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Regulatory Expectations and Challenges in Alcohol-Induced Dose Dumping Studies: A Review

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ABSTRACT

The purpose of this review is to look at the recommendations and guidelines issued by various regulators about in vitro alcohol-induced dose dumping (AIDD) studies for modified released (MR) products. Drug release in MR systems is typically controlled via a polymer matrix or a polymer film coating, and dose dumping may occur if the release control is compromised by the controlling agent's breakdown in hydroalcoholic liquids. There is a risk of dose dumping when MR products are taken with concomitant consumption of alcoholic beverages. The US Food and Drug Administration (FDA) recently published guidelines that provide comprehensive information on how to undertake in vitro AIDD study for MR drug products. However, there are various regulatory guidelines, and if not harmonized, can cause complexity for formulation developers. This review compares and contrasts several regulatory standards in light of current trends, including the FDA, European Medicines Agency (EMA), Health Canada, and Australia's Therapeutics Good Administration (TGA). If the formulation and its performance under in vivo and in vitro circumstances are unaffected by the addition of 0–40% alcohol, then the patient risk is regarded to be low.

KEYWORDS: In vitro, modified release, alcohol, dose dumping, polymer, dissolution

INTRODUCTION

The term "dose dumping" refers to the rapid dissolution of a large portion of a dose within a short period of time. Dose dumping can occur when the controlling agent's breakdown in hydroalcoholic liquids compromises the release control in modified release (MR) systems. These cases involve the release of drugs through polymer matrixes or coatings. Taking alcohol within close proximity to the administration of a drug can lead to dose dumping, which is known as alcohol-induced dose dumping (AIDD) (*1*, *2*). With alcohol having similar physiological effects to anesthetics, some patients with chronic pain and depression may use alcohol as a coping mechanism because it has similar physiological effects to anesthetics (*3*). Owing to the Palladone case in 2005, regulatory authorities became more aware of AIDD. Ammonio methacrylate copolymer type B and ethylcellulose, both soluble in ethanol, were used as release-controlling polymers in the Palladone capsules containing hydrocodone (*3–5*). A pharmacokinetic study in healthy subjects found that mixing 240 mL (8 ounces) of an 80 proof (40% alcohol) alcoholic beverage with a 12-mg Palladone capsule resulted in approximately six times the peak plasma concentration of hydromorphone when consumed with water alone. It is possible to die from these high concentrations. This led to Palladone's withdrawal from the US market. Consequently, AIDD has been taken into account when developing formulations, which led to improved guidance (*4–6*).

MR dosage forms are designed in such a way that drug release is carefully controlled. Unlike immediate release (IR) dosage forms, oral controlled release (CR), MR or extended-release products offer dosing convenience and sustained therapeutic blood levels. In contrast to IR tablets and capsules, MR dosage forms contain more of the active pharmaceutical ingredient (API) as well as various excipients, which enables a controlled, delayed release of the medication. One method of preventing dose dumping is to entrap the drug in a matrix that contains hydrophobic and/or hydrophilic polymers that control drug release (*7–10*).

The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) AIDD regulations are not

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entirely harmonized. FDA testing requires 40% ethanol, whereas EMA requires 20%, which is a substantial difference. To reach a 40% alcohol concentration in the stomach, 240 mL of alcohol with a 56% alcohol content (based on 100 mL of gastric fluid already present in the stomach) is required. Apart from that, alcohol is swiftly absorbed and passed through the colon and stomach, typically in less than 30 minutes (*5*, *11*–*13*).

Accordingly, robustness in an in vitro study with 40% ethanol seems more relevant to abuse deterrence, whereas a 20% concentration is likely a better approximation for accidental AIDD. This discrepancy between FDA and EMA guidelines may make it difficult for formulators to determine which guideline to follow. Although 40% ethanol may or may not be physiologically relevant, formulators may have to build resistance to it because many pharmaceutical businesses operate globally and would prefer not to offer different formulations in different countries. The development of effective formulations might be delayed due to this technical challenge (*12*, *14*–*16*).

