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Review article

The design of controlled-release formulations resistant to alcohol-induced dose dumping – A review

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ABSTRACT

The concomitant intake of alcoholic beverages together with oral controlled-release opioid formulations poses a serious safety concern since alcohol has the potential to alter the release rate controlling mechanism of the dosage form which may result in an uncontrolled and immediate drug release. This effect, known as alcohol-induced dose dumping, has drawn attention of the regulatory authorities. Thus, the Food and Drug Administration (FDA) recommends that in vitro drug release studies of controlled-release dosage forms containing drugs with narrow therapeutic range should be conducted in ethanolic media up to 40%. So far, only a limited number of robust dosage forms that withstand the impact of alcohol are available and the development of such dosage forms is still a challenge. This review deals with the physico-chemical key factors which have to be considered for the preparation of alcohol-resistant controlling dosage forms. Furthermore, appropriate matrix systems and promising technological strategies, which are suitable to prevent alcohol-induced dose dumping, are discussed.

1. Introduction

Alcohol-induced dose dumping effects in controlled-release oral dosage forms have received increased attention in recent years. Dose dumping, which is defined as "*unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form*" [1], can have dangerous effects. For example, in 2005 the FDA withdrew a hydromorphone-modified release drug formulation, Palladone™, from the US market, since taking it together with alcohol fatally increased the peak plasma concentrations of hydromorphone [2]. Currently, the FDA recommends to assess the risk of alcohol-induced dose dumping for opioid and non-opioid drugs with a narrow therapeutic index, such as metoprolol succinate (ß-blocker) and venlafaxine HCl (antidepressant) [3–5]. Especially, prolonged-release formulations, which offer a reduced dosing frequency and a prolonged therapeutic effect due to higher drug amounts, are of specific interest. For example, in the treatment of (chronic) pain controlled-release opioid dosage forms have been used as first choice formulations [6–8]. However, if patients suffer from pain, they often turn to alcohol to cope with the pain-related stress and to reduce the pain perception [9]. A study examining the relationship between pain and alcohol reported that both problem drinkers and non-problem drinkers consume alcohol to manage pain [10]. If patients are treated with opioid analgesics numerous side effects, including respiratory depression, nausea and/or urinary retention might occur [11]. The most deleterious effect is the first one which may arise due to rapid dose escalation. Thus, if the dosage form is consumed with ethanol, the drug release can increase immediately, resulting in an overdose and leading to respiratory depression followed by hypoxia and even death [12]. Regarding non-opioid drugs, alcohol might enhance sedation (through synergistic interactions), decrease in motoric skills and may lead to orthostatic hypotension [13].

Apart from side effects associated with ethanol, the mechanistic understanding of the oro-gastrointestinal absorption and hepatic metabolism is important. After oral administration of a dose-dumping susceptible formulation co-ingested with ethanol, a major part of the drug is dissolved in the stomach immediately. After a sufficient gastric retention time, the entire amount of the dissolved drug is uncontrollably emptied into the small intestine. Thus, absorption occurs which may result in high plasma concentrations [14]. Generally, the onset of intestinal drug absorption mainly depends on the gastric emptying rate which can individually vary in normal healthy subjects from 120 to 180 min

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in the fasted state [15]. Lennernäs et al. showed that for in vitro studies an experimental duration of 2 h is necessary to mimic gastric physiology (emptying) and rationally screen possible ethanol-drug interactions under physiological conditions [14].

Moreover, it is known that the consumption of alcoholic beverages may prolong the gastric emptying rate and therefore the onset of drug absorption due to the caloric content of alcohol, which is comparable with the lightly-fed state after the consumption of a meal [15–17]. For example, carbohydrate-rich and fermented beverages, such as beer and red wine, induce a prolonged gastric emptying rate in comparison with strong alcoholic drinks (whiskey, gin, etc.) [16]. Thus, several FDA guidelines for drugs with narrow therapeutic window suggest to test possible alcohol dose dumping effects over a period of at least 2 h in ethanolic media with different ethanol concentrations [3].

Frömming et al. were the pioneers who studied the influence of ethanol on the in vitro and in vivo drug liberation from acetylsalicylic acid sustained-release tablets. The authors reported faster drug release from tablets if co-ingested with 120 ml commercial brandy, which was proved by urinary excretion data [18]. Because of the ethical issues associated with in vivo-testing in human volunteers, mostly in vitro studies have been performed [19,20]. The in vitro approach requires drug release studies to be conducted in acidic media to simulate the stomach with alcohol concentrations of 5%, 20% and 40% (*v*/*v*) over a period of 2 h [21]. The different ethanol contents in the dissolution media represent different alcoholic beverages: 5% ethanol for beer, 20% for mixed drinks and 40% for hard liquor [21]. Quantification of the dose-dumping effect of a drug formulation is still an open issue without a regulatory decisional framework. One suggestion is to classify whether the drug formulation is "rugged" or "vulnerable" [22]. Here, the drug release of the formulation is investigated in ethanolic media and standard media (without ethanol) and a f_2 similarity test to distinguish between these categories [22,23] is performed. The similarity factor f_2 is a logarithmic reciprocal square root transformation of the sum of the squared error. According to Moore and Flanner [24] the f_2 value is calculated by the following expression (1):

