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The Impact of Cyclodextrin on Fasting and Fed Bioequivalence Studies in Solid Oral Immediate-Release Drug Products

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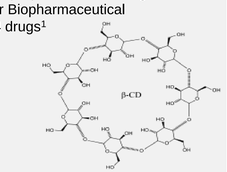
PURPOSE

- Cyclodextrin (CD) is a family of cyclic oligosaccharides consisting of a macrocyclic ring of glucose subunits joined by α-1,4 glycosidic bonds
  - Commonly used 6-8 linked α-D-glucopyranoside-creating ring shape structure[1]
- CD is used for the improvement of water-solubility and bioavailability (BA) of drug products in a variety of dosage forms such as oral tablets, aqueous parenteral solutions, nasal sprays, and eye drops[1]
- Betacyclodextrin (β-CD), or betadex, is a common 7-glucose subunit ring of CD that is gaining presence as an excipient in solid oral immediate release (IR) drug products
  - Previously, literature has demonstrated CD has potential to stabilize formulation and improve organoleptic properties, increasing the dissolution rate and improving BA for Biopharmaceutical Classification System (BCS) 2 and 4 drugs[1]
- β-CD has the potential to impact the drug pharmacokinetic (PK), which may subsequently impact between generics and new drugs bioequivalence (BE) outcomes



OBJECTIVE(S)

- This study aimed to examine the use of CD in solid oral immediate release (IR) drug products and its impact on the (BE) outcome under fasting and fed conditions.

METHOD(S)

- We collected U.S Food and Drug Administration (FDA) approved New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) for solid oral IR drug products containing β-CD as an excipient
- Individual drug product formulation composition, fasting and fed PK BE data, and in vitro dissolution data were analyzed

12 unique API oral drug products with CD as an excipient were screened

→ Excluded oral solution and extended-release tablet

10 unique API solid oral IR drug products

→ Excluded 4 unique API drug products with no approved generics

6 unique API solid oral IR drug products with approved generics

→ Excluded Orally-disintegrating tablet without fed studies

5* unique API solid oral IR drug products with both fasting and fed PK studies and approved generics

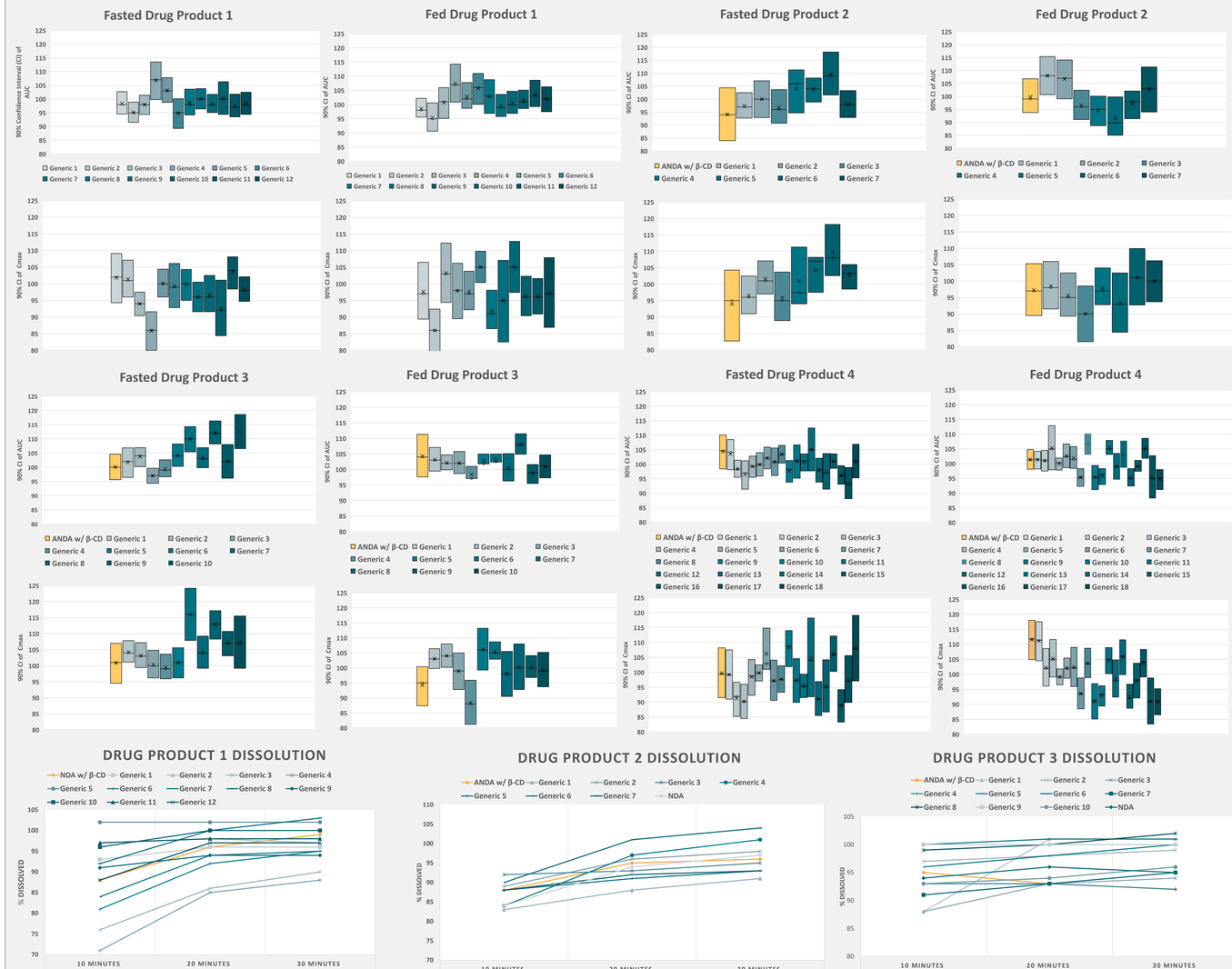
*1 unique API with multiple applications that include CD

