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Ethanol effects on drug release from Verapamil Meltrex®, an innovative melt extruded formulation

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ABSTRACT

The potential effect of ethanol to accelerate drug release from sustained release (SR) oral formulations is a general concern. Marketed Verapamil is a calcium channel blocker, mainly used as antihypertensive and anti-anginal drug and available in various dose and dosage forms. One is Verapamil Meltrex®, combining an innovative and unique SR formulation and technology that achieves a stable solid dispersion of drug by using melt extrusion technology. The aim of this investigation was to determine the influence of ethanol on the *in vitro* rate of release of marketed Verapamil (240 mg) Meltrex®, in contrast to three compressed marketed Verapamil (240 mg) SR formulations. Dissolution was tested under standardized conditions, with mediums containing ethanol concentrations of 0, 5, 20, and 40%. The dissolution profiles for Verapamil Meltrex® showed no differences between 5 and 40% ethanol versus 0% ethanol ($P > 0.05$). The mean dissolution percentage (%) was identical at 1 h (19%) in 0% versus 40% ethanol. In contrast, the three comparators showed significant increases in dissolution in 20 and 40% ethanol versus 0% ethanol ($P < 0.001$). An initial rapid release (within 2 h) was observed in 20 and 40% ethanol, with a mean dissolution of 99% (range 73–107%). Therefore, unlike the three SR Verapamil formulations tested, Verapamil Meltrex® was found to be resistant to *in vitro* dose dumping when combined with readily accessible ethanol concentrations.

1. Introduction

Controlled release formulations have distinct advantages, such as enhanced patient compliance due to reduced frequency of dosing and reduced side effects through reduced fluctuations in blood plasma levels of drug and a time-tailored efficacy profile which results from the release characteristics of the active ingredient into the bloodstream. The controlled release formulation contains a higher amount of the active drug relative to its immediate release counterpart. If the controlled release portion of the formulation is easily defeated, the end result is an increase in exposure to the active drug (dose dumping) resulting in possible safety issues, and changes in clinical efficacy. More recently the impact of concomitant intake of ethanol on the *in vivo* release of drugs from modified release oral formulations has become an increasing concern. This was also revealed by the new clinical finding that co-ingestion of alcohol resulted in a potentially serious dose dumping of hydromorphone from Palladone™, a controlled release capsule dosage form (FDA Alert, July 2005). The World Health Organization estimates that there are approximately two billion people worldwide who consume alcohol (WHO Report, 2004). Since alcohol is one of the most socially acceptable, widely used and easily obtained drugs, the potential for drug interactions is imminent. Thus, in order to improve the safety profile of modified release drugs, a resistance to the effect of potential dose dumping of such formulations, in ethanol, should be of great benefit.

Unlike standard tabletting processes, where drug-containing powders or granules are compressed, in the case of Verapamil Meltrex®, melt extrusion is an innovative process where the drug containing polymer melt is directly shaped. This Meltrex® formulation is considered to be an efficient and specialized technology embedding poorly soluble drugs as solid dispersion/solid solution into a biocompatible polymer matrix. However, as demonstrated in this example, it can be used also to tailor dissolution profiles. In addition, melt extrusion technology has the advantage of being a solvent-and dust-free process, frequently used for the manufacture of uniform systems or bulk intermediates, which allows for a clean processing environment with a reduction in environmental pollution, explosion proofing and residual organic solvents (Breitenbach and Lewis, 2003). The therapeutic advantages of melt extrusion technology and in particular Meltrex®,

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as applied to drug formulations, include improved dissolution kinetics, enhanced bioavailability and therefore efficacy, improved safety, and the ability to tailor-make release profiles (Breitenbach, 2002; Breitenbach and Lewis, 2003). By selecting the optimal polymer composition, a very hard and "plastic" like tablet can be manufactured with very low brittleness. Meltrex® tablets cannot be crushed into a fine powder, as in the case of standard tablets, and thereby reduces the physical tampering potential. Such technology can be applied to numerous active drug ingredients which may benefit from reduced frequency of daily dosing, and may aid to deter tampering (*e.g.* opiates, stimulants), improve safety and sustain the time release profile. This melt extrusion technology (Meltrex®) has been applied to Verapamil hydrochloride, a marketed antihypertensive and anti-anginal drug which may potentially interact with alcohol (Covera-HS Product Monograph, 2006).

The aim of this investigation was to determine the influence of ethanol on the *in vitro* release rate of Verapamil Meltrex® from melt extruded tablets (Form A) in contrast to three other direct compressed Verapamil sustained release formulations (Forms B–D).

