

Method to Recover a Lipophilic Drug From Hydroxypropyl Methylcellulose Matrix Tablets

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ABSTRACT A reverse-phase high-performance liquid chromatographic (HPLC) method for recovery of the lipophilic drug, alprazolam, from matrix tablets containing the hydrophilic polymer hydroxypropyl methylcellulose (HPMC) was developed. Lipophilic drugs, such as alprazolam, are difficult to completely extract and quantitate from tablets containing HPMC polymer. The percentage of recoveries of alprazolam from placebo powder spiked with alprazolam stock solution and from placebo powder mixed with alprazolam powder were about 100% and 85% to 95%, respectively. The validated method using water to completely dissolve HPMC before the addition of a strong solvent to dissolve and extract the drug from the HPMC solution was shown to be the most reproducible method. Different molecular weight distributions of the HPMC polymer, such as HPMC-K4M and HPMC-K100LV, did not influence the dissolution results of alprazolam using this validated method. Similarly, the excipients composing the matrix tablet formulations, such as dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, calcium sulfate dihydrate, sucrose, dextrose, and lactose monohydrate, did not influence the percent recovery of alprazolam. The recovery method reported herein was shown to be the most efficient to achieve complete recovery of alprazolam from powder blends and tablets containing a variety of excipients and different grades of HPMC.

KEYWORDS: Alprazolam, hydroxypropyl methylcellulose, HPMC, matrix tablet, liquid chromatography.

INTRODUCTION

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad U.S. Food and Drug Administration acceptance [1]. The hydrophilic polymer matrix system consists of hydrophilic polymer, drug, and other excipients distributed throughout the matrix. This dynamic system is dependent on polymer wetting, hydration, and dissolution for controlled release of drug. At the same time, other soluble excipients or drug substances will also wet, dissolve, and diffuse out of the matrix, whereas insoluble excipients or drug substances will be held in place until the surrounding polymer, excipient, or drug complex erodes or dissolves away [2].

Hydroxypropyl methylcellulose (HPMC), which is commonly used in hydrophilic matrix drug delivery systems, is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration rate of HPMC depends on the nature of these substituents, such as the molecular structure and the degree of substitution. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH independent [1]. HPMC can be slowly dissolved in cold water to form a viscous solution, but is not very soluble in hot water. Additionally, it can be dissolved in most polar organic solvents or binary systems of methylene chloride or chloroform and alcohol [3-5]. It is practically insoluble in pure chloroform, ethanol, or ether [6]. Therefore, the recommended method to prepare HPMC aqueous solutions is to first thoroughly disperse and hydrate the powder in a portion of hot water (about one third of the total

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volume) heated above 90°C with vigorous stirring to prevent lumping. Complete solubilization is then accomplished by adding the remaining portion as cold water (two thirds of the total volume) to lower the temperature of the dispersion. As the temperature is lowered, HPMC becomes water soluble, resulting in increased viscosity ("hot/cold" techniques) [7]. The viscosity of the aqueous solution can be increased by increasing the molecular weight distribution of the polymer or the concentration of the polymer or decreasing the temperature of the solution.

In tablet manufacturing, quantification of the drug substance (ie, content uniformity or composite assay) in the drug product is a mandatory requirement for release. Typically, a content uniformity assay is performed by pulverizing a tablet into powder and extracting the drug substance using an organic solvent(s) with sonication or mechanical stirring [8]. However, extracting a lipophilic drug substance from gelling HPMC tablets is much more complicated because of the highly lipophilic nature of the drug substance and the gelling properties of HPMC polymer. Dortunc et al. described a content uniformity method for hydrophilic matrix tablets containing HPMC K4M or K15M and pindolol in a buccoadhesive matrix tablet. A pulverized tablet was treated with enough pH 6.8 phosphate buffer solution:methanol mixture (98:2), in which pindolol had a high solubility (222.2 µg/mL) when compared to its solubility in pH 6.8 buffer solution alone (8.2 µg/mL). However, the percent drug recovery and drug content uniformity results were not reported [8]. Also, quantification of acetazolamide in matrix tablets containing HPMC K4M or K15M was reported, but the quantitative assay method and drug content uniformity results were not reported [9]. A review of the literature indicated that no specific method has been reported for quantification of a lipophilic drug substance contained in HPMC matrix tablets.

