

## The Effect of *In Vitro* Dissolution Parameters on the Release Rate of a Low Dose, Low Solubility Drug from Extended Release Hypromellose Matrix Formulations

### ABSTRACT SUMMARY

Colorcon's HyperStart<sup>®</sup>, oral solid dose formulation service, is based on predictive modelling, designed to assist formulators with starting matrix formulations, was utilized to investigate a felodipine 5mg ER hypromellose tablet. This formulation was compared to a leading commercially available reference product in terms of *in vitro* dissolution parameters effect on drug release.

Keywords: felodipine, hypromellose, extended release, dissolution, hydrodynamic effects

### INTRODUCTION

Felodipine is a calcium channel blocker used in the treatment of hypertension.<sup>1</sup> An ER tablet formulation of felodipine was developed in order to achieve more sustained plasma levels, thereby minimizing peak concentration dependent side-effects and extending the duration of the antihypertensive effect.<sup>2</sup> It has been reported that felodipine formulations, based on the hydrophilic matrices, exhibit a nearly constant drug release rate over several hours, both *in vitro* and *in vivo*, with the drug absorption rate correlating to the rate of erosion of the matrix.<sup>3&4</sup>

Felodipine is a challenging drug to formulate due to its low solubility (0.001mg/mL) and low dose. This study investigates the development of an ER felodipine 5mg formulation based on hypromellose (hydroxypropyl methylcellulose, HPMC) using Colorcon's HyperStart service; and the effect of dissolution parameters on drug release from the developed matrices compared to a reference product.<sup>5</sup>

### EXPERIMENTAL METHODS

Table 1 shows the felodipine ER matrix formulation suggested by Colorcon HyperStart service. Felodipine (Spodefell, mean particle size = 9.2µm), half of the lactose (Fast Flo, Foremost) and the fumed silica (Aerosil 200, Degussa) were blended in a Turbula mixer for 5 minutes. This blend was then screened using a 500µm sieve, returned to the mixer with the hypromellose (METHOCEL™, premium cellulose ethers, K100LV CR, Dow Chemical Company) and the remaining lactose, and blended for 5 minutes. Finally, the magnesium stearate (Peter Greven) was added and the formulation was mixed for a further 2 minutes.

**Table 1. HyperStart Formulation**

Material	% w/w	mg/tablet	g/batch
Felodipine	2.50	5.0	12.5
METHOCEL™ K100LV CR	37.00	74.0	370.0
Lactose	59.50	119.0	297.5
Fumed Silica	0.50	1.0	2.5
Magnesium Stearate	0.50	1.0	2.5
Total	100.00	200.0	500.0

200 mg tablets were manufactured using an instrumented 10 station rotary press (Piccola, Riva), fitted with 7 mm normal concave tooling, at 20rpm and 20kN. Tablet mechanical strength was determined using hardness (Schleuniger, Germany) and friability (Copley, UK) testers.

Content uniformity analysis was conducted according to the USP monograph <905>.<sup>6</sup>

Dissolution testing was performed in a USP compliant dissolution bath (Sotax, UK) in 500mL of pH 6.5, 0.1M phosphate buffer and 1% w/v sodium lauryl sulfate at paddle speeds of 50rpm (USP method <724>) and 100rpm (test method). The quadrangular baskets of stainless steel wire specified in the USP were replaced with small sinkers (Sotax). The amount of drug present was determined by UV detection at 362nm.<sup>3</sup> Samples were taken over a 24 hour time period.

Drug release profiles from the same formulation, at different media agitation rates were compared using the  $f_2$  metric test.<sup>7</sup> An  $f_2$  value of between 50 and 100 indicates that the two dissolution profiles are similar.

The release exponent  $n$  from the Power Law Model equation  $Q = kt^n$  was used to determine the mechanism of drug release from the developed and the reference formulations.<sup>8</sup> This equation was applied to 5 - 60% portion of the dissolution curves. For matrix tablets,  $n$  value of near 0.5 indicates diffusion and  $n$  value of near 1.0 indicates erosion control.

