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Drug Development and Industrial Pharmacy (2008) i*First*, 1–5

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040801929240

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Influence of Alcohol on the Release of Tramadol from 24-h Controlled-Release Formulations During In Vitro Dissolution Experiments

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Recent warnings by regulatory bodies and a product recall by the FDA have generated much interest in the area of dose dumping from controlled-release opioid analgesic formulations when coingested with alcohol. It was the aim of this study to address this issue and in doing so, gain understanding on how alcohol-induced effects may be avoided. In this study, tramadol release from Ultram® ER tablets and T-long® capsules was significantly increased in the presence of ethanol. Conversely, a decrease in the rate of tramadol release was seen from Tridural™ extended-release tablets in the presence of alcohol.

Keywords tramadol; controlled release; alcohol; in vitro

INTRODUCTION

Controlled-release formulations offering once a day delivery, by definition, contain significant amounts of drug which, if ingested as a single bolus dose, could cause severe adverse events. Recently, a number of regulatory bodies around the world, including the US FDA and Health Canada, have issued warnings regarding the safety of controlled-release opioid–analgesic formulations (FDA, 2005a) and, in some cases, products have been withdrawn from the market as a result. These agencies have been specifically concerned with the potential for alcohol interactions with controlled-release technologies of these formulations to result in uncontrolled and early drug release.

Recent interest in the effects of alcohol on the release of drugs from controlled-release formulations arose following the FDA recall of Palladone™ XL (FDA, 2005b). Palladone™ XL was a marketed controlled-release opioid for the treatment of moderate-to-severe chronic pain. It contained the long-acting drug hydromorphone hydrochloride, which in overdose can cause respiratory depression and coma (Spiller & Krenzelok, 1997). In the light of this recall, attention has focused on the effects of coingestion of alcohol on the release profiles of other drugs, and a recent study has examined the release of aspirin in hydroethanolic media from hypromellose matrices (Roberts et al., 2007).

Tramadol hydrochloride (HCl) is a synthetic centrally acting aminocyclohexal analgesic that acts as an opioid agonist with selectivity for the μ-receptor (Obaidat & Obaidat, 2001; Scott & Perry, 2000). Although the analgesic effects of tramadol are comparable with those of strong opioids such as morphine (Beaulieu et al., 2007), the use of tramadol may be preferable to other opioids because at therapeutic doses it lacks the typical opioid side effects producing no clinically relevant cardiovascular effects (Chrubasik et al., 1992; Scott & Perry, 2000) and only mild respiratory depression (Houmes, Voets, Verkaaik, Erdmann, & Lachmann, 1992). Typical adverse events include nausea, vomiting, dizziness, and vertigo, which although not life-threatening may become severe and potentially dangerous to some patients if uncontrolled release occurred; for example, dizziness and vertigo are of particular importance to elderly patients for whom falls could have serious consequences. The half-life of the drug is approximately 5.5 h and thus a sustained release formulation is desirable so as to reduce the frequency of administration and ensure better patient compliance: its high solubility in water (Tiwari, Murthy, Pai, Mehta, & Chowdary, 2003) dictates careful selection of the release-retarding excipients.

To date, there have been no reported studies of the effects of alcohol on the release rate, in vitro, of drug from different

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controlled-release formulations. Accordingly, the aim of this study was to evaluate the effect of increasing doses of alcohol on the controlled-release performance of three once-daily formulations of tramadol and to gain insight into how such interactions might be avoided. Such formulations may be administered to a dose of up to 400 mg/day. The three formulations evaluated were Ultram® ER tablets (developed by Biovail Inc.), Tridural™ extended-release tablets (developed by Labopharm Inc.), and T-long® capsules (initially developed by SMB), which are based on differing release technologies.

Ultram® ER tablets are marketed in the United States by Ortho-McNeil, Inc., and are formulated with SmartCoat® technology. These tablets consist of a solid tablet core that contains the drug, surrounded with a release-controlling coating composed of water-insoluble and water-soluble polymers and plasticizer (Ultram® ER package insert). These polymers of opposite wettability act in concert to control the drug release from the tablet.

