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Regulatory Considerations for Alcohol-Induced Dose Dumping of Oral Modified-Release Formulations

This article looks at the current status of alcohol-induced dose dumping of modified-release formulations and the need for regulatory harmonization in handling this challenge.

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Over the past decades, modified-release (MR) systems have revolutionized the delivery of APIs. Patient compliance is improved and side effects are reduced through more consistent plasma levels, leading to more effective therapies. The vast majority of patients benefit from the pharmacological advantages and administration convenience of MR formulations. However, there is a subgroup of patients who are vulnerable to accidental overdose through concomitant consumption of alcoholic beverages with these medications. As drug release in MR systems is either controlled by a polymer matrix or by a polymer film coating, dose dumping may occur if the release control is compromised through dissolution of the controlling agent in hydro-alcoholic liquids. “Dose dumping” refers to the rapid release of the entire dose or a significant fraction thereof in a short period of time (1). Depending upon the therapeutic index, the pharmacokinetics, and the therapeutic indication of the API, critical side effects or even fatality can result. Dose dumping resulting from consumption of alcoholic beverages in timely connection with the administration of a medication is referred to as “alcohol-induced dose dumping” (ADD).

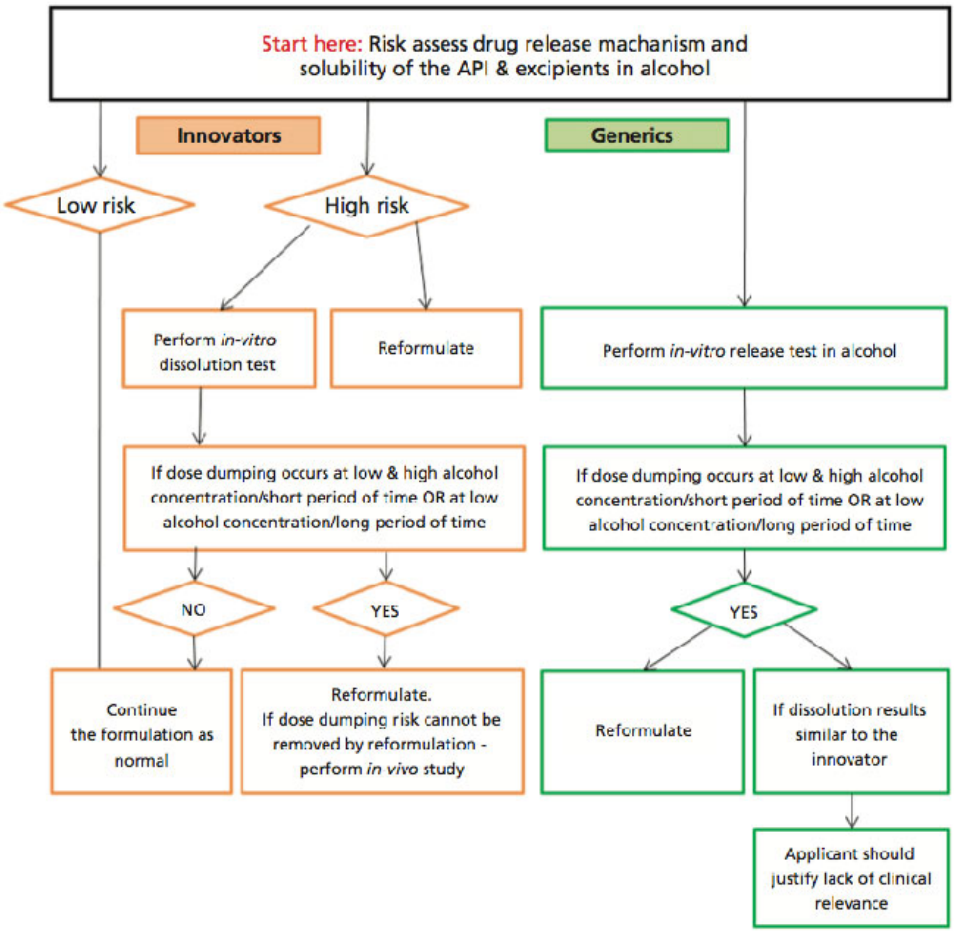
Modified release—a benefit, but also a risk