2. Materials and methods

2.1. Materials

Ethanol of analysis (99.9%, v/v) was standard reagent grade (Baker, Germany). Sodium chloride (Merck, Germany), hydrochloric acid (Baker, Germany), and potassium phosphate (Fluka, Switzerland) were all used as received. Deionised water was received from the in house water system ionic exchanger.

2.2. Drug formulations

Verapamil formulations Isoptin SR-E 240 mg (Meltrex®, Form A) (Abbott Laboratories Poland Sp. z o.o.), sustained release (SR) Isoptin SR 240 mg (Form B) (Abbott Laboratories S.A.), VeraHEXAL® RR 240 mg retard (Form C) (Hexal Pharma Ltd., Germany), and Verapamil retard-ratiopharm® 240 mg (Form D) (Ratiopharm, Germany) were used as received. Form A (melt extruded) contained verapamil hydrochloride in a hydroxypropylcellulose and hypromellose matrix. Form B (sustained release), C (sustained release) and D (sustained release) contained verapamil hydrochloride in a natrium-alginate matrix (as a retarding agent).

2.3. Dissolution testing

Dissolution testing for Form A (melt extruded) and Form B was performed using a buffer addition method, according to the United States Pharmacopeia (USP) standards. For consistency, the same method and conditions were used for formulation C and D in this study.

2.3.1. HCl buffer addition method

Drug release was monitored using a (Dissolution Apparatus as per Ph.EUR, USP) (Paddle) with a rotation speed of 100 rpm in 900 mL of medium at 37.0 ± 0.5 °C. Media comprised of a potassium phosphate buffer, adjusted with hydrochloric acid (0.08N) with 0, 5, 20 or 40% (v/v) ethanol (pH 6.4–7.2). For each medium, six tablets were tested and drug release was monitored spectrophotometrically at 250–300 nm. The exception to this was Form C, which was tested using four tablets in the 0% ethanol medium only. Sampling was generally conducted at 60, 120, 240, and 480 min and at 600 min for Form B, according to the valid product specification, and Forms C and D. Additional samples were collected at 300 min for Form A (40% ethanol), Form A (0 and 20% ethanol in place of 240 min), Form B (40% ethanol), and Forms C and D (0% ethanol). For Forms C and D (0% ethanol only) additional samples were collected at 30, 90, 180, and 360 min.

2.4. Drug solubility

The drug release of the test formulations in different hydro-ethanolic dissolution media were determined spectrophotometrically (Fa Agilent, Type 8453, Agilent Technologies Inc., Santa Clara, CA, USA) using UV detection at a wavelength between 250 and 300 nm at room temperature. A reference standard containing verapamil (Chemical Reference Substance of Ph.EUR) was used.

2.5. Data analysis

Dissolution was calculated as a percentage (%) based on the amount of drug (mg) measured per volume, accounting for changes in volume during testing over time. The dissolution profiles (Figs. 1–4) were illustrated using the mean dissolution percentage and standard deviation, as derived from the raw scores from six trials (four trials for Form C at 0% ethanol), over time (hours). Comparative statistics for each formulation were calculated using the *t*-test (assuming a two-tailed distribution and 2 sample equal variance), from the weighted means (dissolution percentage over all time points not including 0) calculated for each trial per dissolution medium.

3. Results

The dissolution profiles of Verapamil Meltrex® release from Form A (melt extruded, Verapamil Meltrex® formulation), tested in 5 and 40% ethanol medium over 8 h did not significantly differ from the 0% alcohol condition ($P > 0.05$). The dissolution profile under 20% ethanol was significantly lower compared to the 0% ethanol condition ($P = 0.02$). This difference was most prominent at 8 h, where the mean dissolution percentage (%) was lower in the 20% ethanol condition (64%) relative to the 0% ethanol condition (77%). For both extreme conditions of 0 and 40% ethanol, the mean dissolution percentage was identical at 1 h (19%) and at 8 h was only slightly higher in the 40% ethanol medium (81%) compared to the 0% ethanol medium (77%). Release profiles under all conditions were characterised by an initial rapid release rate which progressively decreased over time, suggesting a sustained release mechanism with a near zero-order release (Fig. 1).

