Utilizing Viscous Media to Assess Food-Induced Viscosity Effects on Immediate Release Tablet Disintegration and Drug Dissolution

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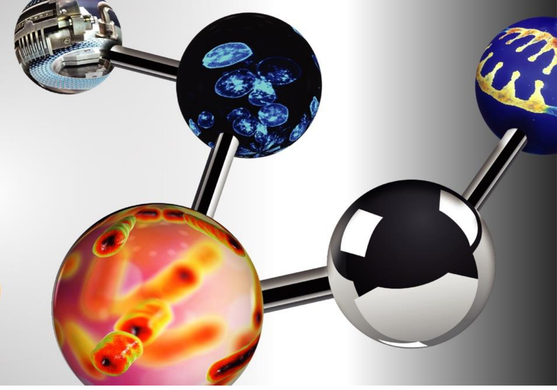


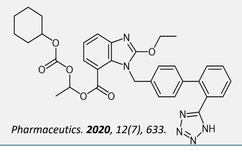
PURPOSE

Studies have shown that an increase in viscosity of dissolution medium, simulating the ingestion of a solid meal, may drastically impact tablet disintegration and dissolution of a Biopharmaceutical Classification System (BCS) Class III drug.[1-4] The aim of the present study is to determine the effect of meal-induced viscosity on the in vitro tablet disintegration and dissolution of a BCS Class II drug (candesartan cilexetil) with innovator (ATACAND, reference listed drug) and generic formulations. The study results may potentially help develop dissolution methods to better simulate in vivo fed conditions.

METHOD(S)

- Simulated fed and fasted conditions using standard buffer media with and without a viscosity enhancing additive (HPMC).
- Standard buffer media prepared using current United States Pharmacopeia (USP) Buffer Solutions protocols.
- Viscous media prepared by dispersing the required amount of HPMC to the heated compendia buffer solutions.
- Disintegration and dissolution conducted using a disintegration tester and USP Apparatus II dissolution system.
- Characterized media, reference listed drug, and generic drug.
- Dissolution carried out in a staged and unstaged process.
  - Unstaged: Viscous media used following current USP-NF candesartan cilexetil tablet protocol (USP41-NF36–662).
  - Staged: Viscosity incrementally decreased by addition of non-viscous diluent at predetermined times.
- Tablets: ATACAND 32 mg, NDC 62559-643-30, Lot 504759; Generic 32 mg tablet (manufacturer: Alembic), NDC 62332-060-30. Lot 2005001794.

Figure 1: Skeletal formula and solubility of candesartan cilexetil



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pH	Solubility (mg/mL)
1.2	$7.10 \cdot 10^{-3} \pm 5.00 \cdot 10^{-4}$
4.5	$9.74 \cdot 10^{-2} \pm 4.00 \cdot 10^{-4}$
6.8	$1.11 \cdot 10^{-1} \pm 1.00 \cdot 10^{-3}$

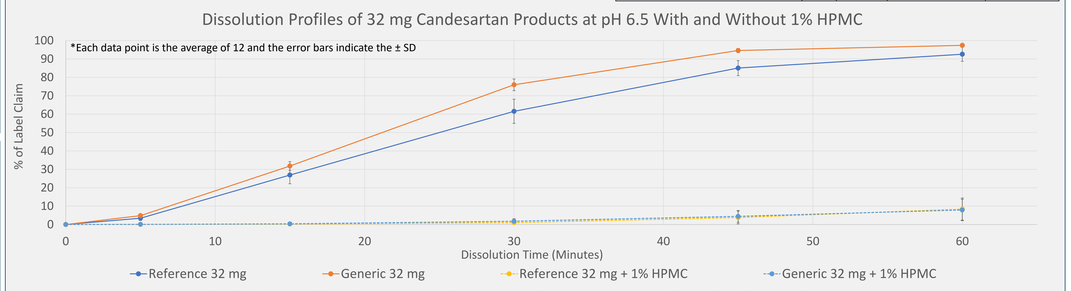
RESULTS

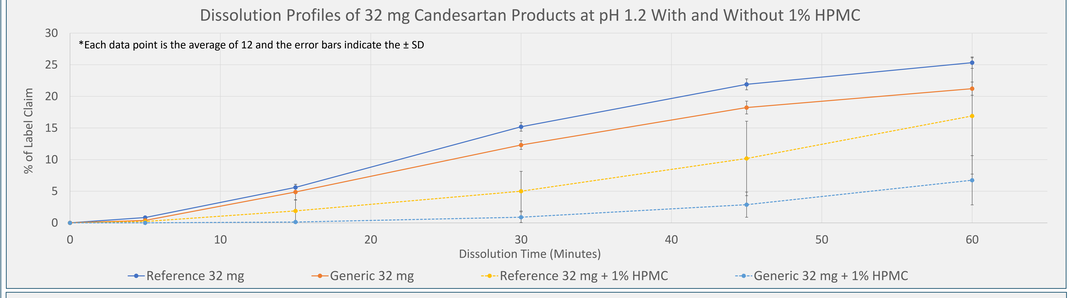
Table 1: Physical characteristics of the 32 mg candesartan cilexetil tablets

