix applications because of its safety, availability, global compliance and physicochemical/mechanical characteristics.[1–3]

HPMC has been widely studied for its applications in hydrophilic matrices.[3–5] It hydrates rapidly on contact with water and forms a gelatinous barrier layer around the wetted tablet. Drug release occurs by diffusion of the active through the gel layer and/or by gradual erosion of the gel, exposing fresh surfaces containing the drug to the dissolution medium.

Diffusion is the dominant mechanism controlling the release of water-soluble actives, and erosion of the matrix is the dominant mechanism controlling the release of water-insoluble actives. Typically, however, drug release occurs by a combination of these two mechanisms.[6–7]

The most basic matrix formulation consists of the active, polymer, flow aid and a lubricant. Developing a formula that can produce the exact required release profile is quite challenging. The pharmaceutical scientist is confronted with a large number of variables that can influence the processing of the HPMC ER formulation and drug dissolution.

The release rate from the matrix is dependent upon factors such as polymer type and level; drug solubility and dose; polymer:drug ratio; filler type and level; polymer:filler ratio; particle size of drug and polymer; porosity and shape of the matrix.[3, 8–13]

Traditional approaches to new product development rely on a slow iterative process that includes experimental programs to identify desirable formulation ranges. These processes require significant investment in manpower and time.

Experimental approach

A number of model drugs with a range of solubilities and concentrations (may not represent therapeutic doses) have been utilized in the development of HyperStart.[14] Here, three examples of the actives are illustrated (Table 1), with water solubilities ranging from freely-soluble through to practically insoluble.

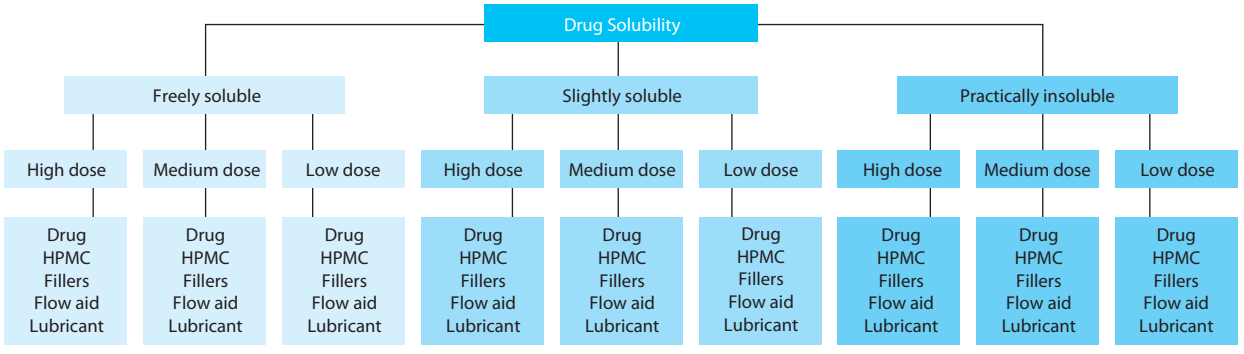
Fillers are generally used to improve processing of tablet formulations (such as flow, compressibility and bulk) and may have a significant impact on the release profiles from HPMC matrices. In the HyperStart model, four commonly used fillers (lactose monohydrate [soluble], microcrystalline cellulose [insoluble], dicalcium phosphate [inorganic-insoluble] and pregelatinized starch [partly soluble]) were investigated.

Figure 1 shows nine formulations in a simple decision tree that were used to obtain release profiles for three drug solubility and three dose ranges. The

Table 1 Three model drugs used in the development of HyperStart.

Drug	Solubility in water	Solubility classification
Chlorpheniramine maleate	1 in 4	Freely soluble
Theophylline	1 in 120	Slightly soluble
Indomethacin	1 in 20 000	Practically insoluble

Figure 1 Initial HPMC decision tree system.



experimental study conducted to develop HyperStart included HPMC (Methocel; The Dow Chemical Company) polymers with various chemistries and viscosity grades, as well as different fillers to achieve release profiles ranging from a few minutes to 24 hours. This design acknowledged the complexity associated with developing these systems, but also provided a wide experimental space for later definition by statistical modelling.

All powder blends were prepared by a standardized process to minimize any random error introduced through formulation preparation variation. The drug, HPMC, filler and 0.5% w/w flow aid (fumed silica, Aerosil 200; Degussa) were mixed in a Turbula blender (Model T2C, Willy A Bachofen UK Ltd) for 5 min. Magnesium stearate (0.5% w/w) was then added as a lubricant and the formulation was mixed for a further minute. Tablets were manufactured using an instrumented 10 station rotary tablet press (Piccola; Riva) at 20 rpm and a compression force of 10 kN.

