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In vitro dissolution of oral modified-release tablets and capsules in ethanolic media☆

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ABSTRACT

In 2005, Palladone, an extended-release capsule, was withdrawn from the market after clinical testing showed subjects who took the product with alcohol had increased levels of drug in their blood. To better understand this phenomenon, we studied the in vitro drug release of 27 oral modified-release products in alcohol-containing media. In 40% alcoholic medium, 9 of 10 capsules and 2 of 17 tablets show accelerated drug release. When a high percentage of the total dose is released in a short period of time, the extended-release product is then performing like an immediate release formulation. Products were also tested in 5% and 20% alcoholic media and in simulated gastric fluid (without enzyme) containing 20% alcohol. No tested capsules or tablets exhibited a significant increase in drug release in media containing only 5% alcohol. The current study indicates that in vitro dissolution may provide evidence regarding the ruggedness of formulations to ingested alcohol.

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1. Introduction

Oral modified-release products represent a popular form of medication because they are convenient to use and provide more uniform blood levels of the drug over an extended time period relative to immediate release formulations. The requirement of needing only one tablet or capsule every 12–24 h makes these modified-release dosage forms popular with patients. These advantages prompt drug manufacturers to reformulate their products as oral modified-release products on an ever increasing basis. A disadvantage of modified-release products is, under adverse circumstances, high doses of the active ingredient may be released into the bloodstream (dose dumping).

The release of high doses of active pharmaceutical ingredient in a short amount of time or "dose dumping" is a potential safety or efficacy concern. Dose dumping may result in harm for a patient if the released dose for a drug is close to its toxic dose. This is not unlike the well-recognized problem for all oral formulations that drug release rate may be altered by foods according to Hendeles et al. (1985). The Center for Drug Evaluation and Research (2002) has written suggestions for the design of studies to assess the effects of food on drug release. This guidance suggests conducting clinical trials that show the effects of taking the drug product without food and after eating a high fat and high calorie meal while water consumption by the subject is controlled. Although the CDER guidance also recommends special attention be given to drug products that are to be mixed with food or drink for administration, the situation where alcohol consumption occurs simultaneously with drug product dosing is not addressed. Dose dumping is a particular concern for drugs used to manage pain such as Palladone, an opioid analgesic. Palladone was withdrawn from the market in July 2005 because a clinical pharmacology study demonstrated that some subjects who took Palladone with alcohol had six times the amount of drug in the blood as those who took Palladone with water (FDA, 2005). Such a high dose of this powerful drug constituted a significant safety risk.

We conducted in vitro dissolution studies in alcohol-containing media on Palladone and other opioids, antidepressants, antiarrhythmics and other therapeutic classes. Because the target behavior (dose dumping in alcoholic media) may be dosage form dependent (*i.e.*, some dosage forms may be more vulnerable to alcohol than others), we focused on therapeutic use rather than product name, choosing product classes that may pose higher risk to the patient if dose dumping were to occur. Although the products surveyed were considered to present potential safety or efficacy risk were there to be dose dumping, only Palladone carried a warning that consuming alcohol while taking the drug might lead to rapid release of the entire dose. Subsequent to this work and studies performed elsewhere (Chandaroy, 2009; Emeje et al., 2008; Johnson

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et al., 2008; Levina et al., 2007; Sathyan et al., 2008; Walden et al., 2007; Wills et al., 1982), the labeling for several other products has been updated to provide such a warning. In addition, similar warnings have appeared in the pharmaceutical trade press (Owens, 2009). An overview of formulation types for opioids evaluated is provided by Amabile and Bowman (2006). Dissolution media with alcohol concentrations of 5%, 20% and 40% were used to represent the situation where a person might take the selected medication in conjunction with the consumption of alcohol. The 5% alcoholic mixture is the equivalent of several beers and 20% may be attainable by an experienced drinker consuming hard liquor. The 40% alcoholic mixture, while perhaps not realistic, is used to simulate a worst case scenario. A summary of the present state of work in this area along with recommendations for in vitro evaluation has recently been published (Lennernäs, 2009).