To develop a method to recover a lipophilic drug from controlled-release matrix tablets containing HPMC, alprazolam-a benzodiazepine-was chosen as the model drug. It has a rapid onset of action coupled with a relatively short half-life, and is indicated for managing anxiety disorders and anxiety associated with depression. The drug substance occurs as a

white to off-white crystalline powder and melts in the range of 228°C to 229°C [3]. Greenblatt et al. reported the high value of the partition ratio between n-octanol and aqueous buffer at physiological pH 7.4 of alprazolam to be about 18, indicating its high degree of lipophilicity [10-11]. Also, Carelli et al. determined the partition coefficient of alprazolam between n-octanol and normal saline containing 0.035% formaldehyde (as a preservative) of the drug from their permeation study through hairless mouse skin to be about 132 [12]. In addition, it has been reported that the partition coefficient of alprazolam between human callus (tissue) and the normal saline containing 0.035% formaldehyde determined from a permeation study through human skin in vitro was about 17.5 mL/g [13]. Alprazolam is insoluble in water, soluble in chloroform and alcohol, and slightly soluble in acetone and ethyl acetate. The solubility of alprazolam is pH dependent. Solubility determined in the present study showed that the drug has higher solubility in an acidic pH solution (ie, 12 mg/mL in USP buffer pH 1.2) than in a basic pH solution (0.04 mg/mL in phosphate buffer pH 6.8). The structure of alprazolam is shown in Figure 1.

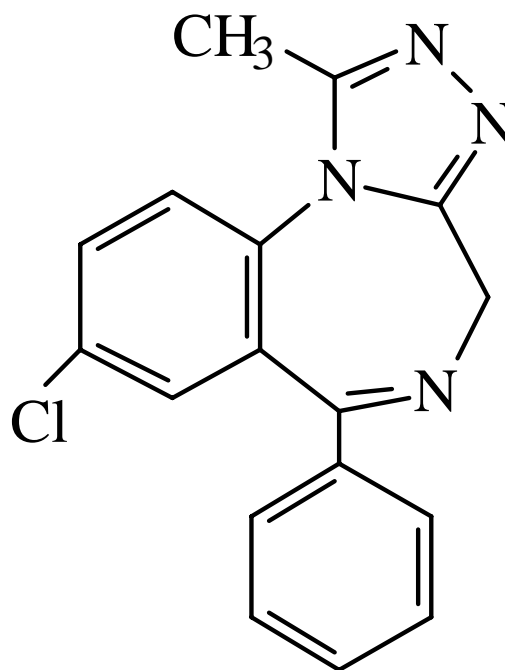


Figure 1. Structure of alprazolam.

The objective of this study was to develop a suitable analytical method for the recovery of a lipophilic drug from controlled-release matrix tablets containing HPMC. In addition, the influence of formulation composition, such as HPMC type and excipient type, on drug recovery is reported.

MATERIALS AND METHODS

Materials

The following materials were used to prepare matrix powder blends and matrix tablets: alprazolam USP (ALP; Spectrum Quality Products, Gardena, CA); hydroxypropyl methylcellulose USP (HPMC substitution type 2208, Methocel K100 Premium LVCR EP [22.8% methoxyl content, 8.7% hydroxypropyl content, and 107 centipoise (cPs) apparent viscosity as a 2% aqueous solution] or Methocel K4M Premium CR [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 NF (Avicel PH 200, FMC Corporation, Philadelphia, PA); lactose monohydrate NF (modified spray-dried, Foremost Farms USA, Baraboo, WI); dicalcium phosphate dihydrate (Di-Tab, Rhodia North America, Chicago Heights, IL); dicalcium phosphate anhydrous (A-Tab, Rhodia North America, Chicago Heights, IL); sucrose (DiPac, Domino Sugar, Baltimore, MD); dextrose (Emdex, Penwest Pharmaceuticals Company, Patterson, NY); calcium sulfate dihydrate (Compactrol, Penwest Pharmaceuticals Company, Patterson, NY); silicon dioxide (Cab-O-Sil M5P, Cabot Corporation, Tuscola, IL); and magnesium stearate USP/NF (Spectrum Quality Products, Gardena, CA).

