

The Influence of Ethanol on the In Vitro Verapamil Release from Meltrex®, an Innovative Melt Extrusion Formulation, Relative to Marketed Sustained Release Verapamil Formulations.

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INTRODUCTION

Controlled release formulations have distinct advantages, such as enhanced patient compliance due to reduced frequency of dosing, 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 [1]. The World Health Organization estimates that there are approximately 2 billion people world wide who consume alcohol [2].

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 tableting processes, where drug-containing powders or granules are compressed, in the case of Verapamil Meltrex®, melt extrusion, an innovative and efficient technology embedding poorly soluble drugs as solid dispersion/solid solution into a biocompatible polymer matrix, is used. However, as demonstrated in this example, it can be used also to tailor dissolution profiles [3]. By selecting the optimal polymer composition, a very hard and “plastic” like tablet with very low brittleness can be manufactured by directly shaping the drug containing polymer melt. 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 [4].

References

- [1] U.S. Food and Drug Administration alert for healthcare professionals 2005. Alcohol-Palladone™ interaction.
- [2] World Health Organization Global Status Report on Alcohol 2004.
- [3] Breitenbach J., 2002. Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm. 54, 107-117.
- [4] Product Monograph Covera-HS™ (verapamil hydrochloride) controlled-onset extended release tablets. Pfizer Canada Inc. 2006.

OBJECTIVES

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%.

MATERIALS AND METHODS

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.

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).

Dissolution Test

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.

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 minutes and at 600 minutes for Form B, according to the valid product specification, and Forms C-D. Additional samples were collected at 300 minutes for Form A (40% ethanol), Form A (0% and 20% ethanol in place of 240 minutes), 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 minutes.

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 250-300 nm at room temperature. A reference standard containing verapamil (Chemical Reference Substance of Ph.EUR) was used.

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 (Figures 1-4) were illustrated using the mean dissolution percentage and standard deviation, as derived from the raw scores from 6 trials (4 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.

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RESULTS

The dissolution profiles for the melt extruded formulation Verapamil (240 mg) Meltrex® (Form A), showed no significant differences between the 5% and 40% ethanol media (P>0.05) and the 0% ethanol medium, and a statistically significant decrease in release for the 20% ethanol medium compared to the 0% ethanol medium (P=0.02) (Figure 1). For both extreme conditions of 0% and 40% ethanol, the mean dissolution percentage was identical at 1 hour (19%) and at 8 hours was only slightly higher in the 40% ethanol medium (81%) compared to the 0% ethanol medium (77%). In contrast, the three marketed comparators (Forms B-D) showed statistically significant alterations in dissolution profiles at higher ethanol concentrations (20 and 40% ethanol) compared to the no ethanol condition (0%) (p<0.001) (Figures 2-4). At higher ethanol concentrations (20 and 40%) an initial rapid release was observed, showing a mean dissolution percentage of 99% (range 73-107%), within the first 2 hours of testing. Dissolution at low/no ethanol concentrations (0 and 5%) showed a near zero-order release and no statistically significant differences were observed between the two conditions (p=0.5, Form D, figure 4), which had a mean dissolution percentage of around 25% within the first 2 hours.