2. Materials and methods

2.1. Materials

The oral modified-release products in Table 1 are labeled as extended-release, sustained release or controlled release. All products were purchased from US distributors. Aqueous dissolution media were prepared using water filtered through Milli-Q UV Plus filtration system. The aqueous media were degassed according to Moore (1996). Alcoholic media were prepared by adding by volume appropriate degassed aqueous medium and 95% ethanol (Aaper Alcohol and Chemicals, industrial grade). After the ethanol was added, the alcoholic medium was stirred, allowed to equilibrate overnight then further degassed by stirring under vacuum for 5 min.

2.2. Methods

Methods were obtained either from the United States Pharmacopeia or from the product manufacturer. The aqueous dissolution medium differed for each product. Some methods require the product to be in acid for several hours followed by immersion in buffered medium for the remainder of the test. Other methods required simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) which were made according to USP but without enzyme. Ethanol was added to each medium to obtain concentrations of 5%, 20% and 40% alcohol-aqueous media. Measurements of pH were made only on the aqueous solutions since separate calibration and scale for each mixed-solvent medium would be required (IUPAC, 1997). Concentrations of drug released were determined using an UV spectrophotometer or a standard HPLC system as specified in the dissolution method. A Distek 2100A dissolution system fitted with either paddle or basket, as specified in the method, was used for all products. Vessel evaporation covers with stoppers were used during testing. For each product, in one dissolution apparatus, three vessels were used to test three units (tablets or capsules) in the method-specified medium plus three vessels for three units in 40% alcoholic medium. For products exhibiting increased release rate in 40% alcoholic medium, testing was continued with three units tested in a medium containing 5% alcoholic medium and three units in 20% alcoholic medium. Samples were withdrawn using a Distek 4300 DS sampler. Polyethylene filter tips with 10 μm pore size were used with the sampler for samples that were analyzed by ultraviolet spectrophotometry. No filter was used with the sampler for samples analyzed by high-performance liquid chromatography because samples were manually filtered through 0.45 μm nylon syringe filters.

Table 1
Oral modified-release products.

Therapeutic Use	Number and type of products tested
Antiarrhythmic	2 tablets, 3 capsules
Stimulant for ADHD	1 capsule
Antidepressant	3 tablets
Antiangianal	2 tablets
Calcium channel blocker	4 tablets, 3 capsules
Opioid analgesic	6 tablets, 3 capsules

2.3. Calculations

Dissolution results are reported as %dissolved (D_n) by first calculating the concentration of drug released from the dosage form into the dissolution medium at time point (n) using either spectrophotometric (UV) or by chromatographic (HPLC) analysis.

$$C_n = C_{Std} * \frac{Abs_{Sample,n}}{Abs_{Std}} \quad (UV)$$

or

$$C_n = C_{Std} * \frac{Area_{Sample,n}}{Area_{Std}} \quad (HPLC)$$

where is the C_n is the sample concentration at time point (n); C_{Std} is the concentration of standard (mg/mL); $Abs_{Sample,n}$ is the absorbance of sample solution for dissolution time point (n); Abs_{Std} is the absorbance of standard solution; $Area_{Sample,\ n}$ is the HPLC peak area for sample solution for dissolution time point (n); $Area_{Std}$ = HPLC peak area for standard.

The sample concentration is then used to calculate %dissolved.

$$D_n = \frac{100 * [C_n * (V - a * (n-1)) + a * \sum C_{n-1}]}{L}$$

where volume (V) is the initial vessel volume (mL); aliquot (a) is the sampling volume (mL); time point (n) is the sampling number; Label Claim (L) is the weight of API in product (mg).