Tridural™ extended-release tablets manufactured by Labopharm Inc. (distributed in Canada, and marketed in Europe as Contramal® UNO, Dolpar®, Monoalgic® L.P., Monotramal® L.P., Noax™ UNO, Tradorec XL, Tramadolor®, and Unitrama) comprise a core tablet consisting principally of Contramid®-modified pregelatinized starch and tramadol. In contact with water, the Contramid® technology forms a semipermeable release-controlling membrane that provides zero-order drug release for sustained analgesia. The core tablet is surrounded by a polyvinylpyrrolidone–polyvinyl acetate copolymer/xanthan gum/tramadol coating matrix that effects rapid, yet controlled release to allow early analgesic onset (Rahmouni et al., 2005).

T-long® capsules (manufactured by SMB and marketed in Germany by AWD.pharma GmbH & Co. KG, also marketed in Europe under brand names Dolodol™, Monocrixo® LP, Tralodie®, and Tramium™) are hard gelatin capsules containing controlled-release film-coated tramadol pellets. Here the drug is dispersed into pellets comprising microcrystalline cellulose, saccarose stearate, hypromellose, and other excipients. The pellets are coated using Eudragit® NE30D, a release-controlling polymer, and filled into a capsule.

It is often difficult to obtain detailed and precise performance information for the proprietary controlled-release mechanisms used in sustained-release products; in consequence, it is equally difficult to provide information to the physician and the patient regarding potentially dangerous performance deficits when such products are taken with common beverages including alcohol. By determining the effect of commonly imbibed alcohol concentrations on release performance of each formulation under test in vitro and ascribing this to a particular aspect of the composition, we aimed not only to assist the user and prescriber, but also the formulator of controlled-release products. Alcohol concentrations of up to 40% (wt/wt) were used, equivalent to those present in undiluted spirits such as whisky and vodka.

MATERIALS AND METHODS

Materials

High-performance liquid chromatography (HPLC) grade acetonitrile and absolute ethanol were purchased from Fisher Scientific (UK). Ammonium hydroxide (28–30%, wt/wt), perchloric acid (70%), potassium phosphate monobasic, and sodium hydroxide pellets were purchased from Acros Organics Ltd. (UK). Tramadol HCl (99.6%) was obtained from Chemagis Ltd. (Israel), 200 mg Tridural™ tramadol HCl extended-release tablets were obtained from Labopharm Inc. (Canada), 200 mg Ultram® ER tablets from PriCara™ (Canada, a unit of Ortho-McNeil, Inc., NJ, USA), and T-long® 200-mg capsules were obtained from AWD Pharma (Germany). Water was purified using a Milli Q system.

Methods

Buffer Preparation

Phosphate buffer, pH 6.8, was prepared using potassium phosphate monobasic (68 g) and sodium hydroxide (9 g). These were weighed into a 10-L volumetric flask to which 5 L of deionized water was added. When fully dissolved, the volume was made up to 10 L using deionized water. The pH was adjusted to 6.8 ± 0.05 with sodium hydroxide solution (2 M).

Phosphate buffer, pH 6.8, containing 20% (vol/vol) ethanol was prepared by adding 1 L of absolute ethanol to 4 L of phosphate buffer, pH 6.8, in a 5-L Erlenmeyer flask. Phosphate buffer, pH 6.8, containing 40% (vol/vol) ethanol was prepared by adding 2 L of absolute ethanol to 3 L of phosphate buffer, pH 6.8, in a 5-L Erlenmeyer flask.

Mobile Phase Preparation

In a 1-L volumetric flask, 5 mL perchloric acid was added to approximately 950 mL of water. The contents were mixed and 3.4 mL ammonium hydroxide solution was added. The contents were mixed again and made up to volume using water. The pH of the final solution was confirmed to be between 2 and 3. Acetonitrile (230 mL) was added to 770 mL perchloric acid–ammonium hydroxide solution, mixed, filtered through a 0.2-µm nylon membrane filter, and degassed.

HPLC Assay

Samples were assayed by HPLC using a Waters 2695 Alliance Separation Module with a Waters 2487 dual-wavelength absorbance detector with subsequent analysis using Empower Pro Software version 5.00. A Lichrospher 5 µm RP Select B 60 Å column (4 mm i.d. × 125 mm) fitted with a RP select B Guard Column were used. The mobile phase consisted 77% aqueous solution (as prepared above) and 23% acetonitrile. Detection was by UV at 273 nm with an injection volume of 20 µL and a flow rate of 1 mL/min. The retention time of tramadol HCl was 8.8 min.

