Evaluation on Biorelevant Dissolution Behavior of Propranolol HCl Encapsulated in Various Capsules

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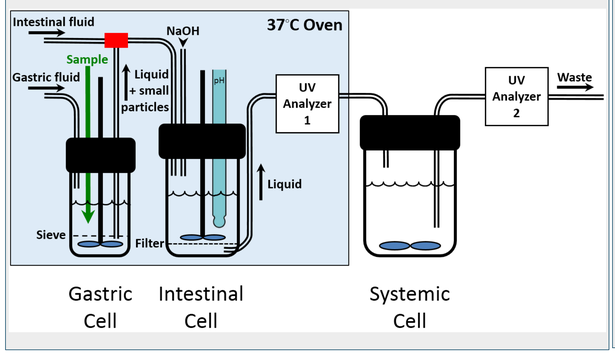
PURPOSE

Two-piece hard capsules continuously serve as widely used oral drug and dietary supplement dosage forms. Hard gelatin capsules are used in 20% of all oral dosage forms but have numerous shortcomings especially with potential crosslinking with the active ingredient, the growing consumer preference for non-animal products and concerns about bovine spongiform encephalopathy (BSE or mad cow disease). The most common polymer used to replace gelatin in hard capsules is hydroxypropyl methylcellulose (HPMC) or hypromellose. In this study, Propranolol HCl was used to evaluate dissolution behavior and to assess equivalence of HPMC capsules with gelatin capsules using biorelevant testing. DuPont's FloVitro ™ technology was used to simulate a biomimetic system utilizing a flow through approach with a series of solid transfer cells that incorporates drug pharmacokinetic characteristics. It is a biorelevant *in vitro* test that reflects physiological environment in the test conditions with a purpose of correlating *in vitro* with *in vivo* drug absorption. FloVitro ™ has the unique ability to generate dissolution curves that match plasma profiles directly without the need for mathematical modeling. Therefore, both Modified USPII and FloVitro ™ technology were used to study dissolution behavior of Propranolol HCl in various commercial gelatin and HPMC capsules.

METHODS

Commercially available empty hard gelatin capsules (HGC capsules) were purchased from Health Hut, Midland, Michigan. Hard gelatin capsules and HPMC capsules without gelling agents (HPMC capsules) supplied by CapsCandada were also used in this study. All types of capsules were clear and transparent without any color additives. Each type of capsule shells was loosely filled with ~80 mg Propranolol HCl neat compound. A modified USP II with paddles was used for traditional *in vitro* dissolution experiments with Distek 2100 and spectrophotometer Agilent 8453. Dissolution study using a FloVitro™ system was carried out on each capsule dosage using three connected cells containing biorelevant media representing gastric, intestinal, and systemic environment respectively. Media automatically transfers dispersed/dissolved drug particles from the first cell to the second cell and then from the second cell to the third cell. Data is collected from the third cell at intervals of 0.5 minutes. Media volumes and fluid flow rates are identified according to starting point algorithm (SPA) and optimized for the highest relationship based on plasma drug concentration-time profiles from immediate release *in vivo* data. Both 80 mg Propranolol HCl Inderal LA IR capsules and 80 mg Propranolol HCl filled capsules were tested using the same procedure reported in reference 1-3.

Figure 1. FloVitro™ Technology: 3 cell system under biorelevant conditions.



RESULTS

Biorelevant *in vitro* test using FloVitro ™

Figure 2. Mean concentration and recovery of Propranolol HCl released over 16 hours for both gelatin and HPMC capsules using FloVitro ™.

❖HPMC capsules showed similar dissolution profile as gelatin capsules

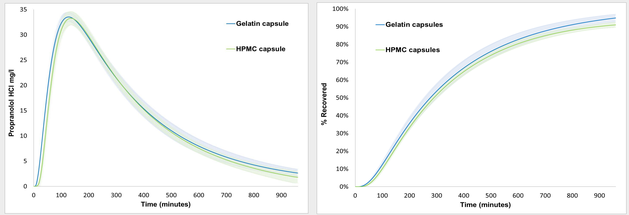


Figure 5. Statistical analysis of T_{max} and C_{max} on data obtained from FloVitro ™.