Form B, a sustained release compound prepared by conventional wet granulation, blending and subsequent compression technol-

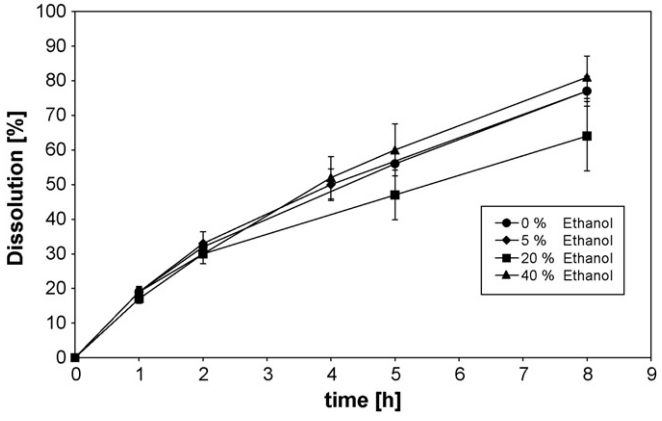

Fig. 1. Dissolution profiles (mean dissolution % [±S.D.]) of Verapamil release from Form A (Meltrex®) over time (hours), with increasing ethanol concentrations.

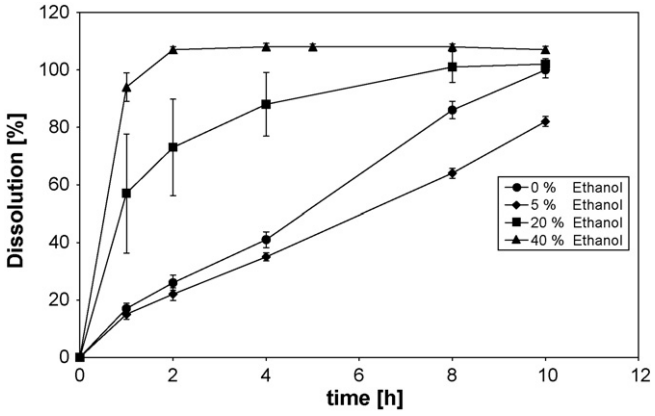

Fig. 2. Dissolution profiles (mean dissolution % [±S.D.]) of Verapamil release from Form B (SR) over time (hours), with increasing ethanol concentrations.

ogy, showed significant alterations in dissolution profiles at higher ethanol concentrations (20 and 40%) compared to the no ethanol condition (0%) ($P < 0.001$), conducted over 10 h. At low/no ethanol concentrations (0 and 5%), a near zero-order release was observed and no statistically significant differences were observed between the two conditions ($P = 0.5$). At higher ethanol concentrations (20 and 40%), an initial rapid release was seen within the first hour. This effect was dependent on ethanol concentration and a higher mean dissolution percentage (%) was reached in the 40% ethanol medium (94%) compared to 20% ethanol medium (57%), both of which were significantly higher compared to the 0% ethanol condition (17%) ($P < 0.001$). For the 20% ethanol medium, a continued release was observed over time and a plateau was reached at approximately 8 h (mean dissolution 101%). This plateau was reached sooner for the 40% ethanol concentration, at approximately 2 h (107% dissolution). At 2 h, a mean dissolution of 73 and 107% was observed for ethanol concentrations of 20 and 40%, respectively, compared to a mean dissolution of 26% observed with 0% ethanol, demonstrating a 3–4-fold increase in dissolution at higher alcohol concentrations (Fig. 2).

Similar to Form B, the same alterations in the dissolution profiles at higher ethanol concentrations (20 and 40%) were observed for the two sustained release formulations, Forms C and D. Form C showed significant increases in the dissolution profiles at higher ethanol concentrations (20 and 40%) compared to the no ethanol condition (0%) ($P < 0.0001$), conducted over 10 h. At higher ethanol concentrations (20 and 40%), an initial rapid release was seen within the first hour, where the mean dissolution percentage at 1 h was higher in the 20% ethanol medium (102%) compared to the 40% ethanol medium (64%). The higher ethanol conditions, however, were both significantly higher at 1 h compared to the 0% ethanol condition (15%) ($P < 0.00001$). For the 20% ethanol medium, a plateau in drug release was reached at approximately 1 h (mean dissolution 102%). This plateau was slightly later for the 40% ethanol concentration, at 2 h (mean dissolution 106%). At the lower ethanol concentration (5%), the dissolution profile for up to 4 h was nearly identical to that observed for 0% ethanol ($P = 0.4$ at 1 h). Between 4 and 10 h, the dissolution profile was lower for the 5% ethanol condition, resulting in an overall significantly lower dissolution relative to 0% ethanol ($P < 0.001$). The differences between both conditions was most prominent at 8 h, showing a mean dissolution percentage difference (%) of 10% between the 5% ethanol condition (76%) compared to 0% ethanol condition (76%) ($P < 0.001$). Mean dissolution percentages for the 0 and 5% ethanol conditions reached close to 100% dissolution at 10 h, showing 97 and 92% mean dissolution, respectively (Fig. 3).