The relative change in amount of dissolution ($D_{A/N}$) in alcoholic medium compared to that in purely aqueous medium provides a means of quantifying the dose dumping phenomenon and is used here to gauge the vulnerability of products to alcoholic media. An increase in susceptibility to alcohol-induced "dose dumping" will be reflected by an increase in $D_{A/N}$ at 30 min.

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

where $D_{A/N}$ is the differential %dissolved in alcohol relative to %dissolved in "non-alcoholic" media (expressed as a fraction); D_A is the percent drug dissolved in alcoholic medium; D_N is the percent drug dissolved in "non-alcoholic" medium.

3. Results and discussion

The impact of ethanol was described using the $D_{A/N}$ value at 30 min. A positive $D_{A/N}$ value indicates greater drug release in alcohol. All capsules had positive $D_{A/N}$ values with 40% ethanol as shown in Table 2, whereas most tablets had negative $D_{A/N}$ values indicating decreased dissolution in alcohol. Graphic examples are shown in Figs. 1 and 2. For the opioid analgesics (Fig. 1), no enhancement was observed for any of the tablets. Two of the calcium channel blocker tablets in Fig. 2 had high $D_{A/N}$ values (>200) in 40% alcoholic media. Both of these tablets contain hypromellose (HPMC) which is used in many oral modified-release products to decrease drug release rate in SGF. Roberts et al. (2007) reported an increase in drug release with increase in alcohol concentration for aspirin tablets made using HPMC when testing was done in 0, 10, 20, 30 and 40% ethanol. HPMC is just one of many excipients in oral modified-release products that may be vulnerable to ethanol.

Table 2
$D_{A/N}$ values at 30 minutes in 40% and 20% Alcoholic Media[a].

Therapeutic use	Dosage type	$D_{A/N}$ in 40% EtOH	$D_{A/N}$ in 20% EtOH
Antiarrhythmic	Capsule	934	300
	Capsule	495	102
	Capsule	372	142
	Tablet	(24)	
	Tablet	(42)	
Antiangianal	Tablet	125	
	Tablet	93	
Calcium channel blocker	Capsule	409	50
	Capsule	326	38
	Capsule	128	12
	Tablet	430	37
	Tablet	202	91
	Tablet	110	
	Tablet	41	
Antidepressant	Tablet	(22)	
	Tablet	(22)	
	Tablet	(24)	
Opioid analgesic	Capsule	776	42
	Capsule	527	362
	Capsule	500	50
	Tablet	(10)	
	Tablet	(19)	
	Tablet	(23)	
	Tablet	(25)	
	Tablet	(28)	
	Tablet	(44)	
Stimulant for ADHD	Capsule	64	(1)

[a] Each value represents three determinations for each product; negative values are in parentheses.

Most of the capsules were conventional bead- or pellet-filled hard gelatin capsules except the opioid analgesics which were made by melt extrusion technology (see patient information sheets) or contained a mixture of immediate release and enteric-coated delayed release pellets (1:1). Further research is needed into the effect of ethanol on excipient performance as it affects drug release.

The products that had high $D_{A/N}$ values in 40% alcoholic media were then tested in 20% alcoholic media. The $D_{A/N}$ values for 20% alcoholic media shown in Table 2 are much less than those values obtained when the media contained 40% alcohol.

Dissolution testing in SGF with 20% alcohol (Table 3) demonstrates the same trend observed with the dissolution media containing 40% alcohol. A few drugs, including some of those that showed rapid release in 20% alcohol, were tested in 5% alcohol. None of these products tested at the lowest alcohol concentration exhibited drug release within the first hour that was significantly different from the amount released in purely aqueous media. For a few drugs tested at the lowest alcohol concentration, a small increase over aqueous media was observed by the fourth to eighth hour.