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\} \quad (1)$$

where n corresponds to the number of dissolution time points considered and R_t and T_t are the percent drug dissolved of the reference and test formulations at time point t. It is a simple and effective tool to assess the similarity of two dissolution profiles: the value of f_2 ranges from 0 to 100 and dissolution profiles are considered similar when the f_2 value exceeds 50 [25]. Values below 50 indicate that the formulation is not alcohol-resistant. The aim is to mitigate the potential dose-dumping risk at the early stages of development of a controlled-release drug formulation [26]. Note, that low f_2 values are also obtained, if drug release is significantly slower in ethanolic media.

A second strategy to assess alcohol resistance of drug formulations is to calculate the relative change in amount of dissolution ($D_{A/N}$) in ethanolic media compared to pure media [27] as given in Eq. (2):

$$D_{A/N} = \frac{100 \times (D_A - D_N)}{D_N} \quad (2)$$

where D_A is the percent drug dissolved in ethanolic medium and D_N corresponds to the percent drug dissolved in pure media [27]. Positive values indicate that ethanol increases dissolution, whereas negative data indicate decreased dissolution in ethanol. However, compared to calculation of f_2 values, no critical values are given. Thus, no classification can be carried out.

Another challenge in the development of safe drug products is tampering with oral controlled-release formulations, which often occurs through chewing or crushing to subsequently snort the drug or to dissolve it in water or ethanol for intravenous injections [28–30]. Many novel drug formulations are under development to counteract these practices, by making the dosage form less prone to abuse. According to Webster et al., formulations can be classified into abuse-deterrent formulations and abuse-resistant formulations [29]. Abuse-deterrent formulations comprise an opioid drug and an opioid antagonist (i.e., naltrexone, naloxone). If the dosage form is applied as suggested in the prescribing information, only the opioid is released. However, if the tablet or capsule is manipulated due to breaking or milling, the antagonist is released and blocks the opioid actions. Thus, opioid euphoria is diminished or even reversed [29]. On the contrary, abuse resistant formulations use physical barriers and mechanical properties, such as increased hardness. Thus, crushing or milling is made impossible and no extraction of the drug is feasible [29].

The aim of this review is to indicate, which physico-chemical parameters must be defined for the rational design of alcohol-resistant controlling dosage forms. Furthermore, we discuss the additives that meet the physico-chemical requirements and describe promising technological strategies for minimizing the risk of dose-dumping.

2. Physico-chemical factors influencing alcohol-induced dose dumping

To develop an alcohol-resistant controlled-release dosage form, key physical and chemical factors of the formulation components must be considered, such as (i) solubility, (ii) wettability, (iii) swellability, and (iv) mechanical properties of the active pharmaceutical ingredient (API) and the excipient(s) in the final dosage form.

2.1. Effect of solubility

Generally, polar molecules are most soluble in polar solvents and non-polar molecules in non-polar solvents. Therefore, the ratio of hydrophilic and hydrophobic groups of the drug plays a crucial role for the solubility behavior in various solvents (Fig. 1). In principal, the aqueous solubility depends on the ability of the drug molecules to form hydrogen bonds with water molecules. Hence, the greater the hydrophilic part of a molecule relative to the hydrophobic part is, the greater the aqueous solubility becomes. In alcohol, which has lower hydrogen bonding capacity than pure water, solubility decreases [31,32]. Moreover, ethanol is less polar compared to pure water, which is reflected by the differences in the dielectric constants (25 and 80 for ethanol and water at 20 °C, respectively) [33]. If ethanol is added to water, a decrease in the dielectric constant in relation to pure water occurs, and thus, the solubility of an in-water poorly soluble drug increases [34]. In contrast, for highly soluble drugs in water the addition of ethanol will reduce the solubility [35]. If the drug shows high solubility in ethanol, it has to be protected by integrating/embedding it in a matrix system.

Generally, drug release from matrix systems is governed by various effects, depending on the drug-product design. These effects include medium penetration into the matrix, hydration, swelling, and drug diffusion and/or matrix erosion [36]. This implies that the drug release rate is influenced to a great extent by the medium to which the matrix system is exposed to [37]. If the matrix system is freely soluble in alcohol, the matrix will immediately start to disintegrate/dissolve in alcoholic environment resulting in an early