Abstract Submission #1091862

Evaluation of the Dissolution Drug Release Profiles of Approved Generic Formulations in Multiple pH Media for Putative Biopharmaceutics Classification System Class III Drugs, Atenolol Tablets and Acyclovir Tablets

Daniela Selaya[a], Robert Hunt[a], Ping Ren[b], David Li[a], Haiou Qu[a], Wen Cheng Yang[b], Jiang Wang[a], Theresa Chan[b, c], Myong-Jin Kim[b], Patrick Faustino[a], Yi Zhang[b]

[a]Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

[b]Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD

[c]Oak Ridge Institute for Science and Education (ORISE) Fellow

CONTACT INFORMATION: Susan.Selaya@fda.hhs.gov

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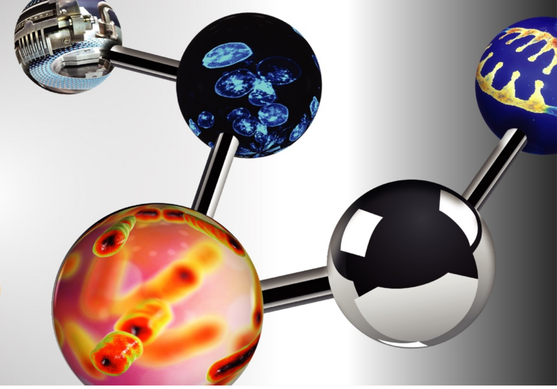


PURPOSE

In general, the bioequivalence (BE) for the immediate-release (IR) oral solid dosage forms of generic products can be established by conducting acceptable in vivo BE studies with the recommended dissolution testing in only one medium. As per ICH Harmonized Guideline, Guidance for Industry: M9 Biopharmaceutics Classification System-Based (BCS) Biowaiver (May 2021), the dissolution testing in only one medium is not sufficient to support the BCS Class III-based biowaiver. Therefore, in vitro dissolution testing in multiple pH media should be conducted to qualify for the BCS Class III-based waiver.

In this study, automated dissolution platforms were used to quantitatively assess the dissolution drug release rate in multiple pH media for approved generic product formulations of atenolol tablets and acyclovir tablets by using a one-batch representative of the commercial manufacturing process for the test products.

OBJECTIVE(S)

(1) Evaluation of the impact of manufacturing procedures;
(2) Evaluation of different strengths of the entire product line;
(3) Evaluation of the impact of multiple dissolution pH media on the drug release of BCS Class III drug product candidates.

METHOD(S)

The dissolution studies were conducted on the approved generic drug products for atenolol tablets (25 mg, 50 mg, and 100 mg) and acyclovir tablets (400 mg and 800 mg) with USP Apparatus II (Teledyne Hanson) in three BCS pH media (1.2, 4.5 and 6.8).

Automated dissolution platforms (Waters Corporation, Milford MA) were used for the dissolution and HPLC studies. The dissolution apparatuses and baths were calibrated according to American Society for Mass Spectrometry procedure for mechanical calibration.

Standard dissolution conditions included:

1) USP Apparatus II (Paddle)
2) Medium volume: 900 mL
3) Stir rate of 50 rpm
4) Bath temperature at 37°C
5) Vessels (n =6)
6) Sampling times of 5, 15, 30, 45, and 60 minutes.

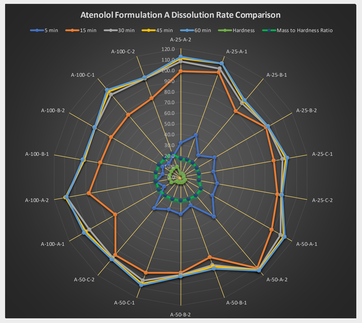
The analytical methods were developed in-house and validated according to USP general chapter <1225> Validation of Compendial Methods for Assay.

RESULT(S)

Atenolol dissolution studies: 75% (27/36) of two approved ANDAs (Formulations A and B) of atenolol tablets, in all three pH media, met the "**very rapidly**" dissolution criteria (i.e., not less than (NLT) 85% in 15 minutes) for biowaiver for BCS Class III drug as specified in ICH M9 guideline. 25% (9/36) of atenolol tablets scattered across all strengths did not meet the "very rapidly" dissolution criteria.

Acyclovir dissolution studies: 92% (33/36) of three approved ANDAs (Formulations A, B, and C) of acyclovir tablets, in all three pH media, met the "**very rapidly**" dissolution criteria. 8% (3/36) of acyclovir tablets mg did not meet the "very rapidly" dissolution criteria only at the lower strength of 400.

