Evaluation of Verapamil HCl (240 mg) Extended Release Matrix Formulations Using USP Apparatus III in Biorelevant Dissolution Media

OBJECTIVES

The objective of this work was to evaluate the performance of two verapamil hydrochloride extended release matrix formulations using USP apparatus III and biorelevant media, and compare to Calan SR, a commercially available verapamil HCl 240 mg extended release caplet.

INTRODUCTION

Hypromellose based matrices are highly popular to achieve extended release formulations. Obtaining a specific dissolution profile with hypromellose using USP apparatus I or II is well established within the pharmaceutical industry. However, there have been studies on the relevancy of these methods as tools for formulation development and optimization.[1] Although these methods are excellent tools for quality control purposes, they may not have the necessary sophistication for prediction of the in vivo performance of the product under development.

USP Apparatus III (reciprocating cylinder) with biorelevant media may provide conditions and information that correlate to in- vivo performance. USP apparatus III was designed for simulating varying physiological conditions as the dosage form traverses the human digestive tract. The dosage form is exposed to a series of dissolution media representing physiological fluids and GI transit in the human digestive tract. The reciprocation rate and screen size can be selected to approximate hydrodynamic conditions. Apparatus III with biorelevant media offers a physiologically based dissolution testing method for studying dosage forms under fasted or fed conditions.

Fasted GI tract conditions are characterized by low gastric pH (~1.8) and higher pH conditions in the duodenum (~6) and jejunum (~6.5 – 6.8).[2] The fasted residence time in GI regions of healthy subjects depends on many factors including the timing of the migrating motor complex.[3] Fed-state conditions in a healthy population are generally characterized by a higher gastric residence time and pH (~4) and lower pH conditions in the duodenum (~5) and jejunum (~5.5 – 6.5).2 Gastric emptying and residence time in the fed-state are also influenced by meal factors such as fat and carbohydrate content, osmotic pressure, and pH.3

Two extended release verapamil HCl matrix formulations suggested by HyperStart®, oral solid dose formulation service, were studied using Apparatus III with biorelevant media. Release profiles were generated in simulated pre- and post-prandial conditions at time zero and after 3 months' 40°C/75%RH storage and compared to Calan SR.

METHODOLOGY

Formulation and Tablet Preparation

The extended release matrix formulations for verapamil HCl were prepared based on the Colorcon HyperStart formulation service. Formulation I and II contained verapamil HCl (USP), hypromellose (METHOCEL™, premium cellulose ethers, K100LV and E5LV), spray dried lactose (Fastflo), colloidal silicon dioxide (Cab-O-Sil M5) and magnesium stearate (USP).

Formulation II also contained microcrystalline cellulose (Emcocel 90M). For formulation I, verapamil HCl and lactose were wet granulated in a Hobart mixer using a 2 wt% aqueous solution of E5LV. After drying in a convection oven and sieving, the blend was added to a twin shell blender with a pre-blended and sieved mixture of Cab-O-Sil and K100LV. Blending was performed for 10 minutes followed by an additional 3 minutes after lubricant addition. For formulation II, the MCC was wet granulated with the drug and lactose. Tablet compositions are shown in Table 1.

Table 1. Verapamil HCl Extended Release Matrix Tablet Compositions

Ingredient	Formulation I (mg)	Formulation II (mg)
Verapamil HCl	240	240
METHOCEL™ K100 LV CR	150	180
METHOCEL™ E5LV	2	2.5
Microcrystalline Cellulose	-	50
Lactose	105	25
Silicon Dioxide	2.5	2.5
Magnesium Stearate	2.5	2.5
Total	502.0	502.0

Tablets were compressed on a 10 station rotary press (Piccola, Riva, Argentina) using 12 kN force with 11 mm diameter standard concave tooling. Target tablet weight was approximately 502 mg. Properties of the powder blends were determined according to USP <616> and are shown in Table 2. Both formulations produced tablets with approximately equal hardness. Dissolution studies were performed immediately after compression and after 3 months' storage at 40°C/75% RH conditions in heat sealed HDPE bottles with cotton but without desiccant.

