The Relevance of USP Methodology in the Development of a Verapamil Hydrochloride (240 mg) Extended Release Formulation

INTRODUCTION

Hydrophilic matrices continue to be a growing area of interest to provide controlled drug delivery to the oral route. Factors that influence drug release through hydrophilic matrices have been extensively reviewed in the literature. Verapamil Hydrochloride (HCl) is a weakly basic drug which has been marketed in extended release (ER) formulations.

The current USP monograph for the extended release version lists five different test methods that may be used to measure drug release from a developmental formulation to match the USP specification.[1] The various tests differ in media composition and pH, dissolution apparatus, presence of sinkers, and in one case the number of different media to which the delivery device is exposed. However, there are no references to specific extended release technologies in relation to various test methods. In this study, the relevance of the USP specification for a verapamil HCl 240mg ER formulation based on a hypromellose (HPMC) matrix was investigated.

METHODOLOGY

Tablet Preparation

A typical hydrophilic matrix formulation based on HPMC was used as shown in Table 1. Verapamil HCl and spray dried lactose (Foremost) were blended in a Hobart mixer for 5 minutes and then wet-granulated with a 2% w/w hypromellose solution (METHOCEL™, premium cellulose ethers, E5). The wet mass was tray dried at 40ºC for 10 hours, passed through an oscillating granulator (12-mesh), and hand screened through a 16-mesh screen. The granules were then mixed with METHOCEL™ K100LV for 10 minutes in a twin shell blender. Finally, the magnesium stearate was added, and blended for an additional 3 minutes.

500 mg tablets containing 240 mg of verapamil HCl were manufactured using an instrumented 10 station rotary press (Piccola, Riva) fitted with 11 mm standard concave tooling at a compression force of 10KN.

Table 1. Verapamil HCl ER Matrix – Formulation 1

Raw Materials	% w/w
Verapamil HCl	48.0
Fast Flo Lactose	21.0
METHOCEL™ K100LV	30.0
Magnesium Stearate	0.5
Cabosil	0.5

Sample Analysis

Tablets were tested for hardness, weight uniformity and friability. Drug release was measured (n=6) according to the USP 28 methods 1, 2, and 3 [50rpm (USP method) and 100rpm (test method)] using an automated dissolution bath (Varian). All methods utilized apparatus 2 (paddles), and 900 mL of simulated gastric and intestinal fluid without enzymes at 37±0.5ºC as the dissolution media. Methods 1 and 3 also utilized wire helices to prevent floating of the dosage form.

The percent drug release was measured {test and reference (IVAX) samples} via UV spectrophotometry at a wavelength of 278 nm in each media. Samples were withdrawn in the gastric phase at 1 hour, and in the intestinal media at 2, 3.5, 5 and 8 hours.

Mechanism of Drug Release

The release exponent "n" from Equation 1 was used to determine the mechanism of drug release.

Equation 1: $(Q = kt^n)$

Where; "Q" is the fraction of drug released in relation to time "t", "n" is the release exponent and "k" is a constant (characteristics of polymer system and the drug). This equation was only applied to the first 60% of the dissolution curve.

Exponent values of 0.5 or below indicate Fickian diffusion and values of 1.0 or greater indicate Case II transport. Values between 0.5 and 1.0 for "n" indicate anomalous (non-Fickian) transport of drug release indicating that diffusion and swelling/erosion mechanisms are contributing to release of the drug.[2]

RESULTS AND DISCUSSIONS

Table 2 provides the physical properties of tablets for formulation 1. The formulation produced low ejection forces, with good Tablet hardness properties and suitable flow.

Table 2. Tablet Physical Properties

Tablet Property	Value
Compression Force (kN)	10.6
Ejection Force (kN)	0.2
Weight Variation (%)	0.84
Hardness (kP)	18.7
Friability (%)	0.00

For simple comparison purposes, drug release from the above formulation at 60 and 300 minute dissolution time points along with the high and low values specified by the USP for each method, are shown in Table 3. Values highlighted do not meet the USP criteria." The release exponent for the Colorcon verapamil HCl ER tablets was calculated and found to be 0.8 (r2 = 0.999), indicating anomalous (non-Fickian) transport of drug release via diffusion and erosion mechanisms.