Drug release was measured in a Sotax dissolution bath using USP Apparatus II (paddles) at 100 rpm with sinkers. The dissolution medium was 1000 mL of purified water at 37.0 °C ± 0.5 °C. A dual beam spectrophotometer (Lambda 25, Perkin Elmer) was utilized for drug detection.

Predictive modelling and analysis were conducted using the Design of Experiments (DoE) Fusion Pro (S-Matrix Corporation) software package. DoE assisted in understanding complex interactions and relationships that may exist between the raw materials in all the tested formulations. With the help of this software, the effects of individual raw materials and the boundaries of operation were explored by progressing in two phases.

Initially, a screening study primarily examined the boundaries of useful inclusion levels for the raw materials, followed by a second phase of optimization. Both phases involved generating and testing several formulations, and the results from these experiments were recorded as dependant variables (i.e., responses). These were interpreted by the software to produce predictive formulations based on desired parameters in the final product.

In some cases, where particular variables could impact the release rate of specific actives, corrective algorithms were applied to the formulations that did not perform exactly as expected. The representative drug release profiles were then fed back into the model for fine-tuning of the system where necessary.

After conducting the required experiments, numerous relationships between formulation parameters and the release profiles of the actives were established, that is:

- Drug solubility and drug:polymer ratio are the most important factors.
- Release rate is faster with more soluble drugs compared with low solubility drugs.
- Release is faster with a soluble filler compared with an insoluble excipient.

Based on these relationships, a mathematical model was produced that would offer a HPMC ER

Table 2 f_2 **values of release profiles calculated from HyperStart compared with experimental data.**

Formulations	10% w/w HPMC	25% w/w HPMC	40% w/w HPMC
Soluble filler	47	59	91
Insoluble filler	55	86	84

Figure 2 Model validation for formulations containing soluble drug, soluble filler and various amounts of the polymer (10%, 25% and 40% w/w).

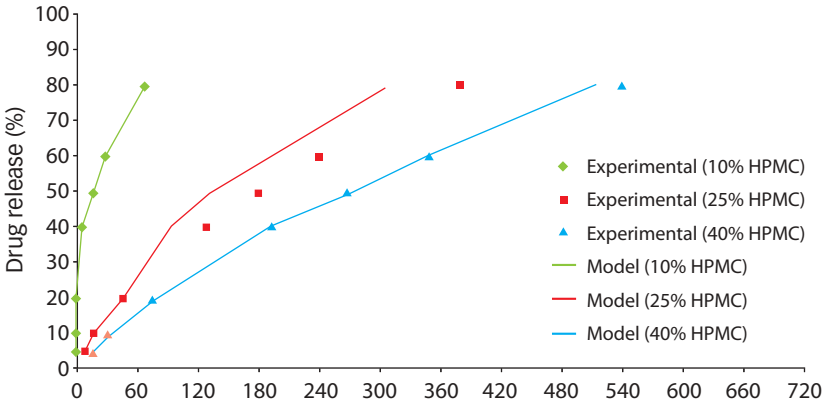
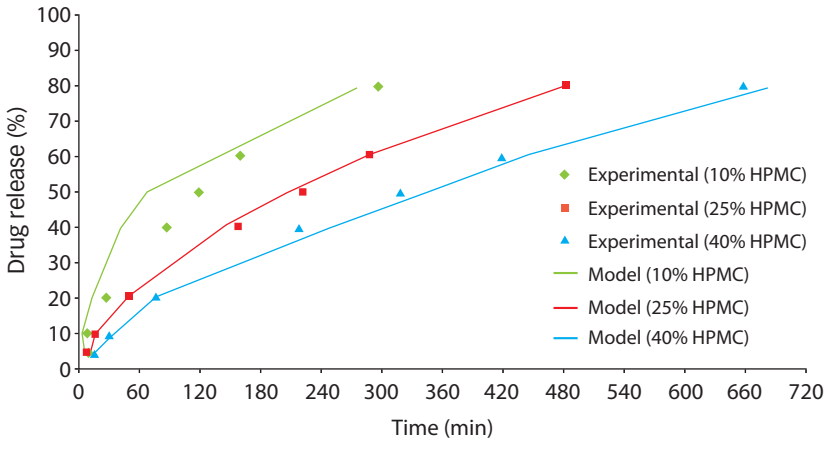


Figure 3 Model validation for formulations containing soluble drug, insoluble filler and various amounts of the polymer (10%, 25% and 40% w/w).



formulation with the desired drug release, taking into account solubility and the dose of the active. This model is a valuable tool that can accelerate the hydrophilic matrix development cycle and reduce the time required for a product to reach the market.