	Hardness (N)		Diameter (mm)		Thickness (mm)		Weight (mg)	
	Reference	Generic	Reference	Generic	Reference	Generic	Reference	Generic
# Values (N)	8	8	8	8	8	8	8	8
Mean ± SD	113 ± 6.70	84 ± 5.10	9.56 ± 0.01	9.58 ± 0.02	3.45 ± 0.02	3.88 ± 0.01	258.8 ± 2.02	260.3 ± 1.79

Table 2: Physical characteristics of each media

Media	pH	Density (g/mL)	Surface Tension mean ± SD (mN/m)	Viscosity mean ± SD (cP)
Phosphate buffer	6.5	0.990	70.97 ± 0.07	0.79 ± 0.14
Phosphate buffer and 1.0 % HPMC	6.5	1.010	46.89 ± 1.73	105.47 ± 4.15
SGF buffer without pepsin	1.2	1.009	68.18 ± 0.24	1.67 ± 0.13
SGF buffer without pepsin and 1% HPMC	1.2	0.992	50.79 ± 1.82	84.20 ± 9.89





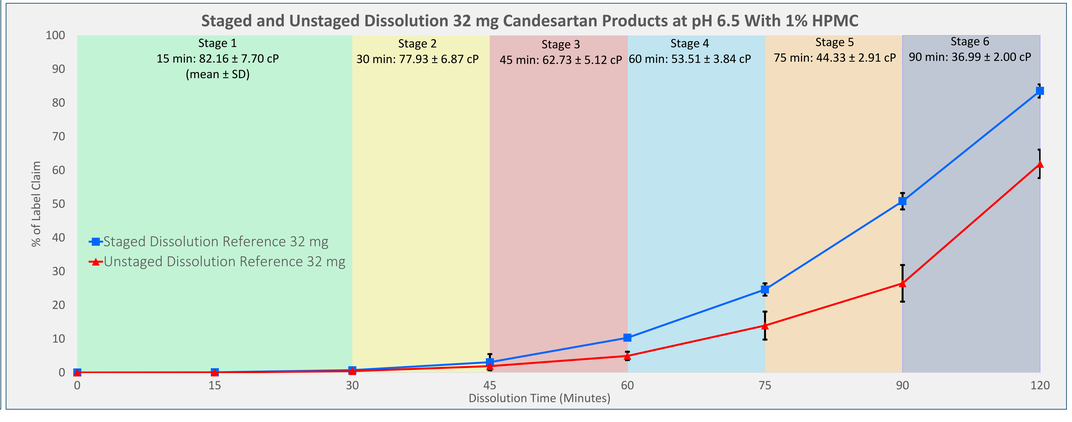


Table 3: Disintegration times of 32 mg candesartan cilexetil tablets (n=6)

Media	Tablet (32 mg)	Average Time ± SD (min:sec)	Reference % Increase With vs Without HPMC	Generic % Increase With vs Without HPMC
Phosphate buffer (pH 6.5)	Reference	8:20 ± 02:52	Increase of 211.8%	Increase of 48.9%
	Generic	13:15 ± 00:32		
1% HPMC + Phosphate buffer (pH 6.5)	Reference	25:57 ± 01:37		
	Generic	19:58 ± 02:02		
SGF w/o Pepsin buffer (pH 1.2)	Reference	13:34 ± 00:13	Increase of 110.6%	Increase of 70.1%
	Generic	15:34 ± 00:42		
1% HPMC + SGF w/o pepsin buffer (pH 1.2)	Reference	28:10 ± 00:22		
	Generic	26:09 ± 00:25		

The general trend of results indicate that with more viscous dissolution media at pH 1.2 and 6.5, the in vitro disintegration for both generic and innovator candesartan cilexetil tablets were significantly delayed, and the in vitro dissolution became incomplete and much slower, thus indicating that food-induced viscosity may play an important role in the disintegration and dissolution process. Our future work aims to investigate the effect that simulated fed state conditions have on the dissolution and disintegration of other BCS class drugs, especially highly soluble and highly permeable drugs. Furthermore, we aim to incorporate physiologically based pharmacokinetic modeling to provide supplemental approaches to predict the in vivo performance of oral immediate release tablets under fed conditions.

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Disclaimer: This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

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