Alcoholic beverage consumption is widespread throughout the world. Certain patient populations, such as people with chronic pain or those suffering from depression, may have the tendency to turn to alcohol as a way to cope with their conditions, because the physiological effects of alcohol are similar to those of anesthetics (2). Accidental ADD may occur when patients combine the consumption of alcoholic beverages with prescribed medication despite product warnings to the contrary. Although concomitant use is often the case, ADD could also be due to residual alcohol that is still present after earlier ingestion. Intentional ADD occurs when a person knowingly uses highly potent alcoholic beverages as a medium to extract high doses of API (usually opioid analgesics) from sustained-release formulations in order to “get high.” This article will not address intentional ADD (including formulations that are commonly referred to as abuse-deterrent formulations or tamper-resistant formulations), but will instead focus on MR dosage forms that require an appropriate, robust formulation to assure patient safety, for example, if the drug has a small therapeutic window.

The “Palladone case” in 2005 raised awareness of ADD among regulatory authorities (3, 4). Palladone was a hydrocodone multiparticulate capsule that used ammonio methacrylate copolymer type B and ethylcellulose (5) as release-controlling polymers, both of which are soluble in ethanol. A pharmacokinetic study in healthy subjects showed that co-ingestion of a 12-mg Palladone capsule with 240 mL (8 ounces) of a 40% (80 proof) alcoholic beverage resulted in an average peak hydromorphone plasma concentration approximately six times higher than when taken with water. These elevated levels could potentially be lethal (6). Palladone was, therefore, subsequently withdrawn from the US market. This case initiated a movement toward new guidance, and consequently, it became a requirement for the industry to take ADD into consideration during formulation development.

Regulatory considerations

Guidance for ADD has been provided by regulatory agencies in various documents in the European Union (7–9), the United States (1, 10), and other countries (11); the International Conference on Harmonization does not provide any guidance. To date, no major regulatory agency has all the pertinent information summarized in one single document.



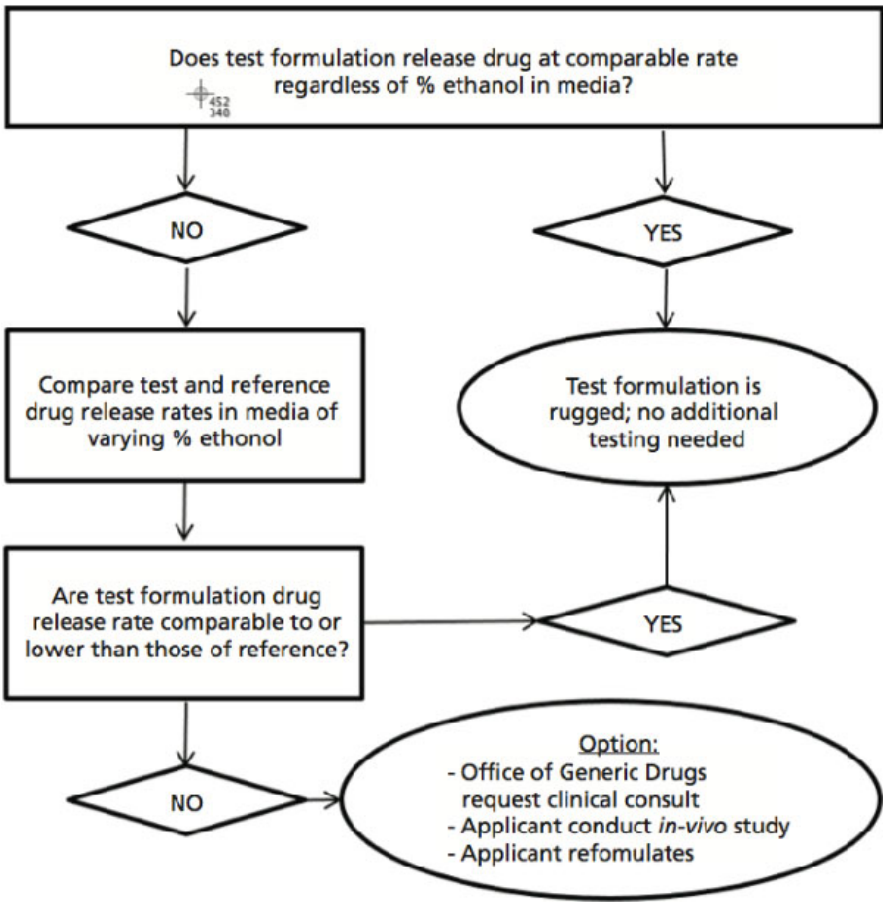
[9]**CLICK FIGURE TO ENLARGE Figure 1: Alcohol-induced dose dumping (ADD) risk evaluation based on the EMA guidance (8, 9).**