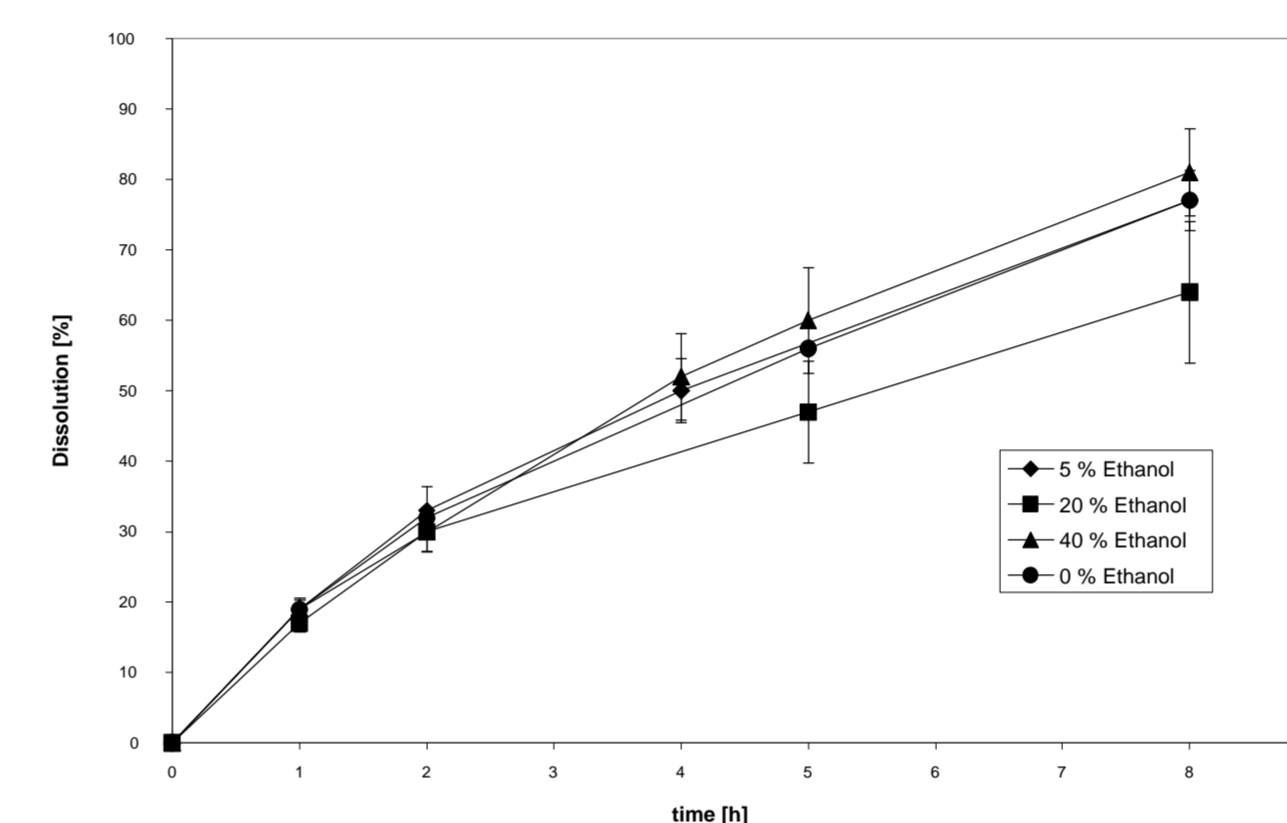


Figure 1. Dissolution profiles (mean dissolution % [±SD]) of verapamil release from Form A (Meltrex®) over time (hours), with increasing ethanol concentrations.