Model validation

The model was validated by comparing predicted drug release with experimental data. Figures 2 and 3 show model validation for formulations with a soluble drug, various amounts of HPMC (10%, 25% and 40% w/w) and either soluble or insoluble filler.

Predicted drug release profiles were compared with the experimental data using the f_2 factor and summarized in Table 2.[15] An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.

For both filler types, it was found that formulations with the higher polymer concentrations (25% and 40% w/w) exhibited significantly better correlation between predicted and experimental drug release profiles compared with tablets containing only 10% w/w HPMC.

These results confirmed that the HyperStart model prediction is reliable, particularly for formulations with moderate to high polymer level (25% or 40% w/w). This range is within current understanding of a reliable HPMC ER matrix system. Our practical experience in the development of HPMC drug delivery devices has identified that polymer concentration has a significant effect on the robustness of a given formulation. With polymer inclusion levels greater than 30%, the effects of any small variations in any of the individual raw materials (including the active principal) are suppressed or eliminated. This then ensures more reliable clinical performance.[17]

Case studies

The following case studies are presented to illustrate the effectiveness of HyperStart in generating robust formulations with desired release profiles for two drugs, a high solubility/high dose and a low solubility/low dose.

Case study 1. Hypromellose matrix with a freely soluble, high dose drug: 500 mg metformin HCl.

Metformin HCl was used as a typical, freely water-soluble, high dose (50% w/w) model active with poor inherent compressibility (Palmer et al, 2005).[14, 18] The solubility and dose (500 mg) of the drug were used as the input parameters by HyperStart to suggest a 12 hour extended release matrix formulation (Table 3), with a release profile similar to the marketed reference product Glucophage XR (Bristol-Myers Squibb).

Microcrystalline cellulose and fumed silica were screened through a 500 µm sieve. All ingredients, with the exception of the magnesium stearate, were then blended in a Turbula mixer for 5 min. Magnesium stearate was then added and the formulation mixed for an additional minute.

Caplets with a target weight of 1000 mg were manufactured using an instrumented 10 station rotary tablet press (Piccola; Riva), fitted with 7 × 18 mm tooling; at 20 rpm and 28 kN compression force. Tablet mechanical strength was determined using automatic tablet (Dr Schleuniger-Pharmatron) and friability testers (Copley).

The drug release profile was measured in a United States Pharmacopeia (USP)-compliant dissolution bath (Vankel) using apparatus II (paddle method) at 100 rpm. The dissolution media was 1000 mL of purified water at 37 °C ± 0.5 °C. A dual beam spectrophotometer (Agilent) fitted with 0.01 mm cells was used for detection of metformin HCl at a wavelength of 233 nm.

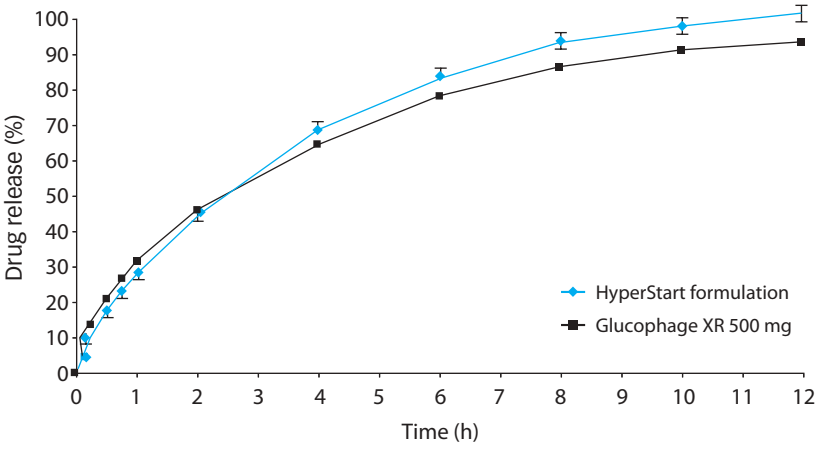
The formulation exhibited good powder flow properties resulting in a low tablet weight variation (<1%). Matrices with a high breaking force (20.8 ± 1.5 kp) and low friability (<0.01%) values were produced. These results were similar to the reference product (<1% weight variation, 19.0 ± 0.2 kp breaking force, 0.01% friability).

The drug release profile from the formulation manufactured was compared with that of Glucophage XR (Figure 4). The calculated f_2 value was 70, indicating good similarity between the two formulations.

Table 3 HPMC ER formulation of metformin HCl 500 mg recommended by HyperStart.