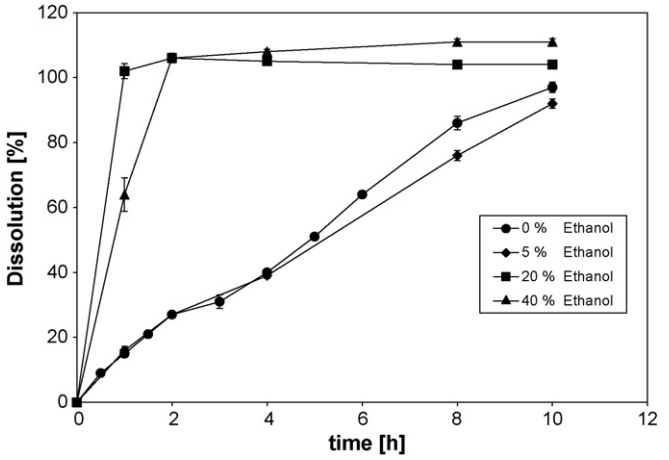

Fig. 3. Dissolution profiles (mean dissolution % [±S.D.]) of Verapamil release from Form C (SR) over time (hours), with increasing ethanol concentrations.

Similar to the trends observed for both Forms B and C, Form D showed significant increases in the dissolution profiles at higher ethanol concentrations (20 and 40%) compared to the no ethanol condition (0%) ($P < 0.00001$), conducted over 10 h. At low/no ethanol concentrations (0 and 5%), a near zero-order release was observed and no statistically significant differences were observed between the two conditions ($P = 0.5$). At higher ethanol concentrations (20 and 40%), an initial rapid release was seen within the first hour. This effect was dependent on ethanol concentration and a higher mean dissolution percentage (%) was reached in the 40% ethanol medium (101%) compared to 20% ethanol medium (93%), both of which were significantly higher compared to the 0% ethanol condition (12%) ($P < 0.0001$). For the 20% ethanol medium, rapid release was observed for the first 2 h, reaching a plateau at 2 h (mean dissolution 98%), which was significantly higher than the 0% ethanol condition (12%) ($P < 0.00001$). This plateau was reached sooner for the 40% ethanol concentration, following a rapid release, at approximately 1 h (101% mean dissolution), which was significantly higher compared to the 0% ethanol condition at 1 h (23%) ($P < 0.00001$). At the final time point of 10 h, full dissolution (100%) was not observed for either the 0% or 5% ethanol conditions, which showed a mean dissolution percentage of 65 and 69%, respectively (Fig. 4).

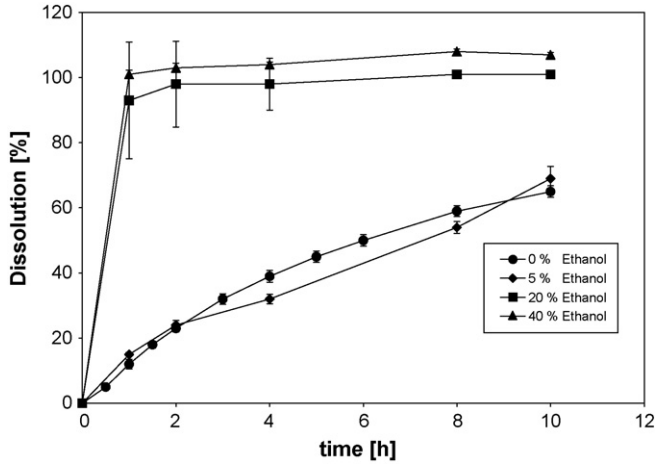

Fig. 4. Dissolution profiles (mean dissolution % [±S.D.]) of Verapamil release from Form D (SR) over time (hours), with increasing ethanol concentrations.