For high-performance liquid chromatographic (HPLC) analysis, the chemicals used were analytical reagent grade. HPLC-grade acetonitrile, tetrahydrofuran (distilled THF), monobasic potassium phosphate, and sodium hydroxide were purchased from EM Science (Gibbstown, NJ). Alprazolam USP reference standard was purchased from US Pharmacopoeia (Rockville, MD). Whatman 0.45 μm (47 mm diameter) nylon membrane filters (Whatman International Ltd, Maidstone, England) and GHP 0.45 μm (GHP Acrodisc 13 mm) syringe filters (Pall Gelman Laboratory, Ann Arbor, MI) were used to filter mobile phase and samples, respectively. Water was purified

with a Milli-Q UV Plus system (Millipore, Molsheim, France).

Methods

Chromatographic analysis

The reverse-phase HPLC method used to determine the amount of alprazolam in the powder blends and pulverized matrix tablets was a modification from the assay method of alprazolam tablets listed in the USP 24/NF 19 monograph [14]. The chromatographic system (Shimadzu, Columbia, MD) consisted of a system controller (Model SCL-10A-VP), a Photodiode Array Detector (Model SPD-M10A VP, deuterium lamp), a chromatographic data control and acquisition system (Class-VP software version 4.2), pumps (Model LC-10AT VP), and an autoinjector (SIL-10A). A Luna 5 μ C8(2) (5 μm , 100 x 4.6 mm, Phenomenex, Torrance, CA), USP packing type L7 column, and a security guard cartridge C8 (4 x 3.0 mm, Phenomenex, Torrance, CA) were used.

The mobile phase was composed of a mixture of 35.34 mM phosphate buffer (pH 6.0 \pm 0.1), acetonitrile, and tetrahydrofuran in a ratio of 68:28:4 (vol/vol/vol). The 35.34 mM phosphate buffer solution was prepared by dissolving monobasic potassium phosphate in purified water, and then adjusting the pH to 6.0 \pm 0.1 with 5.3 M sodium hydroxide solution. Before its use, the mobile phase was filtered through a 0.45 μm nylon membrane filter (Whatman, 47 mm diameter) and degassed with vacuum and sonication for 10 minutes. The flow rate of the mobile phase was 2 mL/min (isocratic) and the injection volume was 20 μL . The absorbance was monitored at 222 nm. The run time was 10 minutes. A calibration curve was prepared by dissolving alprazolam USP reference standard with the diluent (purified water-acetonitrile, 50:50, vol/vol), and the stock solution was diluted to concentrations in the range of 0.005 to 0.06 mg/mL. Replicate standards were injected to ensure repeatability before sample analysis. System suitability criteria were established: the correlation coefficient (r) of the calibration curve, not less than 0.998; relative standard deviation (RSD) of 5 replicate injections, \leq 2.0%; number of theoretical plates, $>$ 500 plates/column; and the peak asymmetry, \leq 1.5 [14]. A check standard of known concentration was inserted between every 5 samples. All samples were filtered through 0.45 μm GHP syringe filters (GHP Acrodisc 13 mm) into HPLC vials.

Sample Preparation Methods

Each sample contained placebo powder and a known amount of alprazolam. A mixture of HPMC polymer (either Methocel K4M or K100LV), microcrystalline cellulose, other excipient(s), silicon dioxide, and magnesium stearate was prepared by geometric dilution in a V-blender. Either alprazolam powder or an aliquot of stock solution containing a known amount of alprazolam was added to an aliquot of the placebo powder blend. Two sample preparation methods (I and II) were investigated to determine alprazolam recovery. Each sample listed in Table 1 was prepared in replicates of 3 using a sample preparation method indicated below.

- **Sample Preparation Method I**

Acetonitrile (ACN) alone was used as the extraction solvent. After final volume adjustment, each sample was filtered through a 0.45 μm GHP syringe filter (GHP Acrodisc 13 mm) into a glass vial. Finally, the drug content was determined by HPLC. The samples investigated (A to J) using method I and orders of addition are described in Table 1. The quantitative composition of each placebo powder (A to J) is listed in Table 2.