Formulation ingredients	Materials and suppliers	% w/w	mg/tablet
Metformin HCl	Ferico Labs	50.0	500
HPMC	Methocel K100M CR; Colorcon	30.0	300
Microcrystalline cellulose	Avicel PH102; FMC	19.0	190
Fumed silica	Aerosil 200; Degussa	0.5	5
Magnesium stearate	Peter Greven	0.5	5
Total		100.0	1000

Figure 4 Metformin HCl release from the formulation suggested by HyperStart and Glucophage XR tablets (n = 6).



The metformin HCl HPMC ER formulation generated by HyperStart produced tablets with good physical characteristics and a drug release profile similar to the reference product. This case study demonstrates that HyperStart can be utilized to develop reliable hydrophilic extended release matrix formulations for high dose/high solubility drugs.

Case study 2. HPMC matrix with a practically insoluble/low dose drug: 10 mg nifedipine. Nifedipine was used as a typical practically water-insoluble, relatively low dose (10 mg) active.[14,19] The solubility and concentration (10% w/w) of the drug was used by HyperStart to suggest an 8 hour extended release matrix formulation (Table 4), with a release profile within pharmacopoeial specifications.[20]

Lactose and Methocel E15 LV were blended in a polyethylene bag for 3 min. The drug was screened through a 420 µm sieve to break up any aggregates, added to the mix and blended for 3 min. Methocel K15M CR was then added and blending continued for a further 3 min. Magnesium stearate and fumed silica were screened through a 150 µm sieve, added to the mixture and blended for a further minute.

Tablets with a target weight of 100 mg were manufactured using an 8 station rotary press (Rimek 2; Karnavati), fitted with 7 mm standard concave tooling, at 20 rpm and 15 kN compression force. The mechanical strength of the tablets was measured using a hardness tester (Pharmatest) and a USP-compliant friabilator (Electrolab). The uniformity of dosage units (weight) was performed in accordance with the USP monograph <905> on nifedipine extended release tablets.[21]

Dissolution testing was performed in a USP-compliant dissolution bath (Electrolab) using Apparatus II (paddle method) at 50 rpm, with sinkers (wire helix; Electrolab). The dissolution medium was 0.1M hydrochloric acid (1000 mL) at 37 °C ± 0.5 °C. A dual beam spectrophotometer (Shimadzu) fitted with 1 mm cells was used to detect nifedipine at a wavelength of 237 nm. Testing was performed for 8 hour using an autosampler. The dissolution bath and the fraction collector vials of the autosampler were covered with aluminium foil to protect the drug from light during sampling and testing.

The formulation exhibited good powder flow properties resulting in an acceptable tablet weight variation (2%). The matrices had acceptable breaking force values of 7.0 ± 0.5 kp and low friability of less than 0.1%.

Figure 5 shows that the nifedipine release profile from the HPMC ER matrix was within pharmacopoeial specifications. Inclusion of 30% hydrophilic polymer resulted in a robust formulation.

The nifedipine 10 mg hydrophilic matrix formulation generated by HyperStart produced a HPMC matrix tablet with good physical characteristics and drug release profile within pharmacopoeial specifications. This case study also demonstrated that HyperStart could be utilized to develop reliable hydrophilic extended release matrix formulations for low dose/low solubility drugs.

Conclusions

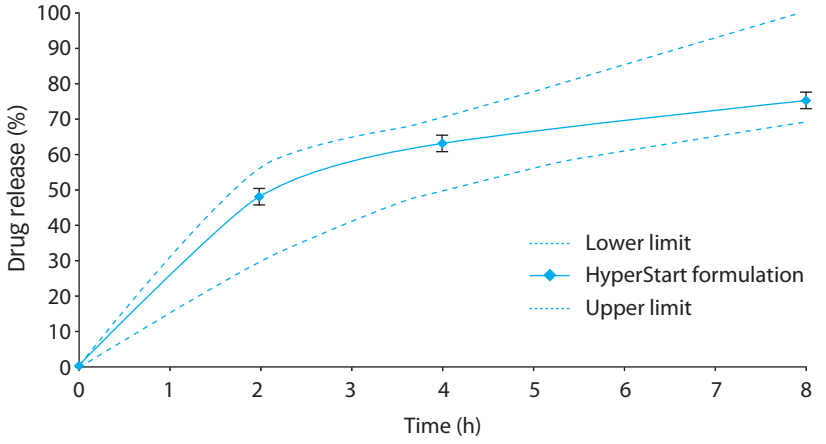
HPMC hydrophilic matrix systems have been well studied and there are many successful products in the market utilizing this versatile extended release technology platform. In an attempt to reduce the formulation time for these systems, the HyperStart predictive model has been created. The model uses experimentally determined relationships that exist between various parameters of a typical HPMC matrix, that is, drug solubility and dose, to suggest a start-up formulation with a desired release profile.