Standard Preparation

Tramadol HCl (55.5 mg) was accurately weighed into a 100-mL volumetric flask and dissolved in buffer, pH 6.8, to create a stock solution of 0.555 mg/mL. This stock solution was sequentially diluted to obtain a calibration curve between 0.0111 and 0.2775 mg/mL. All dilutions were carried out in grade A volumetric flasks using buffer, pH 6.8. When the dissolution studies were carried out in alcoholic buffer, pH 6.8 (20 or 40% ethanol), the stock solution and the subsequent standards were prepared in the same dissolution medium. The limits of detection and quantification were dependent on the dissolution media used and are shown in Table 1 The precision of the assay was determined by conducting repeat injections of selected standards and the relative standard deviation of the repeatability between samples found to be 0.3%.

Dissolution Testing of Formulations

Drug release from the formulations was monitored according to USP (*United States Pharmacopeia*) general chapters section 711 using a Type 1 USP basket apparatus. A volume of 900 mL of media was used in each dissolution vessel with a basket rotation speed of 100 rpm confirmed by use of a tachometer. The dissolution media consisted of either phosphate buffer, pH 6.8, 20% ethanol in phosphate buffer, pH 6.8, or 40% ethanol in phosphate buffer, pH 6.8. Dissolution testing of the three formulations was carried out on 6 tablets/capsules over a 24-h period with sampling time points at 0.5, 1, 2, 4, 7, 9, 12, 16, and 24 h. Samples (3 mL) of media were withdrawn from the dissolution vessels at each time point using a 5-mL syringe connected to compatible, inert tubing. The tubing was then removed and a PTFE filter (pore size 0.45 μm) was connected to the syringe. The first 2 mL of medium was discarded while filtering and the remaining 1 mL was filtered into a HPLC vial. The samples were then analyzed by HPLC using the analytical method described above.

Statistical Analysis

Statistical analysis was performed on the dissolution data in the form of a two-way ANOVA (analysis of variance) using Mini-tab software.

Results

Ultram® ER tablets contain povidone (used as binder) that is soluble in ethanol and ethylcellulose (used as a film coating), the solubility of which depends on the degree of substitution of the epoxy group. However, the grade used in this formulation (Surelease) is soluble in ethanol. Ultram® ER tablets also contain polyvinyl alcohol (used as pore former) that is slightly soluble in ethanol (95%) and the rest of the excipients (lubricant, glidant, and plasticizer) are used in this formulation at very small amounts. The main excipient in the T-long® capsules is Eudragit NE30D (used as a film coating) that is soluble in alcohol. Tridural™ tablets contain Kollidon SR (physical mixture of polyvinylacetate [80%] and povidone [19%]) of which the polyvinylacetate is insoluble in ethanol but povidone is soluble in ethanol. Tridural™ tablets also contain xanthan gum that is practically insoluble in ethanol, and Contramid(that is a cross-linked starch and is insoluble in alcohol.

TABLE 1
Limit of Detection and Limit of Quantification of Tramadol from Various Dissolution Media Using Validated HPLC Method

	Buffer, pH 6.8	20% Ethanol Buffer, pH 6.8	40% Ethanol Buffer, pH 6.8
LOD (μg/mL)	1.6	1.0	1.3
LOQ (μg/mL)	4.8	2.5	3.9

The release profiles of tramadol HCl from the three formulations in each of the tested media are shown in Figure 1. In the absence of alcohol, tramadol release from Tridural™ tablets was approximately 93% after 24 h; the release of tramadol from Ultram® ER tablets was approximately 100% and from T-long® capsules approximately 98% in the same period. These data indicate that under the dissolution conditions used in this study full release of tramadol was observed after 24 h in all cases. However, there was a marked difference in the release profiles of the dosage forms. Tramadol release from the Tridural™ extended-release tablets was zero order across the 4- to 16-h time period. This was not the case with the other two dosage forms where sigmoidal release profiles were generated, that is, they do not follow any classic kinetics rate laws (e.g., zero-, first-, second-order kinetics, or Higuchi). However, the release appears to be fastest from the T-long® capsules.