❖There was no statistically significant difference in key pharmacokinetic parameters between HPMC capsules and gelatin

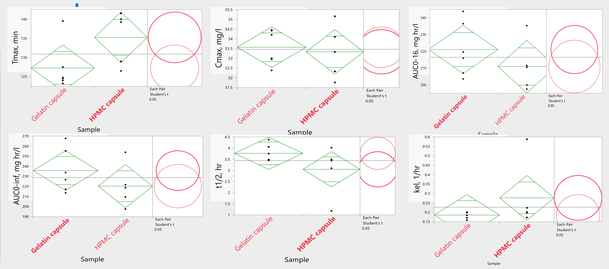


Table 1. Mean pharmacokinetic parameters including standard deviations of Propranolol HCl released over 16 hours for both gelatin and HPMC capsules using FloVitro ™.

Sample Description	C_{max} (mg/L)	T_{max} (min)	$AUC_{0\text{-}16}$ mg hr/l	$AUC_{0\text{-}inf}$ mg hr/l	$T_{1/2}$(hr)	k_{el} (1/hr)
*in vivo (*Inderal LA IR tablets*)*	34.64	120	218.3	230.5	3.4	0.2
Gelatin Capsules (n=6)	33.6 (0.9)	127.5 (6.2)	221.1 (16.0)	235.7 (21.6)	3.8 (0.4)	0.19 (0.02)
HPMC Capsules (n=5)	33.3 (1.36)	135.3 (7.0)	210.9 (15.0)	220.3 (21.0)	3.0 (1.1)	0.3 (0.18)

No significant difference found between gelatin and HPMC capsules for all key pharmacokinetic parameters investigated

Table 2. Geometric mean and confidence interval from log transformed pharmacokinetic parameters to assess equivalency from biorelevant data for both gelatin and HPMC capsules using FloVitro ™.

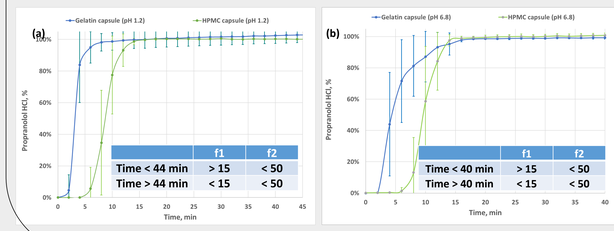
Pharmacokinetic Parameters	Least Square Geometric Means		Ratio of Geometric Means (%)	90% Confidence Interval of Ratio of Geometric Means (%)
	Gelatin	HPMC	HPMC /Gelatin	HPMC /Gelatin
Ln(C_{max} (mg/L))	3.5	3.5	99.3	97.6-100.9
Ln($AUC_{0\text{-}16}$ mg hr/l)	5.4	5.3	95.4	94.8-96.1
Ln($AUC_{0\text{-}inf}$ mg hr/l)	5.5	5.4	93.4	92.1-94.8

90% CI for Cmax, $AUC_{0\text{-}16}$ and $AUC_{0\text{-}\infty}$ are well within the range of 80 - 125.00% required by FDA for bioequivalence

in vitro test using USP II

Figure 7. Dissolution profile of Propranolol HCl in gelatin and HPMC capsules at (a) pH 1.2 and (b) pH 6.8.

❖There is a delay of onset dissolution from HPMC capsules comparing to gelatin capsules in both pH 1.2 and pH 6.8



CONCLUSION(S)

Using USP II method, HPMC capsules showed ~5-6 minutes initial Propranolol HCl delay compared to gelatin capsules in both pH 1.2 and pH 6.8 dissolution media. Using FloVitro™ technology, it was found that the key pharmacokinetic parameters, C_{max}, T_{max}, $AUC_{0\text{-}16}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, and k_{el} of HPMC capsules were not statistically different to that of gelatin capsules. The 90% CI for Cmax, $AUC_{0\text{-}16}$ and AUC $_{0\text{-}\infty}$ are well within the range of 80 -125.00% required by FDA for bioequivalence. This study also demonstrates that DuPont's FloVitro™ technology enables pharmaceutical scientists relatively quickly assess biorelevant information on specific APIs and dosage forms.

Note: all HPMC capsules in this study were gelling agent free HPMC capsules

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