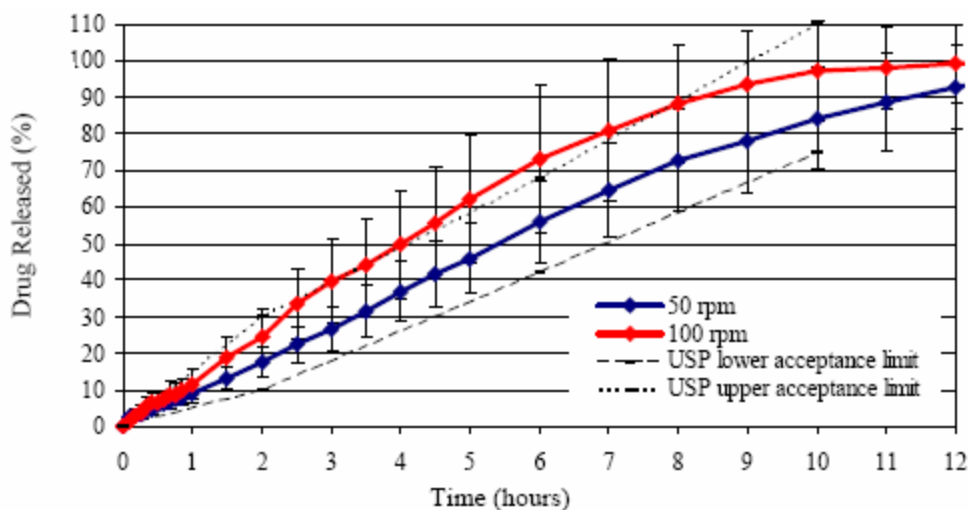
## RESULTS AND DISCUSSIONS

The formulation of felodipine ER suggested by HyperStart produced tablets with low weight variation (0.8%), high breaking force ( $31.4 \pm 04$  kp) and low friability (less than 0.01%) values. The content uniformity results ( $99.4 \pm 1.0$  %) were well within the USP limits and comparable to the reference tablets ( $100.2 \pm 0.9$ %).

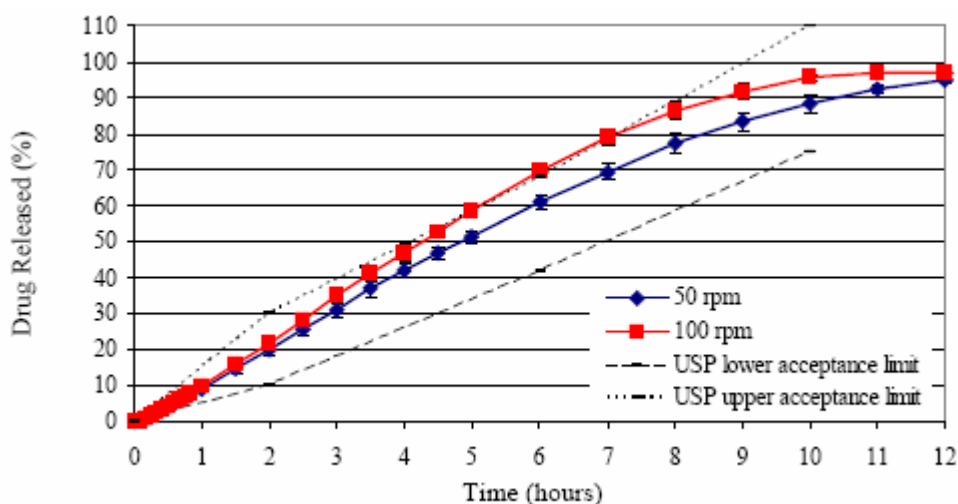
Analysis of the release profile for the felodipine reference tablets showed high variability, with standard deviations of up to 14.4% and 20.0%, for 50rpm and 100 rpm respectively (Figure 1). The rate of drug release appeared to be higher for 100 rpm compared to 50rpm. The calculated  $f_2$  value of 52 indicates borderline similarity of these two profiles.

The HyperStart formulation tablets exhibited significantly lower variability of drug release with standard deviations of up to 2.9% and 2.4%, for 50 rpm and 100 rpm respectively (Figure 2). In addition, hydrodynamic conditions had lesser effects on this formulation with an  $f_2$  value of 67 calculated for 100 and 50rpm. Therefore, the HyperStart formulation appears to be more robust under the test conditions compared to the reference product.

**Figure 1. Drug Release from the ER Reference Tablets**



**Figure 2. Drug Release from the HyperStart Formulation**



The release exponents ( $n$ ) for the both products are listed below, indicating drug release by erosion:

	Reference Product	HyperStart Formulation
50 rpm	0.9442	1.0957
100rpm	0.9572	1.1419

Dissolution media agitation intensity is a critical parameter when determining the erosion rate of a hydrophilic matrix tablet.<sup>9</sup> The current USP <724> drug release test for felodipine ER tablets utilizes a specially made basket that minimizes hydrodynamic effects of the media. This study highlights the need for careful consideration of dissolution parameters during product development.

## CONCLUSION

A felodipine 5 mg ER formulation generated by the Colorcon HyperStart system produced hydrophilic HPMC matrix tablets with good physical characteristics and reproducible drug release profiles at varying hydrodynamic conditions.

Dissolution analysis conducted in this study demonstrated that formulations based on swelling eroding matrices can be sensitive to hydrodynamic conditions. The effect of varying the agitation rate should be considered when developing an *in vitro* dissolution method to ensure adequate robustness of the formulation. Hydrodynamic effects are a critical parameter when determining the erosion rate of a low dose low solubility drug from a matrix based on low viscosity hypromellose. This study suggests that the formulators should utilize dissolution testing at multiple speeds as a screening tool during product development.

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