Formulation and Process Parameters Optimization in Chewable Tablet

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PURPOSE

To developed stable and bioequivalence generic chewable tablets for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) using implementation of Quality by Design (QbD).

METHOD

- Direct blending followed by compression (Target weight 500 mg)
- Mannitol and microcrystalline cellulose (10–70% w/w) were studied for impact on assay and content uniformity while croscarmellose sodium (2–7% w/w) and magnesium stearate (0.5–1.5% w/w) were studied to check impact on disintegration and dissolution.
- Blending revolution (250–500) evaluated for blend uniformity while 20–50 rpm press speed, and 4–10 kN compression force evaluated for content uniformity
- Bioequivalence was evaluated in healthy adults via a randomized, crossover design under fed and fasting states.

RESULT

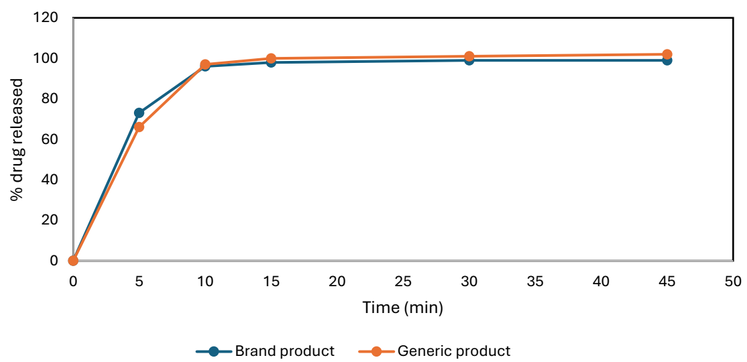
- Mannitol and microcrystalline cellulose (MCC) were used as directly compressible diluents with good flow. Due to low drug load (12% w/w) and high diluent content (78.5% w/w), their ratios significantly influenced assay and content uniformity. Optimal levels were 65.0% w/w mannitol and 13.5% w/w MCC. Disintegrant (2–7% w/w) was optimized at 5.0% w/w. Magnesium stearate (0.5–1.5% w/w), a hydrophobic lubricant, was optimized at 1.0% w/w to avoid delayed disintegration.
- The optimized formulation and process was scaled to 60.0 kg (120,000 tablets) using a 5-cu.ft V-blender (340 blending revolutions for Stage 2 to 4) and Korsch XM-12 press (~ 7 kN main compression force and 35 rpm press speed).
- Pharmacokinetic parameters demonstrated acceptable ratio of least squares geometric means (LSGM) for both Cmax and AUC, with the 90% confidence intervals for both metrics falling within the bioequivalence acceptance range of 80–125%.

CONCLUSION

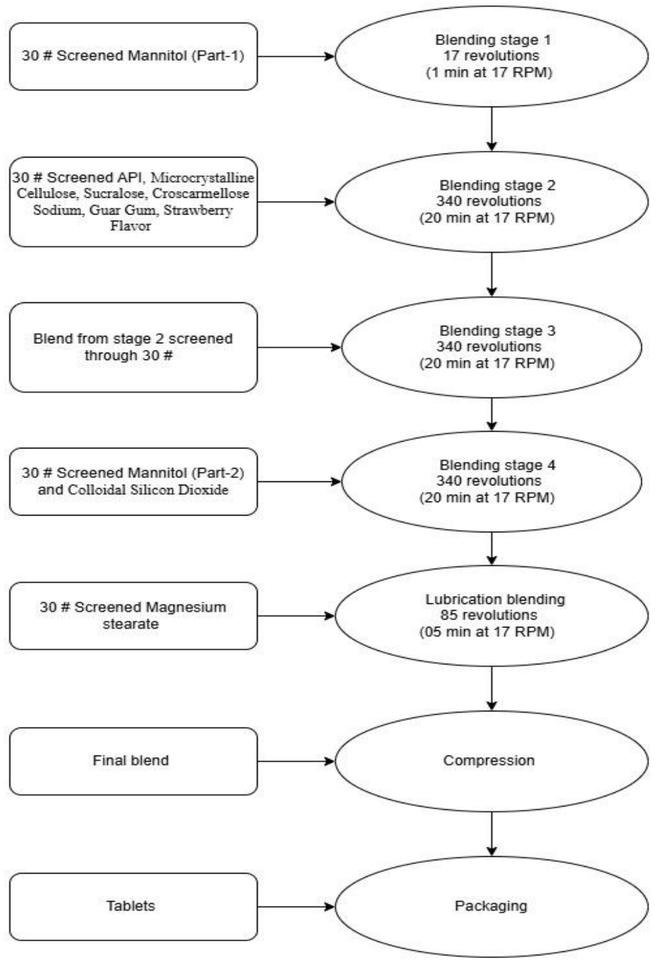
QbD approach enabled the successful development of a stable, bioequivalent generic chewable tablet for ADHD treatment.

Formulation component	% w/w
API	12.0
Mannitol, USP	65.0
Sucralose FCC, NF/USP	1.0
Croscarmellose Sodium, NF	5.0
Guar Gum, NF	1.0
Microcrystalline Cellulose, NF	13.5
N-C Fresh Strawberry Flavor, ART	0.5
Colloidal Silicon Dioxide, N	1.0
Magnesium Stearate, NF	1.0
Total	**100.0**

Drug release comparison of Brand vs Generic



Manufacturing flow diagram



Summary of Pivotal Fasting BE Study

Parameters	Test	RLD	Test/RLD	90 % confidence interval
	Least Squares Geometric Means		Ratio	
Cmax	32.382	33.682	96.61 %	90.14-103.54
AUCt	37.706	38.786	97.11 %	90.82-103.84

Summary of Pivotal Fed BE Study

Parameters	Test	RLD	Test/RLD	90 % confidence interval
	Least Squares Geometric Means		Ratio	
Cmax	17.767	18.183	98.05	90.80-105.87
AUCt	43.151	42.494	102.58	98.55-106.77