Formulations also differed considerably in response to increasing ethanol concentration. Thus, after 4 h, the percentage of tramadol released from the Tridural™ tablets in the absence of ethanol was 38.37%. This decreased to 27.80% in the presence of 20% alcohol ($p \leq .05$) but addition of further alcohol (40%) caused no further decrease (Table 2) This corresponds to a release rate reduction of 25% over the first 4 h of dissolution.

After 4 h, the percentage of tramadol released from the Ultram® ER tablets was 19% in pH 6.8 buffer, but this increased to 27% ($p \leq .05$) and 62% ($p \leq .05$) in 20% ethanol buffer and 40% ethanol buffer, respectively (Table 2) An even larger increase in the percentage release of tramadol from T-long® capsules was found to occur after 4 h. The percentage release increased from 47% in pH 6.8 buffer to 81% in 20% ethanol buffer and 100% in 40% ethanol buffer (Table 1).

DISCUSSION

Controlled-release formulations by definition, contain large amounts of drug and thus the release mechanism must be sufficiently robust to prevent any possibility of uncontrolled release leading to “dose dumping.” This is particularly important with opioid drugs such as tramadol where adverse reactions can be

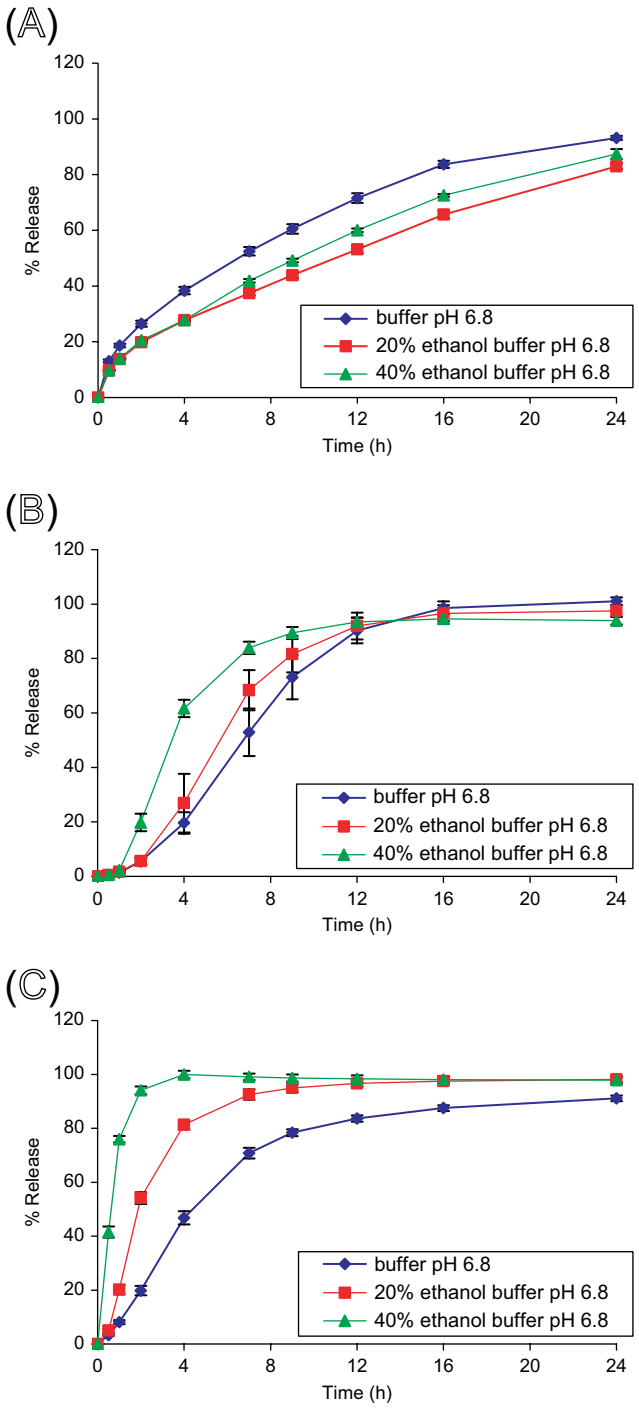

FIGURE 1. The effect of ethanol concentration in the dissolution media on the percentage tramadol hydrochloride released from (A) Tridural™ tablets, (B) Ultram® ER tablets, and (C) T-long® capsules.

