Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 461–468
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Influence of hydroxypropyl methylcellulose polymer on in vitro and in vivo performance of controlled release tablets containing alprazolam

Vorapann Mahaguna[a,1], Robert L. Talbert[a,b], Jay I. Peters[b], Sandra Adams[b], Thomas D. Reynolds[c,2], Francis Y.W. Lam[b], Robert O. Williams III[a,*]

[a]*College of Pharmacy, Austin, TX, USA*
[b]*Department of Pharmacology, The University of Texas-Health Science Center at San Antonio, San Antonio, TX, USA*
[c]*Larkin Laboratory, The Dow Chemical Company, Midland, MI, USA*

Received 28 February 2003; accepted in revised form 30 June 2003

Abstract

The purpose of this study was to investigate the influence of hydroxypropyl methylcellulose (HPMC) molecular weight on pharmacokinetic and pharmacodynamic parameters of controlled release formulations containing alprazolam. Tablet formulations contained alprazolam, excipients, and either HPMC K4MP or HPMC K100LVP. A ten patient in vivo clinical trial using a randomized, open-label, four-way crossover design was conducted in the fed and fasted states. Plasma alprazolam concentrations were determined for 72 h. The pharmacodynamic effects of alprazolam were monitored using subject rated sedation on visual analogue scale for wakefulness, observer rated sedation, and symbol digit modalities test (SDMT). Results indicated that the tablet formulations containing either HPMC K4MP or HPMC K100LVP had similar dissolution profiles, and the dissolution profiles did not change through 6 months at 40°C/75% RH or 12 months at 25°C/65% Relative Humidity (RH). The area under the plasma concentration-time curve, time to peak concentration, and peak plasma concentration were not significantly different between the two tablet formulations investigated in either the fed or fasted states. Pharmacodynamically, no significant differences in SDMT scores between the two formulations were found. In vitro dissolution results predicted in vivo pharmacokinetic and pharmacodynamic results irrespective of formulation or diet used in the controlled release tablet. The controlled release tablets were bioequivalent and pharmacodynamically equivalent irrespective of the tablet formulation.

Keywords: Hydroxypropyl methylcellulose; Alprazolam; Pharmacokinetics; Pharmacodynamics; Bioequivalence; Molecular weight

1. Introduction

Controlled release tablets may contain hydrophilic polymer, drug, and other excipients. Controlled release of drug from the matrix is dependent on polymer wetting, polymer hydration, and polymer dissolution. Hydroxypropyl methylcellulose (HPMC), a non-ionic cellulose ether polymer, is widely used in controlled released matrix tablets. The hydration rate of HPMC depends on the nature of the constituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropoxyl content. The viscosity of the aqueous solution can be increased by increasing the average molecular weight (MW) of the polymer, the concentration of the polymer or decreasing the temperature of the solution. HPMC polymers are non-toxic, have the capacity to accommodate high levels of drug loading, and are not pH dependent [1,2].

The release of drug from controlled release tablets is influenced by factors relating to the physicochemical properties of the drug substance and to the dosage form. Factors associated with polymers, such as MW type (nominal viscosity) [3–6], concentration [2–4,7–9], degree of substitution [1,10], and particle size [1,9], have been

* Corresponding author. College of Pharmacy, Mail code: A1920, The University of Texas at Austin, 2409 West University Avenue, Austin, TX 78712-1074, USA. Tel.: +1-512-471-4681; fax: +1-512-471-7474.
E-mail address: williro@mail.utexas.edu (R.O. Williams III).
[1] Present address: PharmaForm, L.L.C., 1006 East Yager Lane, Building D Suite 101, Austin, TX 78753, USA.
[2] Present address: Pfizer, Ann Arbor Laboratories, 2800 Plymouth Road, Ann Arbor, MI 48105, USA.

0939-6411/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0939-6411(03)00116-4

shown to have a significant influence on drug release. However, the most important factor that affects the drug release rate from HPMC matrices is the polymer concentration or drug:polymer ratio [2,3,8,9].

In tablet formulations containing hydrophilic polymers like HPMC, the release of active drug is controlled by the rate of formation of a partially hydrated gel layer of the tablet surface formed upon contact with aqueous gastric media following ingestion and the continuous formation of additional gel layers. During the manufacturing process of the hydrophilic cellulose ether polymers, variations, such as degree of chemical substitution and MW type may cause concern as to their impact on product manufacturability, reproducibility, and clinical performance. In some cases, these differences may not be acceptable since they have the potential to influence drug release rate from a dosage form, and consequently the bioavailability.