4. Discussion

The results from this *in vitro* dissolution study indicate that the melt extrusion formulation delivered by the Meltrex® technology containing Verapamil withstands the solubilizing effects of ethanol in mediums of 5% ethanol (equivalent to the concentrations found in most beers, wine coolers), 20% ethanol (equivalent to the concentrations found in a strong mixed drink, and slightly higher than those found in most wines (10–15%) and 40% ethanol (equivalent to the concentrations found in most undiluted spirits, *i.e.* vodka, gin). In contrast, the three other marketed sustained release formulations showed a significantly rapid increase in Verapamil release, particularly with higher ethanol concentrations (20 and 40% ethanol). At the highest ethanol concentration (40%), the direct compressed marketed sustained release comparators showed a steep drug release within the first 1–2 h, followed by a plateau in dissolution percentage (reaching 100% dissolution), indicating that the entire dose had been dumped into the dissolution medium. Such "dose dumping" was also observed at the 20% ethanol concentration within 2 h, although this occurred later for Form B, at approximately 8 h. Dose dumping was not observed for Form A (melt extruded Verapamil Meltrex® formulation). The dissolution profiles for Form A, with 5, and 40% ethanol were not significantly different than the 0% ethanol condition. The dissolution profile for 20% was even significantly lower than the 0% condition, the reason for this is unknown. The dissolution profiles for Form A were of a near zero order and did not show an initial spike in release, regardless of condition, as compared to the other marketed formulations under higher ethanol concentrations. At 2 h, approximately 30% dissolution had occurred for Form A (all mediums). Full dissolution had not occurred at 8 h, with a mean dissolution percentage range between 64% (20% ethanol medium) and 81% (40% ethanol medium).

Given the widespread use and accessibility of ethanol, interactions between alcohol and prescription drugs are of great concern. Interactions may occur in various scenarios, which may range from a patient taking medications and consuming an alcoholic beverage to intentional tampering with a formulation to extract a drug from a controlled release formulation, or to enhance the pharmacodynamic effects of both drug and alcohol, as is often seen with drug abusers. Other such scenarios may include dissolving and masking a drug in alcohol for condemnable intentions such as 'date rape', as in the case of gammahydroxybutyrate (GBH) or flunitrazepam (Rohypnol™), the drugs effects of which are further potentiated by alcohol (Schwartz et al., 2001). The robustness of controlled release formulations, particularly because they contain higher drug levels and may pose safety concerns, is an integral feature. Hence an abuse deterrent formulation which is not readily soluble in solvents such as ethanol, such as Form A (melt extruded Verapamil Meltrex®), has distinct advantages over other sustained release formulations that are susceptible to "dose dumping" (McColl and Sellers, 2006).

The intentional and unintentional tampering of drug formulations can be conducted using various physical and chemical manipulations. The dissolution methodology used in this study started with a pH of 1.1–1.2 for 2 h, followed by an increase in pH to approximately 6.8 for up to 6 h. This stimulates the normal gastric emptying time during a fasted state, which is estimated to be approximately 1.5–2 h in the stomach at a low pH, followed by gastric emptying into the intestinal tract at a near neutral pH (Cassilly et al., 2008; Kelly, 1980). Hence the conditions in this study simulated the pH gastric environment when a drug is taken under fasted conditions, which would potentially lead to higher ethanol and possibly drug bioavailability, compared to administration in a fed state. It should be noted that once ingested, the combination of ethanol in the low pH of the gastric environment (pH 2.0) for extended periods, in cases where gastric emptying may be delayed, may demonstrate an altered dissolution profile. Future studies may address this by examining intact and crushed melt extruded tablets for extended periods in an acidified medium or simulated gastric juice medium, containing ethanol. In addition, it is important to note that the etiology of drug interactions is not limited to the physical and chemical interactions between solutes and solvents. Drug interactions may be mediated by pharmacokinetic, pharmacodynamic, genetic and immune factors (Lynch and Price, 2007; Masubichi and Horie, 2007; Vourvahis and Kashuba, 2007). For example, the product monograph for Verapamil warns that the co-administration with ethanol may result in increased blood alcohol levels and therefore enhanced impairment, an interaction of a pharmacokinetic nature (Covera-HS Product Monograph, 2006). Determining the integrity of the formulation in an *in vivo*, clinical trial may also be beneficial in elucidating the potential for a clinically important drug–alcohol interaction.

In summary, this *in vitro* dissolution study has demonstrated that the innovative and unique formulation of Verapamil Meltrex® using melt extrusion technology does not have its release profile altered when tested with ethanol concentrations of up to 40%. In contrast, the three other marketed sustained release Verapamil formulations showed dose dumping effects at higher ethanol concentrations (20 and 40%), reaching approximately 100% dissolution within the first 2 h of testing. This study indicates that this melt-extruded formulation is resistant to dose dumping in an *in vitro* environment, when combined with various concentrations of ethanol. Future studies to determine the robustness of this formulation in an *in vivo* environment could be of added benefit to confirm the potential for a clinically important drug-alcohol interaction and the option to minimize this through selection of the proper delivery system.

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