RESULT(S)

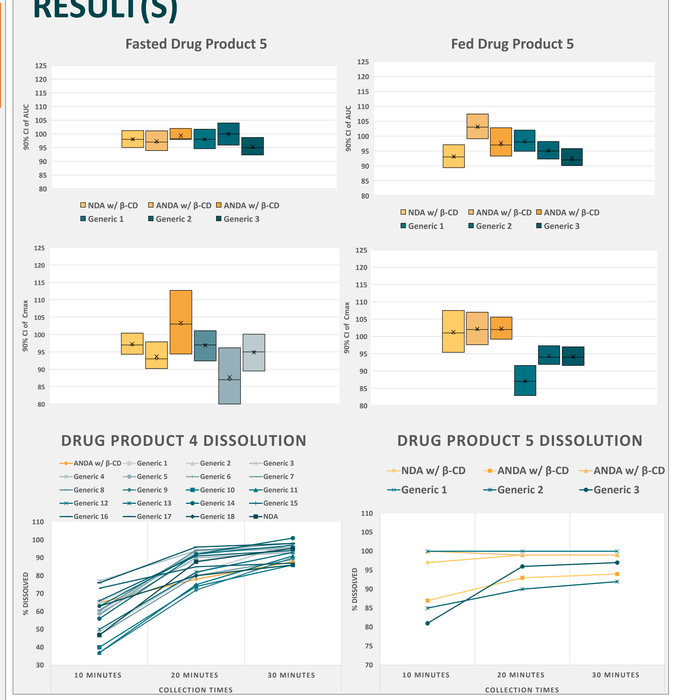
Drug Products	BCS class	Dosage Form	Cyclodextrin (CD)	Function	CD w/w Amount (%)	Non-CD excipient used in other compared ANDAs
Drug Product 1	2	Tablet	β-cyclodextrin clathrate	Stabilize API	< 1	Not substituted
Drug Product 2	1	Tablet	Betadex	Diluent	~60	Mannitol
Drug Product 3	3	Tablet	Betadex	Diluent	~27	Microcrystalline cellulose
Drug Product 4	2	Tablet	Betadex	Diluent	~19	Lactose
Drug Product 5	3	Chewable Tablet	Betadex	Taste masker	~41; ~34; ~17	Magnesium Oxide; Polacrilex resin

Drug Product 1: Fasted β-CD-API complex vs. API only formulation[2]			
PK Parameters	Test 1 vs. ST	Test 2 vs. ST	Test 2 vs Test 1
Cmax	100.9 (89.6 - 113.6)	105.8 (94.0 - 119.2)	104.9 (93.2 - 118.1)
AUC	97.2 (85.3 - 110.7)	104.3 (96.1 - 118.8)	107.3 (94.2 - 122.3)

Test 1: API-β-CD complex oral tablet
Test 2: API only oral tablet
Standard treatment (ST): API in microcrystalline suspension



RESULT(S)



CONCLUSIONS

- β-CD is found to be utilized diversely as a drug stabilizer, diluent, or taste masking agent in the 5 solid oral IR dosage forms drug products.
- β-CD did not pose an impact on the PK differently of BCS Class 1, 2, 3 drugs or affect BE outcomes under both fasting and fed conditions in reviewed applications.
- β-CD did not change product dissolution profiles in reviewed applications.
- Future work may be needed to determine if other types of CD affect PK or β-CD impacts PK of other modified release products or solution products.

DISCLAIMER AND REFERENCES

Disclaimer

- The contents in this poster reflect the views of the authors and should not be construed to represent U.S. FDA's views or policies.
- Specific drug names and application numbers were not disclosed due to confidentiality reasons. However, masking drug names would not affect the conclusions we draw on the potential impact of β-CD on PK or BE under fasting or fed conditions for these oral dosage form products.

References

1. Rajeswari Challa, Alka Ahuja, Javed Ali, and R.K. Khar. Cyclodextrins in Drug Delivery: An Updated Review. AAPS PharmSciTech; 2005 6(2) Article 43.
2. Hartmut Blode, Rolf Schürmann, Norbert Benda. Ethinyl estradiol-beta-cyclodextrin clathrate formulation does not influence the relative bioavailability of ethinyl estradiol or co-administered drospirenone. Contraception; 77 (2008) 171 – 176.