It must be determined if the differences in MW type of the HPMC polymer influence the bioavailability of a drug substance (i.e. are tablets containing different MW types of polymer bioequivalent). It is of great significance to pharmaceutical scientists to determine exactly what degree of variability is acceptable such that the in vivo pharmacokinetic and pharmacodynamic parameters are not changed. It was recently reported that for hard gelatin capsules, the results from gamma scintigraphy indicated that there are no significant differences in the in vivo disintegration properties of cross-linked and non-cross-linked hard gelatin capsules, even though the in vitro dissolution profiles of both capsules were significantly different [11]. In addition, drug release from matrix tablets may be influenced by the presence of food in the stomach. Previous studies showed that food prolongs the residence time of a dosage form administered during or immediately after a meal by keeping the dosage form in the upper half of the stomach [12,13]. Retention of drug product in the stomach provides more time for the dosage form to have intimate contact with the stomach contents. Normally, dosage forms pass through the stomach more rapidly during the fasting state and they are retained longer in the stomach during the fed state. The release of drug from the dosage form, absorption and subsequent bioavailability are influenced by physiological changes in the gastrointestinal tract during the two states [14]. Several studies have reported that a high-fat meal caused increased absorption of drug from a bead or tablet formulation [15–17], whereas some studies found no influence of food on the in vivo pharmacokinetics of drug from a formulation [18,19]. Therefore, the effect of food should be investigated since drug release is influenced by the physicochemical properties of the drug substance and formulation, and retention time in the stomach.

The objectives of this study were to determine the bioequivalence and pharmacodynamic performance of two tablet formulations containing different types and concentrations of HPMC. The model lipophilic drug was alprazolam, and each formulation had equivalent in vitro dissolution.

2. Materials and methods

The following materials were used: Alprazolam USP (Spectrum Quality Products, Gardena, CA); Hydroxypropyl Methylcellulose USP (HPMC substitution type 2208, Methocel K100 Premium LVCR EP (K100LVP, 22.8% methoxyl content, 8.7% hydroxypropyl content, and 107 cPs apparent viscosity as a 2% aqueous solution) or Methocel K4M Premium CR (K4MP, 22.6% methoxyl content, 9.6% hydroxypropyl content, and 4126 cPs apparent viscosity as a 2% aqueous solution), The Dow Chemical Company, Midland, MI; Microcrystalline Cellulose N.F. (MCC; Avicel® PH 200, FMC Corporation, Philadelphia, PA); Lactose Monohydrate N.F. (LAC; Modified Spray-dried, Foremost Farms USA, Baraboo, WI); silicon dioxide (Cab-O-Sil® M5P, Cabot Corporation, Tuscola, IL); and Magnesium Stearate NF (Spectrum Quality Products, Gardena, CA). The reported log P of about 18 for alprazolam indicated the high degree of lipophilicity [20,21]. Alprazolam is insoluble in water, and the solubility and intrinsic rate of dissolution are pH dependent [22]. No drug/excipient incompatibilities have been reported between alprazolam and the excipients, lactose, microcrystalline cellulose, magnesium stearate, or dicalcium phosphate dihydrate [23].

The packaging components used for the stability study included 1-g Silica Gel Pak (Desiccare, Inc., Richland, MS); 60 and 250 cc high density polyethylene (HDPE) wide-mouth white bottles and polypropylene (PP) cap (foam polyethylene and pressure sensitive liner (Berlin Packaging, Arlington Heights, IL).

For the dissolution studies, 1 N hydrochloric acid (HCl) solution (J.T. Baker, Phillipsburg, NJ) and purified water were used for preparation of 0.1 N HCl solution. Samples were filtered (10 μm filters; Vankel Technologies Group, Cary, NC) prior to analysis.

2.1. Preparation of controlled release tablets

Two controlled release tablet formulations containing alprazolam, an insoluble swelling excipient (MCC), a soluble excipient (LAC), a hydrophilic polymer (HPMC), a glidant (Cab-O-Sil), and a lubricant (magnesium stearate), were developed. The two different MW types of HPMC polymer (Methocel K4MP or Methocel K100LVP) were incorporated into the tablet formulations for confirming in vitro equivalence. The components were combined and mixed using a V-blender, then compressed using 11 mm diameter tooling.

2.2. Characterization of controlled release tablets

Each tablet formulation was characterized by weight and hardness variation (Heberlein Hardness Tester Type WTP-3, Fab. Nr. 1082, Heberlein & Co AG). The average tablet weight was 380–420 mg (400 mg target) and the average tablet hardness was 6.5–9.5 kg (8 kg target). Content uniformity and composite assay were performed at release and composite assay was performed at each stability time point Analytical methods were reported previously [24]. The acceptance criteria for composite potency and content uniformity were 90–110% of label claim and percent relative standard deviation (RSD) of less than 6%.