Table 2. Blend & Tablet Properties of Verapamil HCl Extended Release Compositions

Powder/Tablet Property	Formulation I	Formulation II
Bulk Density (g/cm^3)	0.46	0.44
Tapped Density (g/cm^3)	0.64	0.61
Carr Index (%)	28	28
Compression Force (kN)	12	12
Hardness (kP)	11.0	10.6
Actual Weight (mg)	509	506
Weight Variation (mg)	2.9	4.1
Thickness (mm)	6.2	6.4

Dissolution Testing

Formulations I & II were tested according to USP verapamil HCl Extended Release Tablets (Test 3) prior to testing in apparatus III. For apparatus III testing, biorelevant dissolution media for both fed and fasted conditions were based on suggested literature compositions and are shown in Table 3.[2&4] Residence times were chosen to represent typical GI transit of solid dosage forms. pH and bile salt (sodium taurocholate) concentration were adjusted to reflect physiological conditions and the active re-absorption of bile salts from the ileum.[2]

Experiments were performed using an automated Logan Instruments Disso III Classic Tester with reciprocating cylinders. Vessel fill volumes were 250 ml. The dip rate was 5 dips per minute for all media with a 10 cm stroke. Ensure plus was used without pH adjustment because of its tendency to coagulate. Samples were collected at predetermined time intervals and analyzed by HPLC (Alliance 2695, Waters Corp., Milford, MA) Ensure Plus samples were diluted, centrifuged, and filtered for HPLC analysis.

Table 3. Biorelevant Dissolution Media

GI Region	Fasted Condition		Fed Condition	
	Media	**Time, min**	**Media**	**Time, min**
Stomach	FaSSGF 1.8	60	Ensure Plus 6.4	120
Upper Jejunum	FaSSIF 6.5	15	FeSSIF 5.0	45
Lower Jejunum	FaSSIF 6.8	15	FeSSIF 6.5	45
Upper Ileum	FaSSIF 7.2**	30	FeSSIF 6.5**	45
Lower Ileum	Blank FaSSIF 7.5	120	Blank FaSSIF 7.5	45
Proximal Colon	Blank FaSSIF 6.5	720	Blank FaSSIF 6.5	45

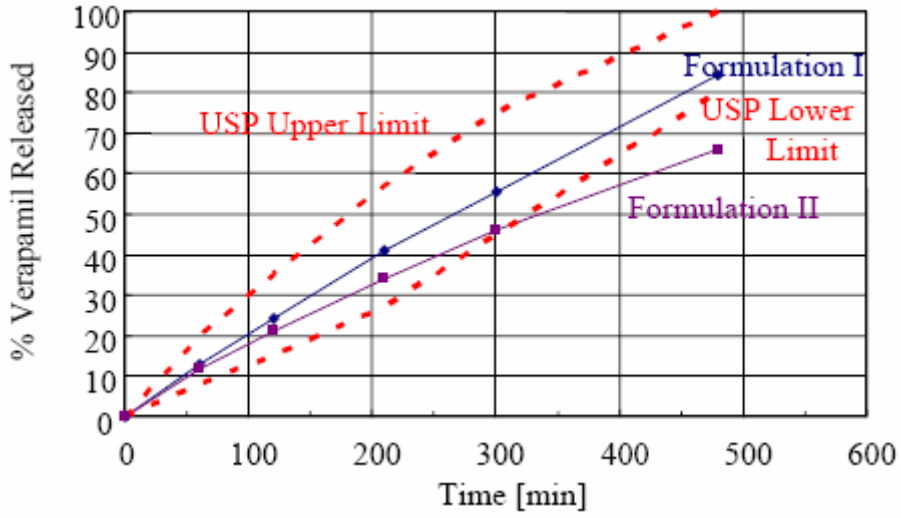
**Halved Bile Salts

RESULTS

Formulations I & II using USP Apparatus II, Test 3

Formulation I met the USP dissolution test 3 requirement for extended release tablets, but formulation II did not (Figure 1). Formulation II showed a slower release rate than formulation I.

Figure 1. Dissolution of Formulations I and II Using USP Apparatus II, with Test 3 Acceptance Criteria



Formulations I & II vs. Calan SR (240 mg) using Apparatus III

The release profiles for formulations I & II and Calan SR using apparatus III are shown in Figure 2 and 3 for fasted and fed states, respectively. Formulation II is a better match to Calan SR in the fasted condition (f2=59), and formulation I is a better match in the fed condition (f2=81). Formulation I has a more rapid release rate than formulation II in both fasted and fed conditions. Calan SR produced an approximately zero order release profile in both conditions.