European Union. *In-vitro* testing in the presence of alcohol is based on one adopted guideline (8) and a Q&A section on the EMA website in the Quality Working Party area (9). The applicant is required to evaluate all types of MR formulations for the risk of unexpected API release. If ADD is observed or suspected, the product should be reformulated. Figure 1 shows the flowchart for the decision pathway.

In 2011, an EMA assessment (12) requested marketing authorization holders (MAH) to present data on their opioid products and their sensitivity to alcohol. Eight applicants submitted data of 14 products. Each applicant, however, used a different set of alcohol concentrations in the evaluation. The method variability in this case was not only inefficient but also made it more difficult for the assessors to judge and compare the data. The recently published EMA Q&A (9) provides better guidance concerning the required alcohol concentrations to be used, for example.

Sustained-release matrix tablets are often considered to be robust against

United States. In 2011, the Food and Drug Administration's Office of Generic Drugs (OGD) provided a simple scheme (13, 14) for supporting the handling of ADD-critical formulations, mainly for generics (see Figure 2)..



[10]CLICK FIGURE TO ENLARGE Figure 2: Possible scheme for the handling of alcohol-induced dose dumping (ADD)-critical generic formulations (13)

A Guidance for Industry (15) from 2014 lists inadequate dissolution data as reasons to refuse to receive an abbreviated new drug application (ANDA). In addition, FDA provides detailed bioequivalence dissolution recommendations for an extensive list of APIs (16), including non-opioids such as metoprolol succinate (17), clonidine (18), memantine (19), metformin and sitagliptin phosphate (20), or trospium chloride (21), which are widely prescribed treatments for chronic conditions. Generally, for these APIs, alcohol testing concentrations up to 40% are required.

Comparison of FDA and EMA requirements

The ADD requirements of EMA and FDA are not fully harmonized and sometimes even conflicting. Table I shows some differences between them for three major topics. Of particular interest is the FDA requirement for testing in dissolution medium containing 40% ethanol, which differs from the 20% required by the EMA. It should be noted that reaching a 40% alcohol concentration in the stomach would require the intake of 240 mL of an alcoholic beverage with 56% alcohol content (based on 100 mL gastric liquid present in the stomach) (4, 22) into an empty stomach. This drastic intake seems to be achievable only in extreme cases of so-called "binge drinking." In addition, alcohol is quickly resorbed and eliminated from the stomach and the intestine, usually within 30 minutes (23).

ADD. Opana ER, an oxymorphone sustained-release matrix tablet was formulated with hydrophilic polymers (TIMERx drug-delivery technology). The MR polymers used—xanthan (30) and locust bean gums (31)—are both alcohol-insoluble hydrocolloids. Opana ER passed ADD dissolution tests *in-vitro* but failed *in-vivo* (32).

Although the transit time of multiparticulate dosage forms through the stomach is much shorter than for monolithic tablets, coated MR multiparticulates are usually considered to be more vulnerable to ADD because of the higher effective contact surface for the ingression of acidic hydro-alcoholic medium. Carvedilol was formulated as a multiparticulate system (Micropump), using methacrylic copolymers in the MR coatings. Methacrylic copolymers are generally soluble in ethanol, and the formulation did indeed fail ADD requirements under *in-vitro* dissolution test conditions. The *in-vivo* performance, however, was not affected in the presence of alcohol (33).

Table I: Comparison of FDA and EMA requirements with regard to *in-vitro* testing of formulations at risk for ADD.