Dissolution testing was conducted at 37°C using USP Apparatus 2 (paddle) at a rotation speed of 50 RPM. The dissolution medium consisted of 900 ml of 0.1 N HCl solution (pH = 1.1). A 4-ml sample was taken from the medium at 1, 2, 4, 6, 8, 10, 12, 14, and 16 h. Each sample was filtered through a 10-μm filter prior to analysis. The amount of drug release was determined by ultraviolet spectroscopy, modified from an assay method of alprazolam in 0.05 M sulfuric acid solution [25]. The dissolution release specifications were as follows: less than 45% release at 2 h, 45–65% release at 4 h, 75–90% release at 8 h, and greater than 90% release at 12 h.

The similarity factor (f_2 factor) was used to compare dissolution profiles. The f_2 factor is a logarithmic reciprocal square root transformation of the sum of squared error. The f_2 factor is used to quantitate agreement between two dissolution profiles. Dissolution testing was conducted under exactly the same conditions [26]. When the f_2 value approaches 100, the two profiles are nearly identical. When the f_2 factor ranges between 50 and 100 ($\leq$10% average difference), similarity between two dissolution profiles was noted [26].

2.3. Stability study of tablets

The tablet formulations were placed on stability according to the International Committee on Harmonization guidelines. The tablets were packaged in high density polyethylene bottles with polypropylene caps (foamed polyethylene and pressure sensitive liner) and silica gel desiccant, and stored at 25 ± 2°C/60 ± 5% relative humidity for up to 12 months and at 40 ± 2°C/75 ± 5% relative humidity for up to 6 months.

2.4. In vivo clinical study

An in vivo clinical study in human subjects was performed at the General Clinical Research Center at the South Texas Veterans Health Care System (San Antonio, TX). Tablets used for the clinical study were manufactured under cGMP at the Veteran's Administration Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center (Albuquerque, NM). Each clinical batch was demonstrated to meet product release specifications prior to conducting the clinical study.

The principal determinations for bioequivalence for alprazolam used in testing the polymers were area under the plasma concentration-time curve (AUC), peak plasma concentration (C_{max}), and time to peak concentration (T_{max}). The current Food and Drug Administration (FDA) guidelines for bioequivalence are that two formulations whose rate and extent of absorption differ by −20– + 25% or less are generally considered bioequivalent. This is based on the concept that a difference of −20– + 25% would not lead to change in therapy for a patient. Additionally, the difference in AUC, C_{max}, and T_{max} of the two formulations are within 80–125% of a reference standard. To verify that the −20%/+25% rule for bioequivalence was satisfied, the student paired *t*-test was used to compare the log transformed data of the AUC, C_{max}, and T_{max} obtained from the bioequivalence study. It was estimated that ten subjects were needed to detect a ±20% difference in AUC with 95% confidence. Given that our estimates were based on a small population and the recommendation from the FDA, 15 subjects were screened with the goal of obtaining ten to 12 completers. Informed consent was obtained for each subject participating in the study. The protocol was approved by the Institutional Review Board of the University of Texas Health Science Center (San Antonio, TX). The research followed the tenets of the Declarations of Helsinki and Tokyo for humans.

2.4.1. Protocol design

The clinical bioequivalence testing was conducted as a randomized, open-label, four-way crossover design. Two alprazolam tablet formulations containing different MW types and concentrations of HPMC polymer (i.e. HPMC-K4MP and HPMC-K100LVP) were used during the study. Each formulation was tested in the fed and fasted state. A standardized breakfast consisting of 1000 kcal with 50% of the kilocalories being fat was given which is consistent with FDA guidelines.

A computer-based randomized procedure was used to determine treatment phase. After obtaining written informed consent, volunteers were screened using medical and medication history, physical examination and routine clinical laboratory tests including hepatic enzymes, β-HCG in females, and CBC with platelet count. The entire sampling period was 72 h since the median half-life ($t_{1/2}$) of alprazolam is about 12 h and to ensure adequate characterization of the AUC, sampling needed to cover approximately five half-lives. Alprazolam 10 mg controlled release tablets were given in the fasted or fed state after the initial baseline blood sample of 10 ml (time 0 h) for determination of plasma alprazolam concentration was taken. The sampling schedule for subsequent blood samples was 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h. Samples obtained at 48 and 72 h were done in an outpatient setting.

Alprazolam pharmacokinetic parameters were determined by model-independent methods with Kinetica™ Software. The following parameters were estimated: C_{max}, T_{max}, AUC from zero to 72 h (AUC_{0-72}), elimination rate constant (k_e), and terminal elimination half-life ($t_{1/2}$). The C_{max} and T_{max} were determined by visual examination of the concentration versus time curves in both study periods for each subject. The k_e was determined by simple linear regression of the terminal segment of the natural log concentration versus time curve for each individual subject's data. Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_e$. The AUC_{0-72} was calculated by the trapezoidal rule, and extrapolation of the AUC to infinity (AUC_{inf}) was determined by dividing the last measured concentration by the k_e.