Figure 2. Dissolution of Verapamil HCl in Fasted Condition

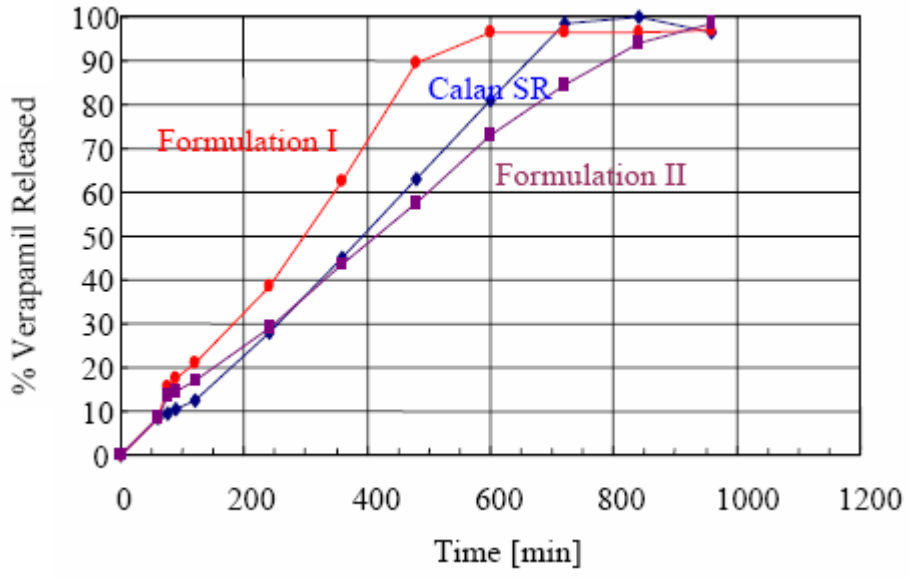
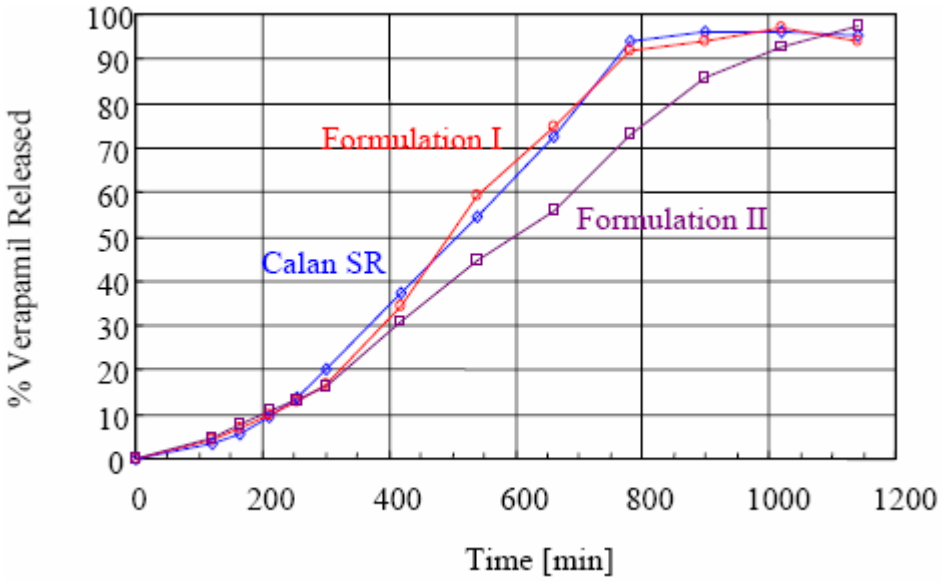