severe. The ability of controlled-release formulations to retain their respective intended delivery profiles in the presence of alcohol is of particular importance, given that some patients are likely to coingest alcohol with these analgesics either accidentally or deliberately. The release of tramadol from Ultram® ER tablets and T-long® capsules in 20% ethanol buffer was increased by almost 40 and 75%, respectively, after 4-h dissolution (Table 2) Conversely, the release of tramadol from Tridural™ extended-release tablets was significantly decreased ($p \leq .05$) by the presence of alcohol in the dissolution media. These effects may be attributed to differences in the controlled-release technologies employed, specifically the solubilities of the inactive ingredients in alcohol.

The Tridural™ formulation comprises core and coat matrices combined to generate a compression coated tablet (Rahmouni et al., 2006). The core blend is predominantly a mixture of Contramid®-modified pregelatinized starch and tramadol, designed to provide a sustained release of the active ingredient and, thereby, 24-h efficacy. Contramid®-modified starch is derived from high-amylose starch (containing between 65 and 75% amylose) (Rahmouni et al., 2006) that is cross-linked, modified, and heat-treated to form a matrix that, on contact with water, swells to form a self-limiting controlled-release material. Within 15 min of exposure to water, a highly organized, uniform, and continuous semipermeable layer forms around the tablet, which limits the rate of water influx into the tablet and thus the hydration of the interior (Rahmouni et al., 2005) thereby providing the required zero-order release. Pregelatinized starches (such as Contramid® starch) are known not to swell in alcohol; thus, in the presence of increasing alcohol concentrations, the formation of the release-controlling membrane would be inhibited slowing drug release (Rahmouni et al., 2006). The coat matrix containing xanthan gum, another complex carbohydrate would be expected to be similarly affected.

The barrier function of the SmartCoat® controlled-release technology employed to formulate Ultram® ER tablets when exposed to ethanol seems to be compromised resulting, as is seen from the data presented here, in an increase in the release rate under these conditions.

T-long® tablets are hard gelatin capsules containing controlled-release film-coated tramadol pellets. Here the drug is dispersed with other excipients into pellets that are coated using Eudragit® NE30D, a release-controlling polymer, and filled into a capsule. As with the Ultram® ER formulation, Eudragit® NE30D is soluble in alcohol (Rowe, Shesky, & Owen, 2006) and, under these conditions, its release-controlling properties would also be compromised.

Given the predictive and directional nature of in vitro dissolution testing, these results suggest strongly that alcohol-soluble excipients should not be included in the release-controlling mechanism of drugs, where dose dumping can lead to dangerous adverse events; opioids such as tramadol, oxycodone, and hydromorphone would fit into this class. These data also suggest that coadministration of alcohol with Tridural™ extended-release tablets will result in a decreased liberation rate of tramadol from the tablet. Should a patient, despite package insert warnings imbibe alcohol with the opioid, then such reduced rates of drug release would be desirable. Therefore it

TABLE 2
Percentage Release of Tramadol After 4 h from Tridural™ Tablets, Ultram® ER Tablets, and T-long® Capsules (Mean ± *SEM*, *n* = 6) in Various Dissolution Media

	Buffer, pH 6.8	20% Ethanol Buffer, pH 6.8	40% Ethanol Buffer, pH 6.8
Tridural™ tablets	38.37 ± 1.31	27.80 ± 0.47	30.40 ± 0.15
Ultram® ER tablets	19.63 ± 3.94	26.91 ± 10.75	61.68 ± 3.17
T-long® capsules	46.78 ± 2.44	81.31 ± 1.65	99.96 ± 1.41

may be advisable that manufacturers include warnings, for both the prescriber and patient, in package inserts stating that the performance of controlled-release formulations may be altered in the presence of alcohol at concentrations achieved in the stomach after consumption of undiluted spirits such as whisky and vodka.

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