- **Sample Preparation Method II**

The composition of placebo powder blend used for sample K preparation and analyzed using method II is described in Table 2. A physical blend of placebo powder blend and alprazolam powder were blended and transferred to a 1 L volumetric flask. To the physical blend, 170 mL of hot water ($\sim 90^\circ\text{C}$) was added with stirring to disperse the physical blend before addition of 330 mL of cold water ($\sim 5^\circ\text{C}$). The slurry was stirred in an ice bath at 2°C for 3 hours to dissolve the HPMC gel. Then, about 450 mL of ACN was added and stirring was continued for 4 hours at 25°C . The sample was adjusted to final volume and then a 50% vol/vol ACN mixture was obtained. Finally, the mixture was filtered through a 0.45 μm GHP syringe filter (GHP Acrodisc 13 mm) into a glass vial for HPLC analysis.

Table 1. Sample Preparation Method I Used for Determination of Alprazolam (ALP) Content

Sample	Form of ALP Added	Solvent (Temperature)	Sample Preparation Procedure
A	Stock solution in ACN	100% ACN (22°C)	Placebo powder blend: ¹ add ACN, add ALP stock solution, mix, and adjust to volume.
B	Powder	100% ACN (22°C)	Placebo powder blend: ¹ add ACN, sonicate for 30 min, add ALP powder, sonicate for 30 min, mix, and adjust to volume.
C	Powder	100% ACN (22°C)	ALP powder: add ACN, sonicate for 30 min, add placebo powder blend, ¹ mix, and adjust to volume.
D	Powder	100% ACN (22°C)	Placebo powder blend: ¹ add ALP powder, add ACN, sonicate for 30 min, mix, and adjust to volume.
E	Powder	100% cold ACN (5°C)	Placebo powder blend: ¹ add ALP powder, add cold ACN, sonicate for 30 min, stir at 25°C for 12 h, mix, and adjust to volume.
F	Powder	100% cold ACN (5°C)	ALP powder: add cold ACN, sonicate for 30 min, add placebo powder blend, ¹ stir at 25°C for 12 h, mix, and adjust to volume.
G	Powder	100% cold ACN (5°C)	Placebo powder blend: ¹ add cold ACN, sonicate for 30 min, add ALP powder, sonicate for 30 min, stir at 25°C for 12 h, mix, and adjust to volume.
H	Powder	100% cold ACN (-10°C)	Placebo powder blend: ¹ add ALP powder, add cold ACN, sonicate for 30 min, stir at 25°C for 12 h, mix, and adjust to volume.
I	Stock solution in ACN	100% cold ACN (-10°C)	Placebo powder blend: ¹ add ALP stock solution, add ACN (-10°C), sonicate for 30 min, stir overnight at 25°C , mix, and adjust to volume.
J	Powder	100% cold ACN (-20°C)	Placebo powder blend: ¹ add ALP powder, add ACN (-20°C), stir at -17°C for 2 h, mix, and adjust to volume.

¹ Placebo powder contained 23% wt/wt of hydroxypropyl methylcellulose K4M premium, 20% wt/wt of microcrystalline cellulose, 56% wt/wt of dicalcium phosphate dihydrate, 0.5% wt/wt of silicon dioxide, and 0.5% wt/wt of magnesium stearate. ACN = acetonitrile; ALP = alprazolam.

Table 2. Placebo Powder Composition for Sample Preparation

Placebo Powder for Sample	HPMC Type (Level)	Excipient Type (Level)	Other Excipients in Tablet Formulation
A to K	K4M (23% wt/wt)	Dicalcium phosphate dihydrate (56% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
L	K100LV (40% wt/wt)	Dicalcium phosphate dihydrate (39% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
M	K4M (40% wt/wt)	Sucrose (39% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
N	K4M (40% wt/wt)	Dextrose (39% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
O	K4M (40% wt/wt)	Dicalcium phosphate anhydrous (39% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
P	K4M (40% wt/wt)	Calcium sulfate dihydrate (39% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)

HPMC = hydroxypropyl methylcellulose.