Figure 3. Dissolution of Verapamil HCl in Fed Condition



Fasted vs. Fed Condition and Effect of 3 months 40°C/75% RH Storage

Formulation I shows a much faster release rate in the fasted condition than in the fed condition (Figure 4). Consequently, differences in bioavailability would be expected from formulation I in the fasted and fed conditions. Three month 40°C/75%RH storage has a minor effect on the performance of formulation I in the

fasted (f2=77) and fed (f2=58) conditions. Formulation II also has a higher release rate in the fasted condition (Figure 5), but the difference is smaller than that for formulation I. This formulation is also stable during 3 months' 40°C/75%RH storage in both fasted (f2=72) and fed (f2=68) test conditions. Calan SR is similar to formulations I & II in that the release rate is more rapid in the fasted condition than in the fed condition (Figure 6). The release rate from Calan SR increased in both fasted (f2=47) and fed (f2=62) conditions during the three month 40°C/75%RH storage period. This suggests that Calan SR may be less stable than the simple HPMC matrix formulations.

Figure 4. Dissolution of Formulation I, Fasted vs. Fed Conditions & Effect of 3 months 40°C/75%RH Storage

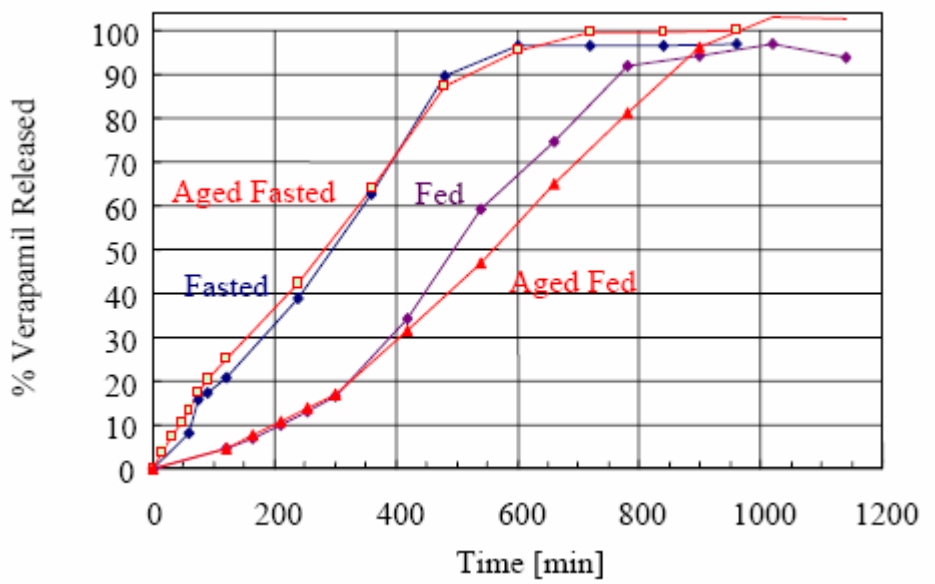


Figure 5. Dissolution of Formulation II, Fasted vs. Fed Conditions & Effect of 3 months 40°C/75%RH Storage