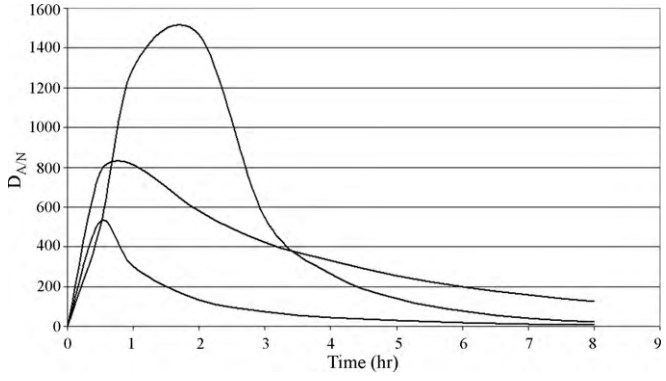

Fig. 1. Opioid analgesic capsules: relative change in amount of dissolution ($D_{A/N}$) in 40% alcoholic medium compared to that in purely aqueous medium as a function of dissolution time.

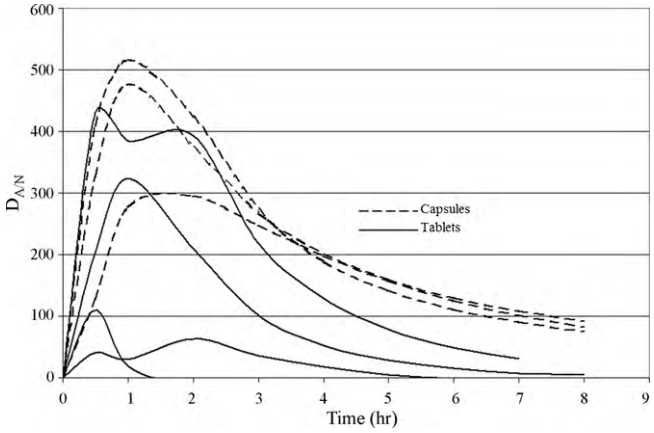

Fig. 2. Calcium channel blockers: relative change in amount of dissolution ($D_{A/N}$) in 40% alcoholic medium compared to that in purely aqueous medium as a function of dissolution time.

Table 3
$D_{A/N}$ values at 30 min in 20% EtOH/SGF[a].

Therapeutic use	Dosage type	$D_{A/N}$ in 20% EtOH/SGF
Antiarrhythmic	Capsule	178
	Capsule	128
	Capsule	136
	Tablet	(18)
Calcium channel blocker	Capsule	10
	Capsule	105
	Tablet	49
	Tablet	53
Opioid analgesic	Capsule	87
	Capsule	787
	Capsule	200
	Tablet	(11)
Antidepressant	Tablet	(21)
Stimulant for ADHD	Capsule	(1)

[a] Each value represents three determinations for each product; negative values are in parentheses.

4. Conclusions

In non-alcoholic media, extended-release oral products typically release less than 10% of their total drug in 1 h. However, consumption of alcohol can cause some extended-release products to release close to 100% of the total drug within that 1-h period, a situation possibly posing substantial danger to the patient, especially if the drug is toxic at that concentration. A low drug release rate is also a health concern since the dose may be medically ineffective if a therapeutic level of drug is not attained.

In this report, we use dissolution testing to study the in vitro effects of alcohol on the drug release of Palladone and other oral modified-release products. For the initial in vitro studies to test for vulnerability to alcohol, dissolution media containing 40% alcohol was chosen as a worse-case scenario. Paddle or basket methods are used as specified in the USP monographs or the drug manufacturers' dissolution methods. For the products tested, both 40% alcoholic media and 20% alcoholic media tend to enhance drug release from capsules, whereas release is inhibited from most

tablets. Differences in dissolution between non-alcoholic medium and 5% alcoholic medium are not significant. The work presented here suggests that in vitro testing can be used to evaluate a formulation's vulnerabilities to an alcohol environment without endangering patients in a clinical study involving ingestion of alcohol. Further research is needed to understand the relationship between dosage form, product formulation and configuration and drug release in the presence of ethanol. The greater understanding of observed phenomena gained from such studies will help to maintain public confidence in the safety of these drug types.

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