Reliable suggestions are made for the ER tablets with moderate to high polymer level. It has been established in the literature and industry that HPMC concentration of at least 30% increases formulation robustness and improves *in vivo* performance of the device.

Table 4 HPMC ER formulation of nifedipine 10 mg recommended by HyperStart.

Formulation ingredients	Materials and suppliers	% w/w	mg/tablet
Nifedipine	Suchem	10.0	10.0
HPMC	Methocel K15M CR; Colorcon	10.0	10.0
	Methocel E15LV; Colorcon	20.0	20.0
Lactose	Borculo; The Netherlands	59.0	59.0
Fumed silica	Aerosil 200; Degussa	0.5	0.5
Magnesium stearate	Vasa Pharma	0.5	0.5
Total		100.0	100

Figure 5 Nifedipine release profile from the formulation suggested by HyperStart.



References

1. P. Colombo *et al.*, *Pharm. Sci. Tech. Today*, **3**(6), 198–204 (2000).
2. IMS data, 2002.
3. C.L. Li *et al.*, *J. Pharm. Pharmacol.* **57**(5), 533–546 (2005).
4. M.A. Longer and J.R. Robinson, Sustained-release drug delivery systems. in A.R. Gennaro (Ed.), *Remington's Pharmaceutical Sciences*, 18th Ed., (Mack Publishing, PA, USA, 1990) pp 1676–1693.
5. A.R. Rajabi-Siahboomi and M.P Jorda, *Eur. Pharm. Rev.* **5**(4) (2000) 21–23.
6. M.V. Velasco *et al.*, *J. Contr. Rel.* **57**(1), 75–85 (1999).
7. J. Siepmann and N.A. Peppas, *Adv. Drug Deliv. Rev.* **48**(2–3), 139–157 (2001).
8. C.F. Rodrigues *et al.* Hydrophilic cellulose derivatives as drug delivery carriers: Influence of substitution type on the properties of compressed matrix tablets, in D.L. Wise (Ed.), *Handbook of Pharmaceutical Controlled Release Technology*, (Marcel Dekker, New York, NY, USA, 2000) pp 1–30.
9. H. Lapidus and N.G. Lordi, *J. Pharm. Sci.* **57**(8), 1292–1301 (1968).
10. J.L. Ford, M.H. Rubinstein and J.E. Hogan, *Int. J. Pharm.* **24**(2–3), 327–338 (1985).
11. J.L. Ford *et al.*, *Int. J. Pharm.* **40**(3), 223–234 (1987).
12. R. Bettini *et al.*, *Eur. J. Pharm. Sci.* **2**(3), 213–219 (1994).
13. M.E. Campos-Aldrete and L. Vallafuerte-Robles, *Eur. J. Pharm. Biopharm.* **43**(2),173–178 (1997).
14. K. Parfitt (Ed.), Martindale: The complete drug reference, (Pharmaceutical Press, London, UK, 1999) pp 45, 320, 330, 405, 765.
15. FDA Federal Register, Volume 60, No. 230, pp 61642 (1995). (5600 Fishers Lane, Rockville, MA 20857, USA).
16. J.W. Moore and H.H. Flanner, *Pharm. Technol.* **20**(6), 64–74 (1996).
17. B. Abrahamsson, K. Roos and J. Sjogren, *Drug Dev. Ind. Pharm.* **25**(6), 765–771 (1999).
18. F. Palmer, M. Levina and A. Rajabi-Siahboomi, *Investigation of a Directly Compressible Metformin HCl 500 mg Extended Release Formulation Based on Hypromellose* (CRS Annual Meeting, Miami, FL, USA, June 2005).
19. A. Gothoskar *et al.*, Colorcon Technical Literature, 2006.
20. Chinese State Drug Specification WS1-(X-055)-2004Z.
21. United States Pharmacopeia 27, United States Pharmacopeial Convention, Inc., (12601 Twinbrook Parkway, Rockville, ML, 20852-1790, USA) 2004, pp 1323.

Marina Levina
is global technical manager, modified release (applications), Colorcon, UK.

Abhijit Gothoskar
is global technical manager, modified release, Colorcon, India.

Ali R. Rajabi-Siahboomi
is global technical director, modified release, Colorcon, USA.

Article Reprinted from the ©July 2006 issue of

Pharmaceutical Technology EUROPE

AN ADVANSTAR PUBLICATION

Article Reprint Number: 0688