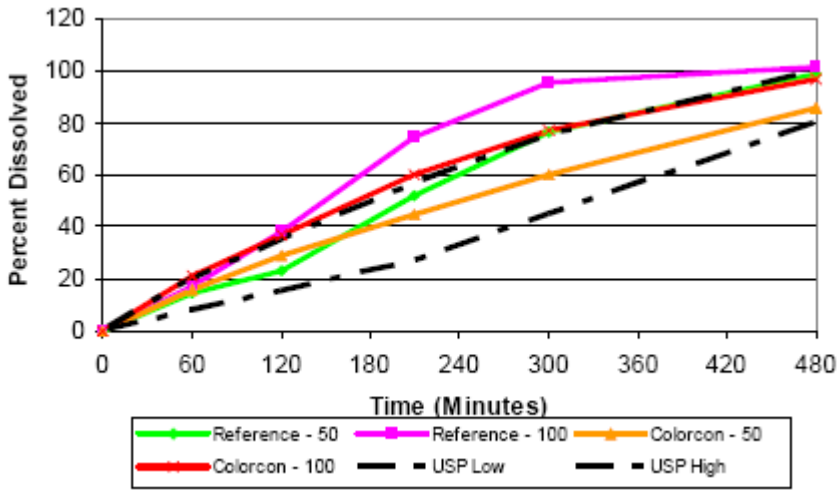
Table 3. Percent Verapamil HCl Dissolved

Method 1				
Time (Minutes) 60 300	USP Low 7 51	Colorcon 16 60	Reference 14 77	USP High 15 75
Method 2				
Time (Minutes) 60 300	USP Low 8 55	Colorcon 15 54	Reference 14 73	USP High 20
Method 3				
Time (Minutes) 60 300	USP Low 8 45	Colorcon 16 60	Reference 14 77	USP High 20 75

Drug release from HPMC matrices is controlled by dissolution, diffusion of drug, and erosion of the outer hydrated gel layer of the matrix. For a matrix formulation of a soluble drug such as verapamil HCl, where drug dissolution and diffusion through the gel is rapid, erosion rate, may play a major part during dissolution testing. In this case varying hydrodynamic conditions of the testing method to better simulate in vivo conditions should be considered.[3] Reason being, it is possible to match the USP specifications based on methods recommended by USP with a formulation that may lead to in vitro "dose dumping".

Figure 1 compares the release profiles at 50 and 100rpm for a reference (a marketed verapamil HCl 240mg ER formulation) and formulation 1, versus the lower and upper limits specified by USP method 3.

Figure 1. Verapamil HCL Drug Release - USP 28 Method 3 50 Versus 100 RPM



Both formulations showed a faster release at higher level of agitation and sensitivity to hydrodynamic conditions. It has been reported that improper formulation techniques such as low levels of the matrix forming polymer can lead to failure of the dosage form with complete, rapid release of the drug in vivo.[4]

Formulation 1 was further modified to meet the established specification for method 3 at 50 rpm, while running the dissolution test at 100 rpm. Increasing the polymer level to 36% and replacing the lactose in favor of 15 parts microcrystalline cellulose to lactose (2/1) yielded a formulation (Formulation 2, Table 5) that met the dissolution release criteria under more vigorous hydrodynamic conditions (100 rpm).

Table 4. Verapamil HCl ER Matrix - Formulation 2

Raw Materials	% w/w
Verapamil HCl	48.
Fast Flo Lactose	5.0
Emocel 90M	10.0
METHOCEL™ K100LV	36.0
Magnesium Stearate	0.5
Cabosil	0.5

Table 5 provides the drug released at 60 and 300 minutes for formulation 2 at 50 and 100 rpm.

Table 5. Percent Verapamil HCl Released

Time (Minutes)	USP Low	50 RPM	100 RPM	USP High
60	8	11	14	20
300	45	46	60	75

CONCLUSION

An in-house HPMC matrix formulation and a marketed product were evaluated under three USP methods for the release of verapamil HCl, including one method under more vigorous hydrodynamic conditions.

Based on these results it was shown that the delivery technology can significantly impact the release of the dosage form. USP methods typically do not specify the method that should be utilized to evaluate a delivery technology. Formulations based on swelling, eroding matrices can be sensitive to hydrodynamic conditions especially if the level of the release controlling polymer is too low. Formulations containing higher polymer levels and insoluble excipients (Table 4) may be more suited to deliver high-dose, soluble drugs under in vivo conditions. Reason being that this formulation exhibited less sensitivity to hydrodynamic conditions by meeting the USP dissolution criteria when tested at either 50 or 100RPM.

This study suggests that the USP should indicate the technology utilized to set a method criterion and guide formulators to utilize dissolution testing at multiple speeds as a screening tool during formulation

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