The pharmacodynamic effects of controlled release alprazolam was monitored using subject rated sedation on visual analogue scale (VAS) for wakefulness, observer rated sedation, and symbol digit modalities test (SDMT). Clinical evaluation using these scales was performed at each schedule blood draw. For subjects randomized to receive alprazolam tablet with food, a standardized high-fat meal was served and all subjects received the meal at the same time. Subjects randomized to receive alprazolam tablet in the fasted state were required to have fasted for 8 h prior to administration and for 2 h after administration of the study medication.

Subjects included healthy, non-pregnant, non-nursing persons aged 18–65 years of age. Patients with abnormal values on initial laboratory screening or positive pregnancy test were excluded. Patients with known hypersensitivity to alprazolam or any benzodiazepine were excluded.

2.4.2. Sample analysis

After each 10-ml blood sample collection, plasma was immediately separated and frozen until assayed. Alprazolam plasma concentrations were quantitated using a validated reverse phase HPLC method with UV detection consisting of an Ultrasphere C18 column maintained at 30°C. The mobile phase was composed of a mixture of 50 mM phosphate buffer (pH 4.0) and acetonitrile in a ratio of 70:30 (v/v). The flow rate of the mobile phase was 1 ml/min (isocratic) and the injection volume was 25 μl. The absorbance was monitored at 221 nm. Nitrazepam was used as an internal standard. The linearity was obtained with alprazolam concentration ranging from 5 to 250 ng/ml. The correlation coefficient (r^2) of the calibration curve was not less than 0.994. The sensitivity of the assay method was 2 ng/ml.

3. Results and discussion

3.1. In vitro results of the controlled release tablets

Two tablet formulations containing different HPMC MW types, K100LV-27 and K4M-42, were developed and investigated. Tablet size, shape and hardness were equivalent for both formulations. The composition of each tablet formulation is shown in Table 1. Both clinical batches (lot no. M0009 for HPMC K4M and lot no. M0010 for HPMC K100LV) met all specifications for initial product release.

Table 1
Formulation of alprazolam matrix tablets for the different MW types and concentrations of HPMC investigated in this study

Rx Ingredient	% w/w	
	M0010	M0009
Alprazolam (10/400 mg tablet), 99.7% potency	2.51	2.51
HPMC K100LVP	45.00	0.00
HPMC K4MP	0.00	37.00
Microcrystalline cellulose (PH200)	20.00	20.00
Lactose, Fast-Flo	31.49	39.49
Silicon dioxide	0.50	0.50
Magnesium stearate	0.50	0.50
Total	100.00	100.00

Note: Tablet size, shape and hardness were equivalent for both formulations.

As can be seen from Table 1, a higher amount of polymer (e.g. 45% w/w) was necessary for tablet formulations containing low MW type or low viscosity grade, HPMC K100LVP, in order to obtain equivalent release profiles to those of tablet formulations containing high MW type or high viscosity grade HPMC, HPMC K4MP (e.g. 37% w/w). Dissolution profiles for initial release testing are shown in Fig. 1. The percent weight variation of 20 tablets randomly sampled from each batch was less than 1%. The average tablet hardness was 6.5 kg for the K4M formulation (lot M0009) and 6.1 kg for the K100LV-27 formulation (lot M0010). The content uniformity of ten tablets was 101.67% (3.59% RSD) and 94.82% (4.55% RSD) of label claim for lots M0009 and M0010, respectively.

The extent of drug release and release profiles in 0.1 N HCl (pH 1.1) dissolution media for both tablet formulations are shown in Fig. 1. The f_2 factor was 91 (2% average difference), indicating that the two profiles were very comparable. Therefore, the two clinical batches containing different MW types and concentrations of HPMC polymer were equivalent in vitro.

3.2. Stability study of matrix tablets

Dissolution profiles at each stability condition are shown in Fig. 1. In comparison to initial dissolution results, the results from each storage condition were within the specifications. At each storage condition, dissolution profiles of the two formulations were similar or equivalent with f_2 factors ranging from 68 to 91 (only 2–5% average difference).

