T1230-09-051

FDA Perspective on Dissolution Testing for Development of High-Risk Oral Drug Products Containing Amorphous Solid Dispersions

Gang Zhao[1], Kevin Wei[2], Duyen Nguyen[1], Hye Lim Lim[1], Bhagwant Rege[2], Dongmei Lu[1], Qi Zhang[1]

[1.] 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; [2.] Division of Product Quality Assessment VI (Biopharmaceutics), Office of Product Quality Assessment I (OPQA I), Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD CONTACT INFORMATION: gang.zhao@fda.hhs.gov

aaps PharmSci 360

PURPOSE

Amorphous solid dispersions (ASDs) have emerged as a promising formulation technique for poorly water-soluble drugs. ASD allows the dispersion of amorphous active pharmaceutical ingredient (API) within the excipient polymer matrix at a molecular level, offering advantages such as enhanced apparent solubility, increased dissolution rate, and improved bioavailability (BA). However, the lack of thermodynamic stability in ASDs may lead to the formation of the crystalline form, posing significant concerns on BA and clinical performance. The recent ICH M13A Guideline describes ASD-containing drug products as “high-risk” of bioinequivalence, emphasizing that their in-vivo performance may be impacted by varying gastrointestinal (GI) conditions between fasted and fed states. It follows that a single bioequivalence (BE) study under either fasted or fed conditions may not be able to detect the performance differences related to different formulation and/or different manufacturing process. This research was to investigate the relationships between formulation, process attributes, dissolution, and in vivo performance on the FDA-approved drug products containing ASD. A profound understanding of these aspects is crucial in the development of BE approaches and to support formulation and manufacturing process changes.

METHOD

We collected information and data of solubility, dissolution, ASD formulation compositions and manufacturing techniques for 45 drug substances in 55 FDA-approved ASD-containing products from new drug applications as of December 31, 2023. Their corresponding dissolution acceptance criteria, method discriminating ability, and clinical relevance information were also researched and collected.

RESULT(S)

Among 55 FDA-approved ASD products, 34 product was classified as new molecular entity (NME) drugs, 11 classified as new dosage form, 6 classified as new formulation, 1 classified as new combination, 3 was classified as NME / new combination and 1 new indication. Figure 2 shows the ASD products approved by 2023. Maximum approval per year was eight ASD products in 2018. Most ASD products were approved after 2009. Figure 3 shows 47% of the ASD products were approved under orphan drug, 75% ASD products were assigned as priority review and 22% ASD products were approved as first in class.

Figure 1. Submission classification of ASD product new drug applications

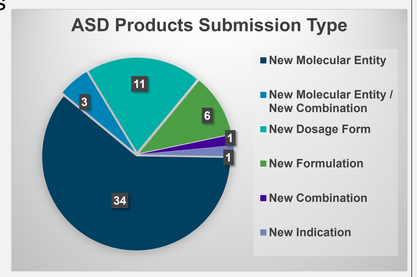


Figure 2. ASD product approved each year.

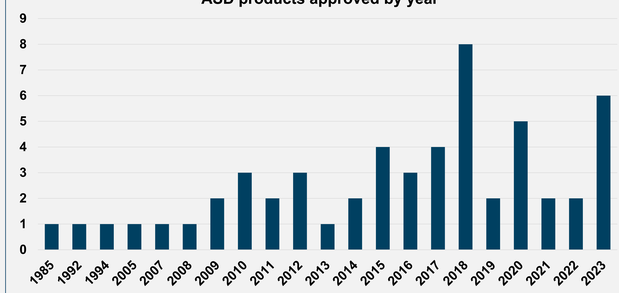


Figure 3. ASD product highlight

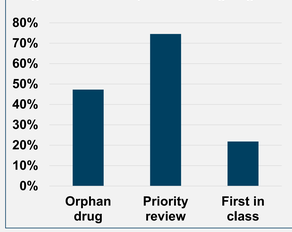


Table 1 shows the number of NME drugs or first in class ASD products approved in each therapeutic indication categories. Cancer and viral infection are the indication categories with most ASD products approved.

Table 1. Novel ASD products approved in different therapeutic categories.

Indication	Novel Drug	First in class
Cancer	13	4
Viral infection	12	4
Cystic Fibrosis	4	2
Progeria	1	1
Psoriasis	1	1
Hyponatremia	1	-
Migraine	1	-
Immunosuppressant	1	-
Antifungal	1	-
Antiemetic	1	-

Among 55 FDA-approved ASD-containing products, the dissolution methods used in 46 products (Figure 4) demonstrated discriminating ability against API particle size, critical formulation attributes (e.g., ratio of drug and polymer), critical process attributes (e.g., tablet compression force), or polymorphic transition (levels of crystalline API). It is noted that both dissolution method and acceptance criterion/criteria were considered when discriminating ability of a proposed dissolution test was evaluated. Among 55 FDA-approved products with ASD, 6 utilized biorelevant two-stage dissolution testing to develop an in vitro in vivo correlation (IVIVC; 3 products) or physiologically based biopharmaceutic modeling (PBBM; 3 products) (Figure 5). However, none of the submitted IVIVC or PBBM were considered acceptable by the FDA to support dissolution “safe space” for a waiver of BA/BE studies due to incomplete dissolution / pharmacokinetic information and data or inadequate model development, verification, or validation.

Figure 4. Summary of discriminating ability of ASD products dissolution method

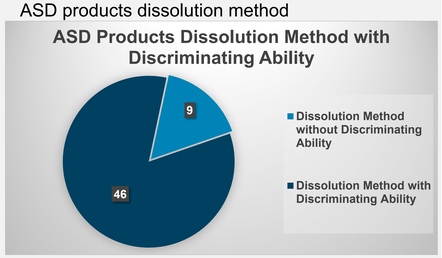
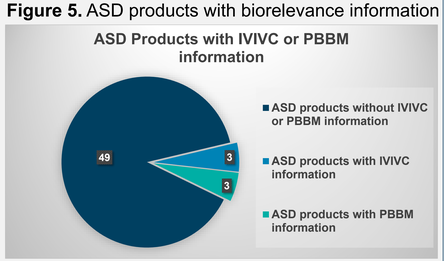


Figure 5. ASD products with biorelevance information



CONCLUSION

When developing a dissolution test for ASD-based drug products, discriminating ability of the dissolution method towards critical bioavailability attributes, including critical material attributes (e.g., crystalline content), critical formulation variables (e.g., levels and/or grade of polymer, surfactant, disintegrant), and critical process parameters (e.g., ASD particle size, compression force/hardness), that could potentially impact the dissolution and BA should be evaluated. Since precipitation impacts absorption time and BA, it is also important to utilize biorelevant two-stage, acid-to-neutral pH dissolution testing that simulates the GI pH shift for assessing the extent of supersaturation in order to establish a meaningful correlation between in vitro dissolution and in vivo absorption for drug products containing ASD. This research consolidates information on formulation attributes, dissolution, and their impacts on clinical performance in FDA-approved ASD-containing products. There is potential to use in vitro dissolution methods to assess and predict in vivo performance, which can guide formulation development throughout different stages of drug product development. This approach could potentially reduce the reliance on clinical BE studies in generic drug development.

DISCLAIMER

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

ACKNOWLEDGEMENT

Dr. Gang Zhao is supported in part 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. Special thanks to Drs. Robert Lionberger and Lei Zhang.

U.S. FOOD & DRUG ADMINISTRATION

ORISE