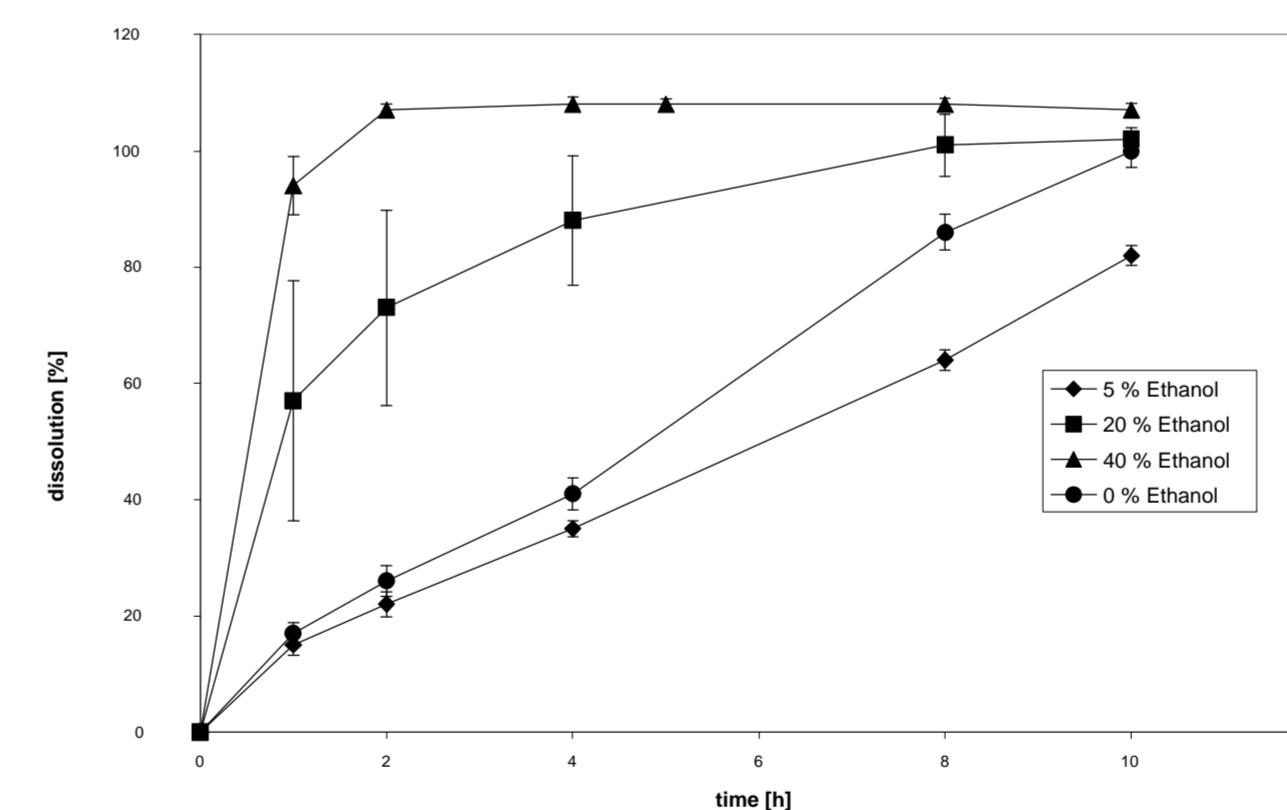


Figure 2. Dissolution profiles (mean dissolution % [±SD]) of Verapamil release from Form B (SR) over time (hours), with increasing ethanol concentrations.

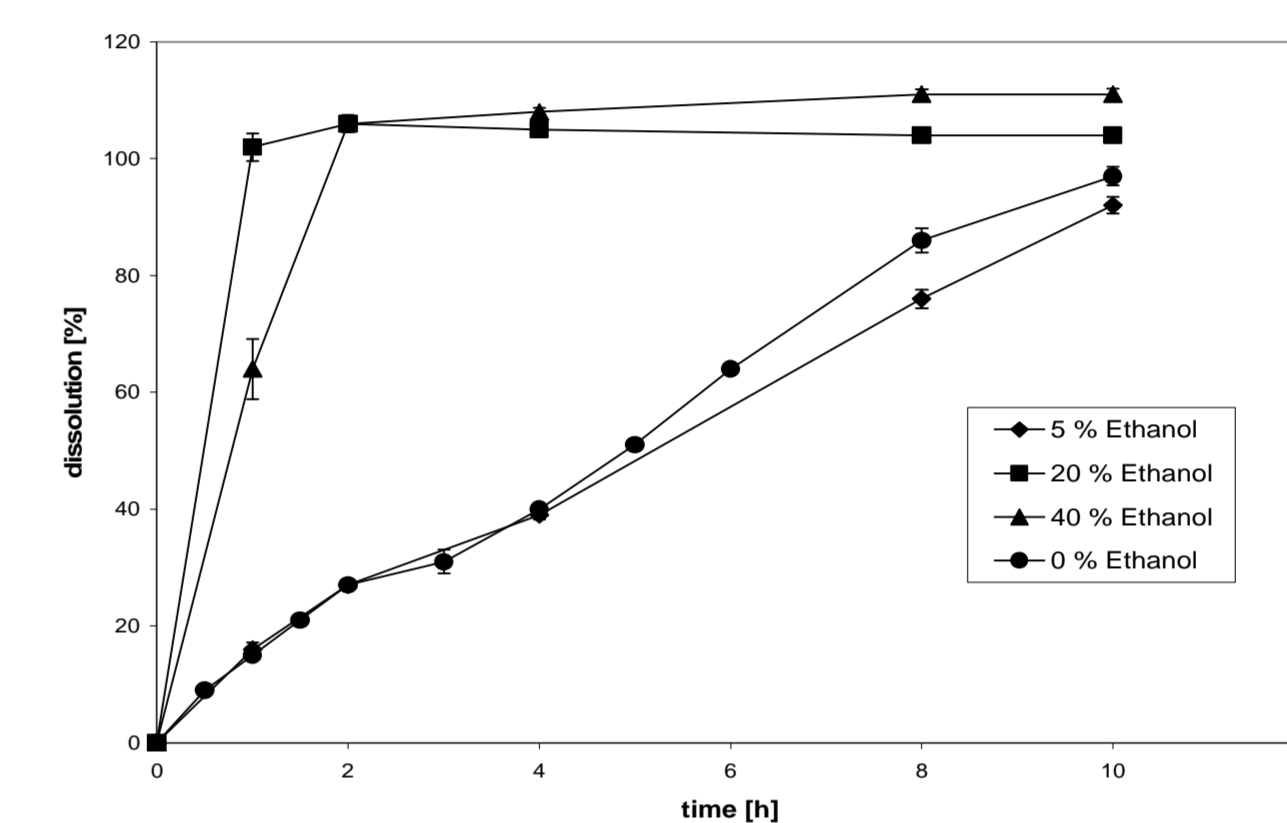


Figure 3. Dissolution profiles (mean dissolution % [±SD]) of Verapamil release from Form C (SR) over time (hours), with increasing ethanol concentrations.

