Impact of Excipients on BCS Class 3 Oral Drug Absorption

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PURPOSE:

- Oral solid immediate release (IR) dosage forms of a BCS class 3 drug (high solubility and low permeability) which dissolve very rapidly may be potential candidates for BCS-based biowaivers.
- A major consideration is the need for excipients to not modulate intestinal permeability and motility.
- Previously, we conducted a bioequivalence (BE) study wherein fifteen common excipients were evaluated. Three test formulations (capsules with each capsule containing three excipients in quantities above the levels typically found in marketed IR tablets) were compared to a commercial reference formulation.
- Cimetidine and acyclovir were previously used as the model BCS class 3 drugs. Capsules with a large amount of either HPMC (9.5%) or magnesium stearate (13.3%) exhibited about 10% reduced drug exposure (i.e. reduced AUC), perhaps due to slower *in vivo* dissolution, leading to bioinequivalence.
- Also, the commercial solution of cimetidine (reference formulation) contained sorbitol and resulted in lower drug exposure compared to test capsules, which did not contain sorbitol, thus leading to bioinequivalence.
- Hence, the objectives of this study were:
  a. To assess whether lower (but still high) quantities of HPMC or magnesium stearate modulate extent of oral drug absorption of a model class 3 drug when formulated as a very rapidly dissolving capsule.
  b. To assess the effects of sorbitol on the oral absorption of a BCS class 3 drug, cimetidine, by comparing the commercial oral solution of cimetidine containing sorbitol with a reference oral solution that does not contain sorbitol.

METHODS:

- Cimetidine was selected as the model BCS class 3 drug.
- Four HPMC-containing capsule formulations and four magnesium stearate-containing capsule formulations were prepared and assessed via *in-vitro* dissolution to identify quantities of HPMC and magnesium stearate that would allow for very rapid dissolution (>85% in 15 min) in pH 6.8 buffer.
- The two identified formulations (Cim Test A and B) and a reference oral solution of cimetidine without sorbitol were manufactured and subjected to AUC evaluation in n=24 healthy volunteers.
- The plasma samples from the subjects were stored at -20°C until quantification by HPLC.
- AUC $_{0\text{-}t}$ and C_{max} were obtained from the plasma concentration-time profiles
- The data was subjected to average BE analysis using Phoenix WinNonlin where each test formulation was compared to the reference sorbitol-free oral solution

RESULTS:

- In order to determine the amounts of HPMC and magnesium stearate to be incorporated in Cim Test A and Cim Test B, respectively, eight different formulations were prepared and evaluated via *in-vitro* dissolution

Formulation	No.	Formula	Excipient	% Dissolved in 15 min[a]
Cim Test A	1	Cimetidine (100mg) ; Microcrystalline cellulose (300mg) ; Sodium lauryl sulfate (25mg)	HPMC: 10mg (2.3%)	92.9 (3.33)
	2 [b]		HPMC: 20mg (4.5%)	89.5 (2.84)
	3 [c]		HPMC: 45mg (9.5%)	38.6 (8.15)
	4		HPMC: 75mg (15%)	23.5 (3.59)
Cim Test B	5 [b]	Cimetidine (100mg) ; Pregelatinized starch (100mg) ; Crosscarmellose sodium (60mg)	Mag st: 20mg (7.1%)	94.5 (2.44)
	6		Mag st: 40mg (13.3%)	60.2 (3.28)
	7		Mag st: 40mg (8%) + Lactose: 200mg	60.0 (4.99)
	8 [c]		Mag st: 40mg (13.3%): turbular mixer	29.0 (5.16)

[a] Mean(SEM); [b] Selected for clinical study; [c] Used in previous study

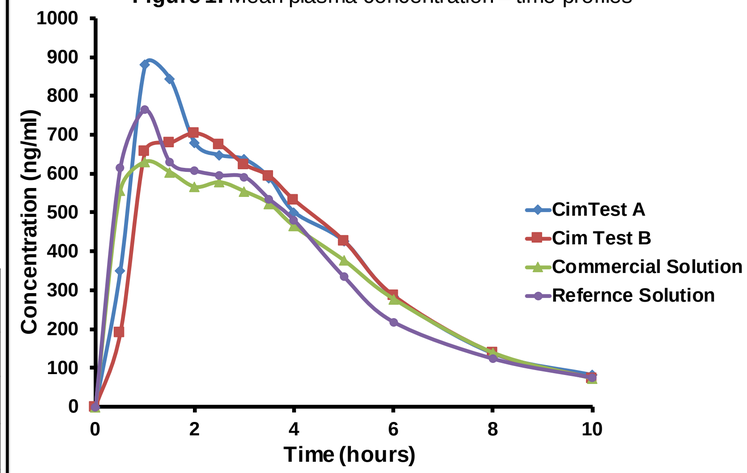
Table 1: Eight formulations with varying amounts of excipients and % dissolved in 15 minutes

- Formulations Cim Test A (ver3) and Cim Test B (ver5) were chosen as the clinical candidates as they satisfied the criteria of being very rapidly dissolving.

Formulation vs Reference solution	C_{max} point estimate	C_{max} 90% CI	$AUC_{0\text{-}t}$ point estimate	$AUC_{0\text{-}t}$ 90% CI
Cim Test A	122.11	109.42–136.28	112.24	104.44– 120.62
Cim Test B	105.08	94.16–117.27	105.21	97.90– 113.07
Commercial solution	86.98	77.94–97.08	100.22	93.26– 107.70

Table 2: Average BE analysis

Figure 1: Mean plasma concentration – time profiles



CONCLUSION:

- Since the 90% CI for AUC complies with the BE limits for the two cimetidine capsules (i.e. CimTest A and CimTest B), we conclude that the studied levels of HPMC and magnesium stearate (and lower) are not problematic excipients regarding BCS class 3 biowaivers.
- The commercial cimetidine solution containing sorbitol exhibited the same drug exposure as solution without sorbitol.

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