Figs 1-2 Comparison of Atenolol Dissolution Profiles for Formulations A and B at 25, 50, and 100 mg



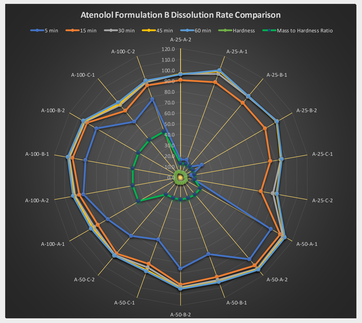


Fig 6. Dissolution Rates of Comparison for Atenolol Formulations

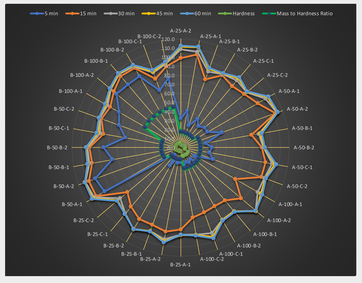
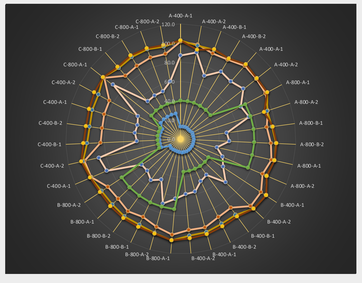


Fig 7. Dissolution Rates of Comparison for Acyclovir Formulations

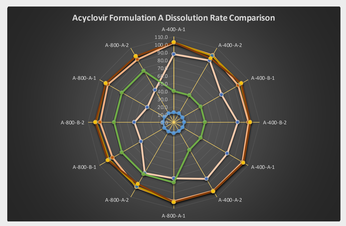


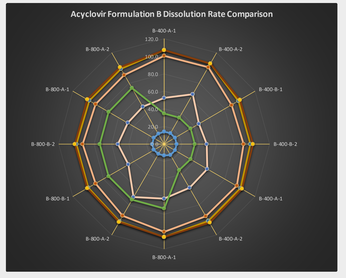
KEY
Batches identified as Formulation- Dosage- pH – Batch #
Formulations A, B or C
Dose strengths: 25, 50 or 100 mg for Atenolol and 400 or 800 mg for Acyclovir
pH- where A= 1.2, B= 4.5, C= 6.8
Batch #: dissolution experiments completed in duplicate in batches using n=6 tablets whereby each batch is listed as -1 or -2

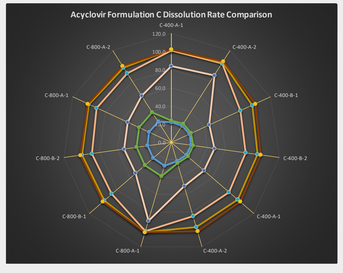
Example: B-25-A-2 for atenolol is formulation B at 25 mg tablet at pH 1.2, Batch 2/2.

Green = Mass relative to Hardness Ratio	
Blue = Hardness (kp)	
5 min dissolution	
15 min dissolution	
30 min dissolution	
45 min dissolution	

Figs 3-5 Comparison of Acyclovir Dissolution Profiles for Formulations A, B, and C at 400 and 800 mg







DISCUSSION

The majority of the dissolution studies conducted for atenolol tablets (75%) and acyclovir tablets (92%) have demonstrated the characteristics of "very rapidly" dissolving in all dissolution media as well as meeting BCS Class III biowaiver dissolution criteria (i.e., NLT 85% drug release at 15 minutes).

Results from a small percentage of dissolution studies showed that they did not meet the BCS Class III biowaiver dissolution criteria, which may be due to the dose strength or minor differences in manufacturing process, such as tablet hardness.

Our multimedia dissolution data trends indicate that the ratio of mass/tablet hardness (Figs 6 and 7) may play a role in drug release. Ongoing studies will assist to clearly identify critical variables that may impact the drug release of BCS class III products.

CONCLUSION

The majority of the dissolution studies demonstrated very rapidly dissolving in all dissolution media as well as meeting BCS Class III biowaiver dissolution criteria for generic atenolol and acyclovir IR tablets. Our data showed that different dissolution rates, either very rapidly or rapidly dissolving, did not appear to impact the in vivo performance of these approved generic drug products. Future dissolution studies on reference products and other putative BCS Class III drug candidates are underway to determine whether the "very rapid dissolving" conditions for supporting the biowaiver for BCS III Class drugs is reasonable.

REFERENCES

- Guidance for industry, M9 Biopharmaceutics Classification System-Based Biowaivers (May 2021). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m9-biopharmaceutics-classification-system-based-biowaivers
- USP (711> Dissolution
- USP <1225> Validation of compendial methods

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

Acknowledgement: Dr. Chan was supported by an appointment to the Research Participation Program at the U.S. Food and Drug Administration administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Food and Drug Administration.

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