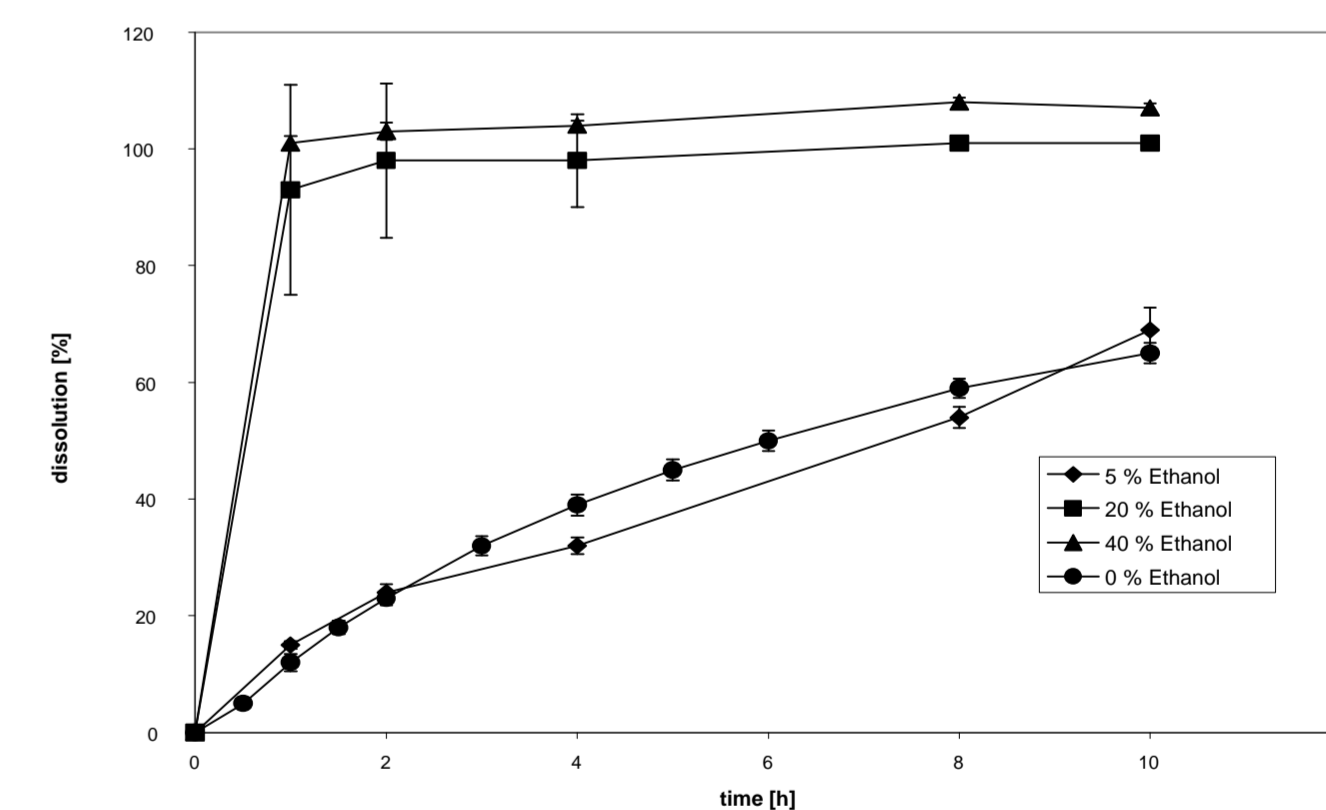


Figure 4. Dissolution profiles (mean dissolution % [±SD]) of Verapamil release from Form D (SR) over time (hours), with increasing ethanol concentrations.

SUMMARY

This in vitro dissolution study has demonstrated that the innovative and unique formulation of Verapamil (240 mg) Meltrex® (Form A) 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 (Forms B-D) showed dose dumping effects at higher ethanol concentrations (20 and 40%), reaching approximately 100% dissolution within the first two hours of testing.

CONCLUSIONS

This study indicates that this melt extruded formulation Verapamil (240 mg) Meltrex®, is resistant to dose dumping in an in vitro environment, when combined with various concentrations of ethanol that are readily accessible. 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.