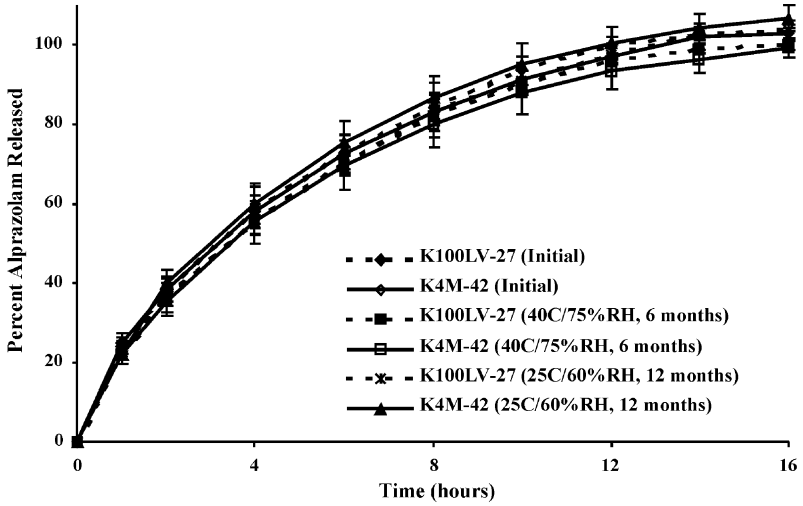

Fig. 1. Dissolution profiles of two alprazolam matrix tablet formulations containing different MW types and concentrations of HPMC at different storage conditions packaged in HDPE bottles with PP caps and silica gel desiccant ($n = 6$).

To investigate the influence of dissolution media on dose dumping of alprazolam from the tablets, pH 6.0 phosphate buffer or purified water was used as the dissolution medium. No dose dumping of alprazolam occurred at any pH investigated, which confirmed the safety for oral administration of alprazolam during the in vivo clinical study. The extent of alprazolam release in either USP buffer pH 6.0 or purified water was significantly lower than the extent of drug release from the same tablet formulations in 0.1 N HCl solution. Additionally, the extent of drug release in buffer pH 6.0 and purified water was incomplete and less than 50% at 12 h, due to solubility limitations of alprazolam in buffer pH 6.0 and purified water.

For each tablet formulation, the f_2 factor was calculated by a comparison of the dissolution profiles at each storage condition with the control at the initial condition. Results of f_2 factors ranged from 76 to 95 or 2 to 5% average difference. Therefore, in vitro dissolution profiles of both tablet formulations packaged in HDPE bottles with PP caps and desiccant, were very similar for up to 6 months at 40°C/75% relative humidity and 12 months at 25°C/65% relative humidity.

In addition to the dissolution profiles, tablet potency results for all stability conditions were within 90–110% of label claim. Overall, results from the stability studies indicated that tablets from both formulations were physically and chemically stable for at least 6 months at 40°C/75% relative humidity and 12 months at 25°C/65% relative humidity.

3.3. In vivo clinical study

Bioequivalence is defined as existing when the drug substance contained in two similar dosage forms reaches the systemic circulation at the same relative rate and to the same relative extent [27]. Ten healthy volunteers participated in the study. The gender ratio of male-to-female subjects was 6:4. The range of age was 18–58 years old with an average age of 33.5 ± 13.6 years old (i.e. average age of male and female subjects was 28.7 ± 14.8 and 40.8 ± 8.3 years old, respectively). The average body weight of the subjects was 83.4 ± 12.6 kg (i.e. average body weight of male and female subjects was 80.7 ± 11.0 and 87.5 ± 15.4 kg, respectively).

A validated reverse-phase HPLC method was previously developed for quantification of alprazolam in plasma samples collected throughout the sampling schedule. Sharp peaks with good separations were observed. The linearity of the calibration curve was excellent with a correlation coefficient (r^2) of no less than 0.994.

The assessments of the data collected throughout the study can be separated into two parts: Pharmacokinetics and Pharmacodynamics.

3.3.1. Pharmacokinetic assessments

Fig. 2 shows the plots of the mean plasma concentrations of alprazolam in each tablet formulation over time at different dosing conditions (i.e. fasted and fed states). Peak plasma concentrations at all conditions occurred 9–17.8 h after oral administration, for all subjects. As seen in Fig. 2, the absorption of alprazolam was delayed for 3 h (3 h lag period) when alprazolam tablets were taken with a high fat meal (i.e. 1000 kcal, 50% fat). High fat diets may have a potential for drug-food interactions and may alter drug absorption [28,29].