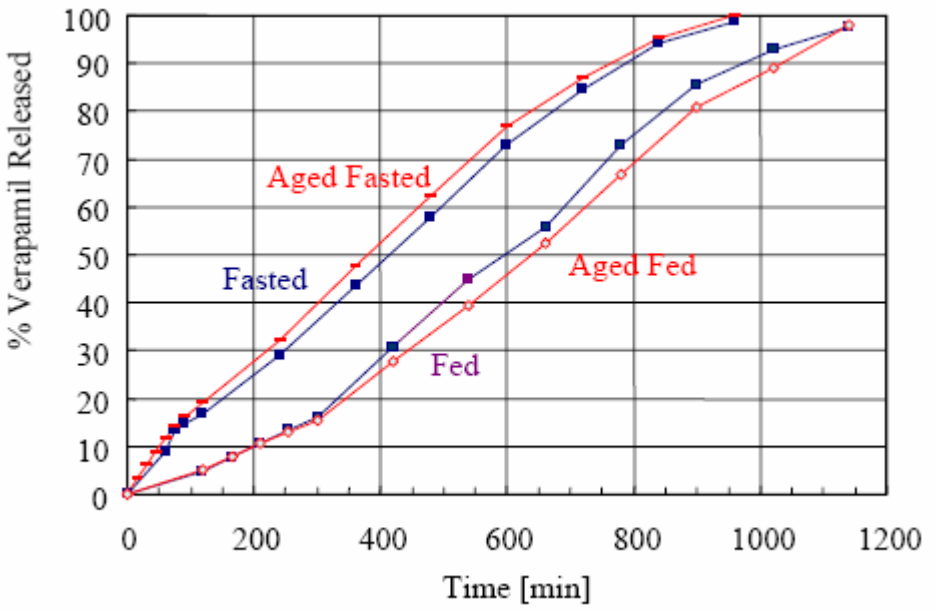
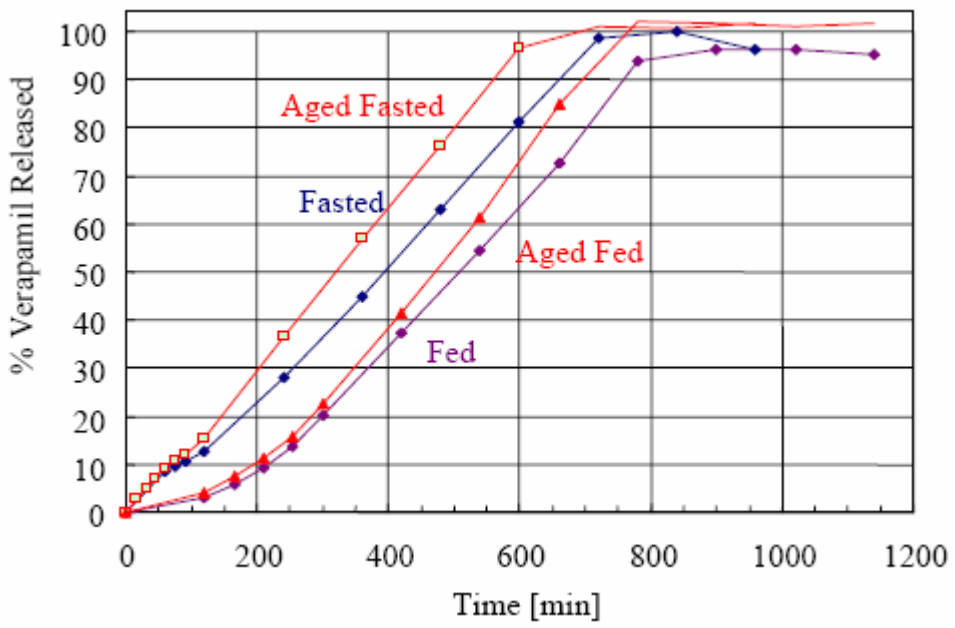


Figure 6. Dissolution of Calan SR, Fasted vs. Fed Conditions & Effect of 3 months 40°C/75%RH Storage



The more rapid release rate of Calan SR in the fasted condition is in qualitative agreement with the pharmacokinetic parameters indicated on the package insert (Table 4). The higher Cmax and shorter tmax in the fasted condition correspond to a higher in vivo release rate in the fasted condition, and Calan SR has higher bioavailability in the fasted condition. Based on the dissolution profiles obtained using apparatus III and biorelevant media, formulations I and II would be expected to show similarly greater bioavailability in the fasted condition relative to the fed condition. These data may indicate a possible effect of the fed state media on solubility/complexation of the drug.

Table 4. Pharmacokinetic Values of Calan SR, Randomized Single Dose Crossover Study 6

Pharmaceutical Parameter	Fasted Condition	Fed Condition
Cmax, (ng/ml)	164	79
tmax, (hr)	5.21	7.71
AUC (0-24 hrs), (ng*hr/ml)	1478	841

CONCLUSIONS

USP apparatus III with biorelevant media allowed collection of more scientifically sound dissolution profiles for understanding in vivo performance than USP apparatus I or II. Formulation I meets the UPS acceptance criteria for verapamil HCl extended release tablets, test 3, but testing in apparatus III indicates that the dissolution rate is much faster than a reference product in the fasted condition. Formulation II does not meet the USP specification, but apparatus III indicates that it may be more bioequivalent to the reference product in the fasted condition than formulation I. The more scientifically sound conclusion disagrees with the result from the simple compendial test. This clearly indicates that apparatus III dissolution profiles with biorelevant media can provide useful information during formulation development.

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