This review discusses and compares the positions of the FDA, EMA, Health Canada, and Australia's Therapeutics Good Administration (TGA) on AIDD studies. Table 1 summarizes and compares the regulatory guidance issued by USFDA, EMA, and Health Canada.

UNITED STATES (FDA)

Drinking alcohol can change the rate at which a drug substance is released from an MR formulation, affecting how the drug is absorbed by the body. For MR, solid, oral dosage forms, the FDA recommends conducting in-vitro studies to assess the possibility of dose dumping from alcohol in vivo. The release of drug from the drug product should be assessed in vitro using media containing varying alcohol concentrations. An in vivo bioavailability (BA) study combining the drug product with alcohol may be needed based on the results of the in vitro study. The manufacturer should evaluate the rate of drug release from the drug product in vitro using dissolution media with varying alcohol concentrations (*17*, *18*).

According to the FDA, when analyzing dose dumping of MR drug products caused by alcohol in vitro, the following points should be taken into consideration (*17*–*21*):

- A dissolution test should be conducted using the right apparatus (e.g., paddle or basket) and agitation speed.
- The dissolution data should be generated at multiple time points using 12 dose units for a complete dissolution profile.
- Alcohol concentrations of 0%, 5%, 20%, and 40% are recommended for in vitro dissolution (for safety reasons, it is recommended to perform in vitro studies in to a closed-vessel system; note that the flash point of a 40% ethanolic-water mixture is approximately 26 °C).

Media selection should take into account the following factors:

- The dissolution profiles can be achieved using 0.1 N HCl (pH 1.2) as the optimal dissolution medium.

Table 1. Comparison of Regulatory Guidance on Alcohol-Induced Dose Dumping (AIDD) Studies

Regulatory Body (Country)	Methodological Requirements			Acceptance Criteria
	Dissolution Medium	Alcohol Concentration (v/v)	Time Points	
Food and Drug Administration (USA)	0.1 N HCl	0%, 5%, 20%, and 40% (v/v)	Every 15 min until 2 h	The formulation of generic drugs should be robust in alcohol. The dissolution rate of the generic formulation should be similar to that of the reference formulation if the API is released more quickly in alcoholic media.
European Medicines Agency (Europe)	The same as that recommended for routine testing.	5%, 10%, and 20% (v/v)	Not specified	The drug product should be reformulated if AIDD occurs. The applicant must justify absence of clinical relevance if AIDD risk cannot be avoided and if the risk is also present with the reference drug product.
Health Canada (Canada)	Not specified	0%, 5%, 20%, and 40% (v/v)	Not specified	Generic drug formulations must be robust against alcohol.
Therapeutic Goods Administration (Australia)	Not specified	Not specified	Not specified	Studies to confirm that alcohol does not cause dose-dumping effects.

API: active pharmaceutical ingredient.

- Dissolution profiles using the above range of alcohol concentrations in 0.1 N HCl and in the proposed optimal regulatory dissolution media are recommended.
- If 0.1 N HCl is not the optimal dissolution medium, profiles using the previously mentioned range of alcohol concentrations are advised.

Additional FDA guidance specifies:

- In the first 2 hours of dissolution, it is vital to examine the dissolution curve to see if the MR properties persist.
- Assess the similarity (or lack thereof) between the dissolution profiles by estimating the f_2 values (with 0% alcohol as the reference).
- Reports should include all data (e.g., individual, mean, standard deviation, comparison plots, f_2 values) collected during the assessment of the in vitro AIDD study.
- Depending on the results of the in vitro evaluations, a BA investigation may be required. Drug manufacturers should contact the relevant review division if they have questions about the design of an in vivo study or suitable labeling.