Table 2 summarizes the pharmacokinetic parameters including $AUC_{0-\infty}$, T_{max} and C_{max}, of both tablet formulations in fasted and fed states. Overall results indicated that the $AUC_{0-\infty}$, T_{max}, and C_{max} were not significantly different between two tablet formulations containing different MW types and concentrations of HPMC (HPMC-K4MP and HPMC-K100LVP) in the fed and fasted states. Therefore, tablet compositions did not influence in vitro or in vivo performance of controlled

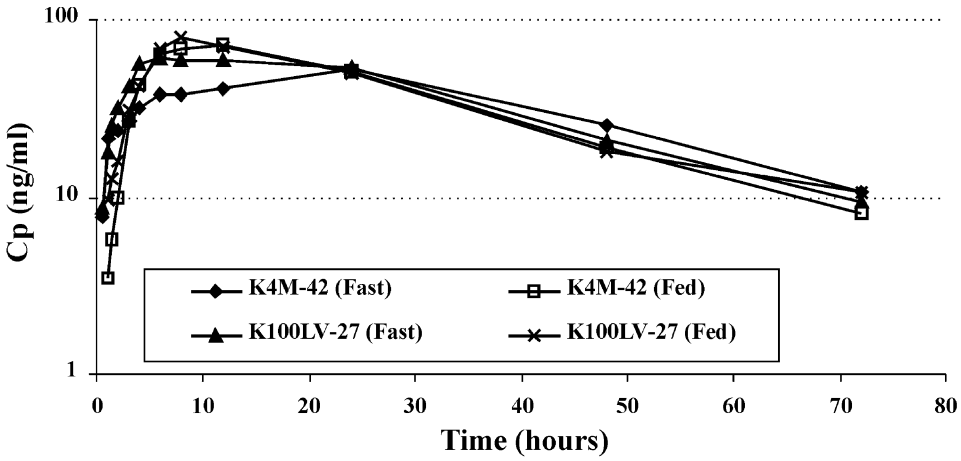

Fig. 2. Plots of mean plasma concentrations over time of different formulations and dosing conditions ($n = 10$ subjects).

release tablets. Furthermore, the in vitro dissolution characteristics predicted the in vivo absorption profile observed in the clinical trial.

3.3.2. Pharmacodynamic assessments

Pharmacodynamic assessments obtained with each blood sample included VAS for wakefulness and SDMT, in which digits are matched to symbols over a time period of 90 s. A different SDMT form was used for each sampling interval to minimize a learning effect. The SDMT is an objective method to assess psychomotor retardation due to the effects of alprazolam. The baseline measurement of SDMT varied considerably from subject-to-subject with a range of values at baseline (without alprazolam) from about 45–60 digit-symbol matches across the subjects tested.

Pharmacodynamic assessments during fasted and fed states are shown in Figs. 3a,b, respectively. During the fasted state, although the formulation containing HPMC-K100LVP polymer produced slightly greater sedation at 4 h, the difference was not statistically significant. The T_{max} for effect was slightly earlier with the formulation containing HPMC-K4MP polymer (3 versus 4 h). Large SD in SDMT scores was seen for both formulations containing different MW types and concentrations of HPMC polymer from 1 through 12 h. The rate of recovery was similar between the two formulations containing different MW types and concentrations of HPMC polymer.

During the fed state, no significant differences were observed in onset, peak effect or duration for sedation rating when compared the formulation containing HPMC-K4MP with the formulation containing HPMC-K100LVP. The presence of a high fat meal (i.e. 1000 kcal, 50% fat) delayed the absorption of alprazolam and lengthened the time of maximal sedation, based on the SDMT scores, compared with the fasted state.

Fig. 4 displays the inverse relationship between SDMT scores and the mean plasma concentrations of alprazolam (Cp) in one selected subject. The Cp of alprazolam increased after oral administration and then reached the maximum concentration (C_{max}) at T_{max} of 9 h. The SDMT scores decreased when the Cp of alprazolam approached the C_{max}, reflecting the sedation due to alprazolam. After 12 h, the Cp of alprazolam gradually decreased, while the SDMT scores of the subject increased toward baseline values.

4. Conclusions

In vivo clinical results indicated that MW types and concentrations of HPMC did not influence in vitro or in vivo

Table 2
Pharmacokinetic parameters in fasted and fed states of alprazolam in matrix tablet formulations containing different MW types and concentrations of HPMC polymer (i.e. HPMC-K4MP and HPMC-K100LVP)

State	Fasted		Fed	
Parameters*	HPMC K4M	HPMC K100LV	HPMC K4M	HPMC K100LV
$AUC_{0-\infty}$ (ng/ml h)	2625 ± 883	2678 ± 991	2590 ± 781	2683 ± 908
P-value	0.82		0.90	
T_{max} (h)	17.8 ± 8.4	9.6 ± 8.0	9.0 ± 2.7	9.2 ± 1.9
P-value	0.2		0.5	
C_{max} (ng/ml)	56.2 ± 17.5	69.4 ± 21.2	80.4 ± 12.9	83.0 ± 13.8
P-value	0.28		0.66	

Note: *Data was collected from ten healthy subjects.