Topic	FDA	EMA
Methodological requirements	Dissolution medium: 0.1N HCl Alcohol concentrations: 0%, 5%, 20%, and 40% Time: every 15 minutes until 2hrs	Dissolution medium: same as that proposed for routine testing Alcohol concentrations: 5%, 10%, and 20% Time: not defined
Products to be tested	At least all (generic) versions for modified-release opioid drug products; more preferably for (all) modified-release drug products with risk of alcohol-induced dose dumping	All oral modified-release applications
Acceptance criterion	Generic drug formulation should show rugged performance in alcohol (24). If a generic drug formulation releases more rapidly in alcohol, the rate should be comparable to that of reference product.	If *in-vitro* alcohol incompatibility of the drug product is demonstrated, product should be reformulated. If alcohol effect cannot be avoided and is present also in the reference product, applicant should justify or demonstrate that it lacks clinical relevance.

[11]

Hence, the requirement for robustness *in-vitro* at an ethanol concentration of 40% seems likely to be more relevant to abuse-deterrence, while a concentration of 20% is likely a more realistic approximation for accidental ADD. These differences between EMA and FDA requirements might create confusion for formulators regarding which guideline to follow. Because many pharmaceutical companies operate globally and would prefer not to sell different formulations in different regions if at all possible, formulators may be forced to achieve resistance to 40% ethanol, whether this is physiologically relevant or not. This represents a significant technical hurdle for formulation development, and may even hinder the launch of valuable medications.

Assessing alcohol sensitivity

Sensitivity to alcohol of the API and/or the excipients does not necessarily mean that a formulation will dose dump. A formulator needs to assess the degree of sensitivity; and to do so, the formulator needs to rely on a practical and commonly accepted tool or guidance. N. Jedinger et al. (25) discussed some interesting approaches on how to handle this issue, including physicochemical factors influencing ADD and appropriate matrix systems and technological strategies to minimize the risk of ADD.

Dissolution profiles may be considered similar by virtue of overall profile similarity including similarity at every dissolution-sample time point. Different approaches are available to compare profiles, but the one discussed most often in FDA documentation (26–28) for NDA and ANDA is as follows:

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (29). The difference factor (f_1) calculates the percent difference between the two curves at each time. The similarity factor (f_2) is a measurement of the similarity in the percent dissolution between the two curves. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) ensure sameness or equivalence of the two curves.

Complicating factors

The regulatory guidance described in the previous sections of this article is related to *in-vitro* testing. This requirement is necessary, given that clinical trials performed to determine the risk of ADD *in-vivo* would expose volunteers to unnecessary risk and would, therefore, be regarded as unethical. Even then, simplification of a complex event can lead formulators to overemphasize some factors (such as solubility of pure polymer in ethanol) and overlook others (such as formulation design). Successful development of a robust formulation includes considerations involving the drug and excipient properties and the formulation design. In fact, *in-vitro* results in 40% hydro-alcoholic media as required by regulatory authorities do not necessarily predict *in-vivo* behaviour. This lack of correlation is due to the complexity of the *in-vivo* environment and is well-illustrated by two selected examples:

These two examples provide evidence that ADD *in-vivo* is a multifactorial event. Therefore, the currently applied standard methods for *in-vitro* characterization are not necessarily predictive for the *in-vivo* behaviour. There is obviously a need for specifically designed test methods. The selection of suitable formulation approaches and processing technologies must always be considered individually, keeping all factors in mind: both API and excipient properties, the formulation design, the therapeutic indication, and the risk in case of dose-dumping.

Summary

ADD of MR dosage forms poses a possible risk to a subsegment of the patient population. Regulatory agencies have, therefore, introduced guidance for formulators to mitigate the risk of a potentially concerned formulation with regard to ADD. However, the necessity of testing in simplified *in-vitro* systems that may not represent probable physiological conditions may create technological hurdles to developing efficacious dosage forms at reasonable costs to patients. The current lack of alignment of requirements between regions increases complexity, and hence, increases cost of medicines for globally active companies.

Given the increasing globalization of the pharmaceutical industry, the FDA and EMA guidelines should be harmonized concerning ADD *in-vitro* testing conditions, reflecting physiologically relevant alcohol concentrations and exposure times.

IPEC Europe ADD Working Group

The IPEC Europe ADD Working Group plans to publish a position paper that will address pertinent aspects of the ADD issue and suggest modifications of the currently available guidelines as well as provide several recommendations for formulators.

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