EUROPE (EMA)

Many, if not most, APIs and excipients in oral dosage forms are more soluble in ethanolic solutions than in water. When alcohol is consumed along with the use of such products, dose dumping may occur. Such formulations should be studied in vitro for release in alcohol solutions. Product reformulation may be required if accelerated API release occurs at either high or low alcohol concentrations over short periods of time or at lower alcohol concentrations over longer periods of time (*17, 22*).

A study demonstrating that an in vitro alcohol interaction is unlikely to occur in vivo can only be permitted when it can be demonstrated that reformulation cannot prevent dose dumping. When AIDD is investigated in vivo, the systemic exposure when the MR product is taken along with a suitable amount of alcohol on an empty stomach should be studied. It is important to evaluate the clinical implications of both the observed individual ratios and mean values in the study's findings. If a major dose-dumping effect is likely in vivo and cannot be prevented by reformulation, the product's benefit/risk must be carefully weighed.

According to EMA guidance, an alcohol-formulation interaction is typically not handled effectively by contraindicating alcohol as the sole remedy. In case of clinically significant potentiation or a negative additive effect with alcohol, product labels should include information about relevant interactions. It is also necessary to talk about other label warnings and risk management techniques (*22–25*). MR formulations must demonstrate their strength with regard to alcohol consumption as a fourth requirement. AIDD is evaluated using the same dissolution medium and apparatus as the validated dissolution method using 0%, 5%, 10%, and 20% ethanol; consider reformulating the product if AIDD is detected or believed to exist (*25, 26*).

CANADA (HEALTH CANADA)

In Canada, a relevant in vitro dissolution test should be available for routine quality control of MR dosage forms (*26*). This test should ideally have an in vivo-in vitro correlation (IVIVC). Depending on the type of dosage form, results indicating how pH influences the dissolution profile should be submitted. Preferably, testing conditions should cover the entire time period of expected in vivo release, such as 12 hours for twice daily dosing, unless a shorter duration is justified (e.g., clinical, bioequivalence, or pharmacokinetic studies). There should be upper and lower limits specified for certain units during each test period. For demonstrating complete release of the pharmacological component, a single-sided limit (e.g., not less than 85%) at the last test point is acceptable.

In the absence of IVIVC or clinical/bioequivalence data to support wider acceptance criteria, the range at each intermediate test point should typically not exceed 20% (e.g., 10% of the intended value). This usually requires a one-time dissolution study in an aqueous media containing ethanol (e.g., 5%, 20%, or 40% ethanol solutions) to mimic ethanol ingestion (*26*).

Health Canada guidelines require drug manufacturers to include information about drug release in the presence of alcohol for opioids and other MR formulations when unintended dose-dumping is potentially fatal for the patient.

AUSTRALIA (TGA)

Australia, MR products (including delayed, sustained, and combination releases) must meet their MR promises. Additionally, they must maintain constant pharmacokinetic performance across dosage units and maintain therapeutic plasma concentrations. Besides the studies required for formulations of IR oral doses,

the following studies must be submitted (or a convincing scientific justification must be provided for their exclusion) (*27*):

i) Comparison of a steady-state product with an appropriate IR product;

ii) IVIVC studies; and

iii) Studies to confirm that alcohol does not cause dose-dumping effects.

CONCLUSION

The US, European, Canadian, and Australian regulatory authorities' perspectives on AIDD studies was reviewed and compared. Certain segments of the patient population may be at risk from AIDD of MR formulations. Regulatory agencies have provided formulators with recommendations to help reduce the likelihood that a formulation will raise AIDD concerns; however, there is a lack of harmonized guidance. Testing in streamlined in vitro systems that might not accurately reflect potential physiological conditions may create technological barriers to developing effective dosage forms at patient-friendly prices. With the growing globalization of the pharmaceutical industry, regulatory bodies should harmonize their criteria for AIDD in vitro testing conditions that reflect physiologically appropriate alcohol concentrations and exposure times.

DISCLOSURES

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