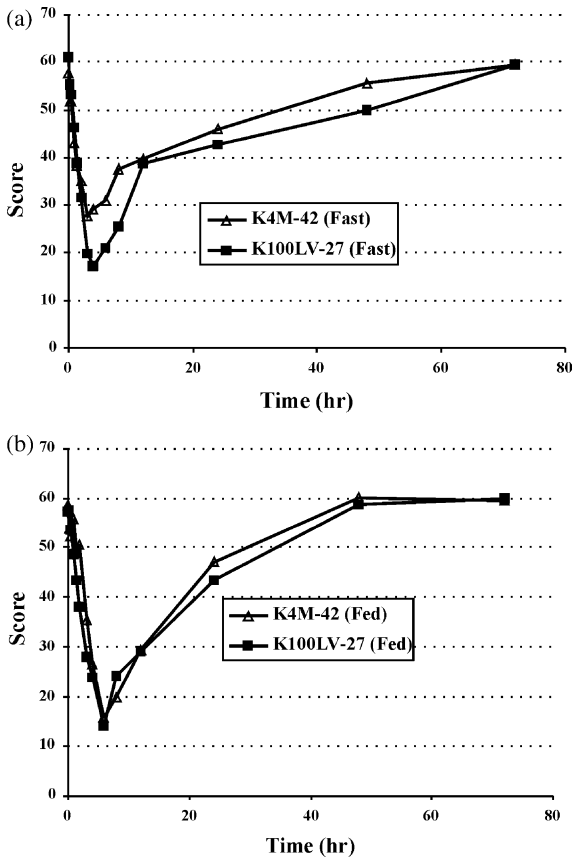

Fig. 3. Mean SDMT scores for HPMC-K4MP and HPMC-K100LVP polymers in: (a) fasted state; and (b) fed state ($n = 10$ subjects).

performance of controlled release tablets containing lipophilic alprazolam. Controlled release tablets with different HPMC polymer types and concentrations provided bioequivalent results in both fed and fasted states. In vitro dissolution conditions sufficiently mimicked in vivo dissolution conditions and produced similar drug release profiles for the two formulations. Similarly for the pharmcodynamic assessment, no significant differences in SDMT scores were noted for either tablet formulations containing different MW types and concentrations of HPMC. Also, no gender effects were observed during the study. Food delayed absorption of alprazolam by approximately 3 h. We showed that different MW types and concentrations of HPMC had no impact on in vitro and in vivo performance of controlled release tablets containing lipophilic alprazolam.

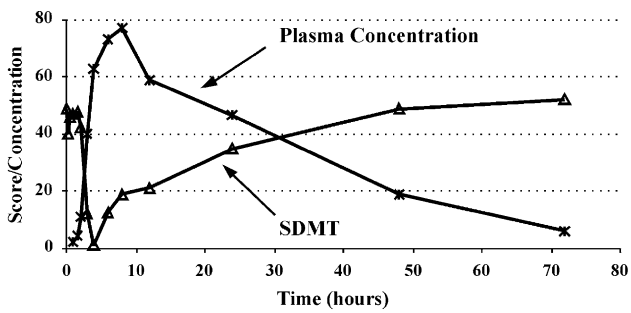

Fig. 4. Relationship between SDMT scores and plasma concentration of alprazolam in one selected subject.

Acknowledgements

The authors gratefully acknowledge the support of The Dow Chemical Company.

References

[1] D.A. Alderman, A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms, Int. J. Pharm. Tech. Prod. Mfg. 5 (1984) 1–9.
[2] M. Helena Amaral, J.M. Sousa Lobo, D.C. Ferreira, Effect of hydroxypropyl methylcellulose and hydrogenated castor oil on naproxen release from sustained-release tablets, AAPS Pharm. Sci. Tech. 2 (2001) 1–8.
[3] J.L. Ford, M.H. Rubinstein, J.E. Hogan, Formulation of sustained release promethazine hydrochloride tablets using hydroxypropylmethylcellulose matrices, Int. J. Pharm. 24 (1985) 327–338.
[4] L.W.S. Cheong, P.W.S. Heng, L.F. Wong, Relationship between polymer viscosity and drug release from a matrix system, Pharm. Res. 9 (1992) 1510–1514.
[5] K. Tahara, K. Yamamoto, T. Nishihata, Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910, J. Controlled Release 35 (1995) 59–66.
[6] I. Krogel, R. Bodmeier, Development of a multifunctional matrix drug delivery system surrounded by an impermeable cylinder, J. Controlled Release 61 (1999) 43–50.
[7] N. Shah, G. Zhang, V. Apelian, F. Zeng, M.H. Infield, A.W. Malick, Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration, Pharm. Res. 10 (1993) 1693–1695.
[8] G. Xu, H. Sunada, Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets, Chem. Pharm. Bull. 43 (1995) 483–487.
[9] M.V. Velasco, J.L. Ford, P. Rowe, A.R. Rajabi-Siahboomi, Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets, J. Controlled Release 57 (1999) 75–85.
[10] K. Mitchell, J.L. Ford, D.J. Armstrong, P.N.C. Elliot, J.E. Hogan, C. Rostron, The influence of substitution type on the performance of methyl cellulose and hydroxypropylmethylcellulose in gels and matrices, Int. J. Pharm. 100 (1993) 143–154.
[11] J. Brown, N. Madit, E.T. Cole, I.R. Wilding, D. Cade, The effect of cross-linking on the in-vivo disintegration of hard gelatin capsules, Proc. 2nd World Meeting AGPI/APV, Paris 25/28 (1998) 163–164.
[12] J.G. Hardy, S.S. Davis, C.G. Wilson, Drug Delivery to the Gastrointestinal Tract, Ellis Horwood, Chichester, UK, 1989.
[13] S.S. Davis, R. Khosla, C.G. Wilson, N. Washington, S.T. Leslie, S. Malkowska, The gastrointestina transit of a controlled release formulation of indomethacin, Int. J. Pharm. 60 (1990) 191–196.
[14] L. Williams, J.A. Davis, J.A. D, T. Lowenthal, The influence of food on the absorption and metabolism of drugs, Clin. Nutr. 77 (1993) 815–829.
[15] A.J. McLachlan, S.E. Tett, D.J. Cutler, R.O. Day, Absorption and in vivo dissolution of hydroxychloroquine in fed subjects assessed using deconvolution techniques, Br. J. Clin. Pharm. 36 (1993) 405–411.
[16] M.T. Borin, K.K. Forbes, G.S. Hughes, The bioavailability of cefpodoxime proxetil tablets relative to an oral solution, Biopharm. Drug Dispos. 16 (1995) 295–302.

[17] G. Paintaud, G. Alvan, S.A. Eckernas, M. Wakelkamp, A. Grahnen, The influence of food intake on the effect of two controlled release formulations of furosemide, Biopharm. Drug Dispos. 16 (1995) 221–232.
[18] J.G. DeVane, J.G. Kelly, B. Geoghegan, Pharmacokinetic and in-vitro characteristics of sustained release verapamil products, Drug Dev. Ind. Pharm. 16 (1990) 1223–1248.
[19] C.J. Kenyon, G. Hooper, D. Tierney, J. Butler, J. DeVane, I.R. Wilding, The effect of food on the gastrointestinal transit and systemic absorption of a naproxen from a novel sustained release formulation, J. Controlled Release 34 (1995) 31–36.
[20] D.J. Greenblatt, R.M. Arendt, D.R. Abernethy, H.G. Giles, E.M. Sellers, R.I. Shader, In vitro quantitation of benzodiazepine lipophilicity: relation to in vivo distribution, Br. J. Anaesth. 55 (1983) 985–989.
[21] P.D. Garzone, P.D. Kroboth, Pharmacokinetics of the newer benzodiazepines, Clin. Pharmacokin. 16 (1989) 337–364.
[22] N. Laihanen, E. Muttonen, M. Laaksonen, Solubility and intrinsic dissolution rate of alprazolam crystal modifications, Pharm. Dev. Technol. 1 (1996) 373–380.
[23] N. Laihanen, J. Yliruusi, Physical stability of alprazolam dihydrate: intact, ground and tabletted samples compatibility with certain commonly used tabletting excipients, S.T.P. Pharm. Sci. 6 (1996) 403–409.
[24] R.O. Williams III, M.A. Sykora, V. Mahaguna, Method to recover a lipophilic drug from hydroxypropyl methylcellulose matrix tablets, AAPS Pharm. Sci. Tech. 2 (2001) 1–9.
[25] M. Acikkol, B.D. Barlaa, S. Rollas, High performance liquid chromatographic and UV spectrophotometric analysis of alprazolam, Pharmazie 46 (1991) 461–462.
[26] J.W. Moore, H.H. Flanner, Mathematical comparison of curves with an emphasis on in intro dissolution profiles, Pharm. Technol. 20 (1996) 64–74.
[27] H.M. Abdou, Dissolution, Bioavailability and Bioequivalence, Mack Publishing, Easton, PA, 1989.
[28] D.J. Greenblatt, C.E. Wright, Clinical pharmacokinetics of alprazolam, Clin. Pharmacokin. 24 (1993) 453–471.
[29] W.N. Charman, Lipids, lipophilic drugs, and oral drug delivery – some emerging concepts, J. Pharm. Sci. 89 (2000) 967–978.