Table 3. Alprazolam Matrix Tablet Formulations (10 mg alprazolam/400 mg tablet)

Formulation	HPMC Type (Level)	Excipient Type (Level)	Other Excipients in Tablet Formulation
Q	K4M (37% wt/wt)	Lactose (42% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)
R	K100LV (45% wt/wt)	Lactose (34% wt/wt)	Microcrystalline cellulose (20% wt/wt), silicon dioxide (0.5% wt/wt), magnesium stearate (0.5% wt/wt)

HPMC = hydroxypropyl methylcellulose.

Influence of molecular weight (viscosity) of HPMC on alprazolam recovery

The two different molecular weight distributions of HPMC polymer (Methocel K100LV having an apparent viscosity of 107 cPs and Methocel K4M having an apparent viscosity of 4126 cPs) were

incorporated into the placebo powder blends (Table 2; samples K and L). Sample K contained the high molecular weight distribution polymer (23% wt/wt of HPMC K4M), whereas sample L contained the low molecular weight distribution polymer (40% wt/wt of HPMC K100LV). Samples K and L were prepared by using sample preparation method II as described in the previous section.

Influence of excipient type on alprazolam recovery

The water-soluble excipients investigated include sucrose and dextrose. The water-insoluble excipients investigated include dicalcium phosphate anhydrous and calcium sulfate dihydrate. The composition of the placebo powder blends used to prepare samples M-P are shown in Table 2. All samples were prepared by using sample preparation method II as described in the previous section.

Determination of drug content in a matrix tablet

• ***Matrix tablet preparation***

Two hydrophilic matrix tablet formulations containing either HPMC K4M or K100LV polymer were prepared for a 300-g batch size. Batch composition in percent weight by weight is shown in Table 3. All ingredients were blended using a geometric dilution technique in a V-blender. Tablets weighing 400 mg were prepared by direct compression using standard tablet tooling (concave, 11 mm diameter) and tablet press (Stokes Dual Pressure Press Model B2, Serial No. B59671, F.J. Stokes Machine Company, Philadelphia, PA). Tablet size, shape, and hardness were identical for both formulations.

• ***Content uniformity assay of matrix tablets***

A content uniformity assay of ground individual tablets and a composite assay of 10 ground tablets from each formulation were determined using sample preparation method II. Alprazolam content in the matrix tablet(s) was quantified by HPLC.

RESULTS AND DISCUSSION

Chromatographic analysis

A reverse-phase HPLC method was developed for quantifying the highly lipophilic model drug substance, alprazolam, which is contained in matrix tablet formulations. System suitability was performed

according to generally accepted laboratory practices to ensure that the HPLC system and recovery procedure were capable of providing accurate and precise data [15]. The wavelength of 222 nm was selected because alprazolam had a maximum absorbance at this level. No interference among any of the components of the powder blend and alprazolam were founded at this wavelength. A typical HPLC chromatogram is shown in Figure 2. The number of theoretical plates (N) was about 3000 plates per column; the peak asymmetry was about 1.1. The retention time of alprazolam was about 4.1 minutes. The sample diluent (50% ACN in water) and sample placebo blend showed no interferences in the region of interest, and excellent method specificity was demonstrated. The linearity of the calibration curve was excellent with a correlation coefficient (r) of 0.999. The precision of the chromatographic method was determined by making 5 replicate injections of a working standard solution. The precision was excellent as indicated by the low magnitude of the RSD (0.9%). Therefore, the system suitability specifications were met.

Sample preparation methods

Different solvents and sample preparation methods were investigated to recover the lipophilic drug, alprazolam, from pulverized HPMC matrix tablets or matrix powder blends. Two studies were conducted to determine the percent drug recovery from the same powder blend formulation (Tables 1 and 2). The first study was focused on finding an extraction solvent that would dissolve alprazolam and not dissolve the hydrophilic HPMC polymer. Acetonitrile was selected as an extraction solvent in sample preparation method I because it has a high solubilizing power for alprazolam, it is a component of the mobile phase, and it is a poor solvent for HPMC as determined in the study. Sample preparation method II was focused on finding a cosolvent system, which would dissolve both alprazolam and HPMC polymer. Acetonitrile was the solvent selected to dissolve alprazolam, whereas water was selected as the solvent to dissolve HPMC polymer.

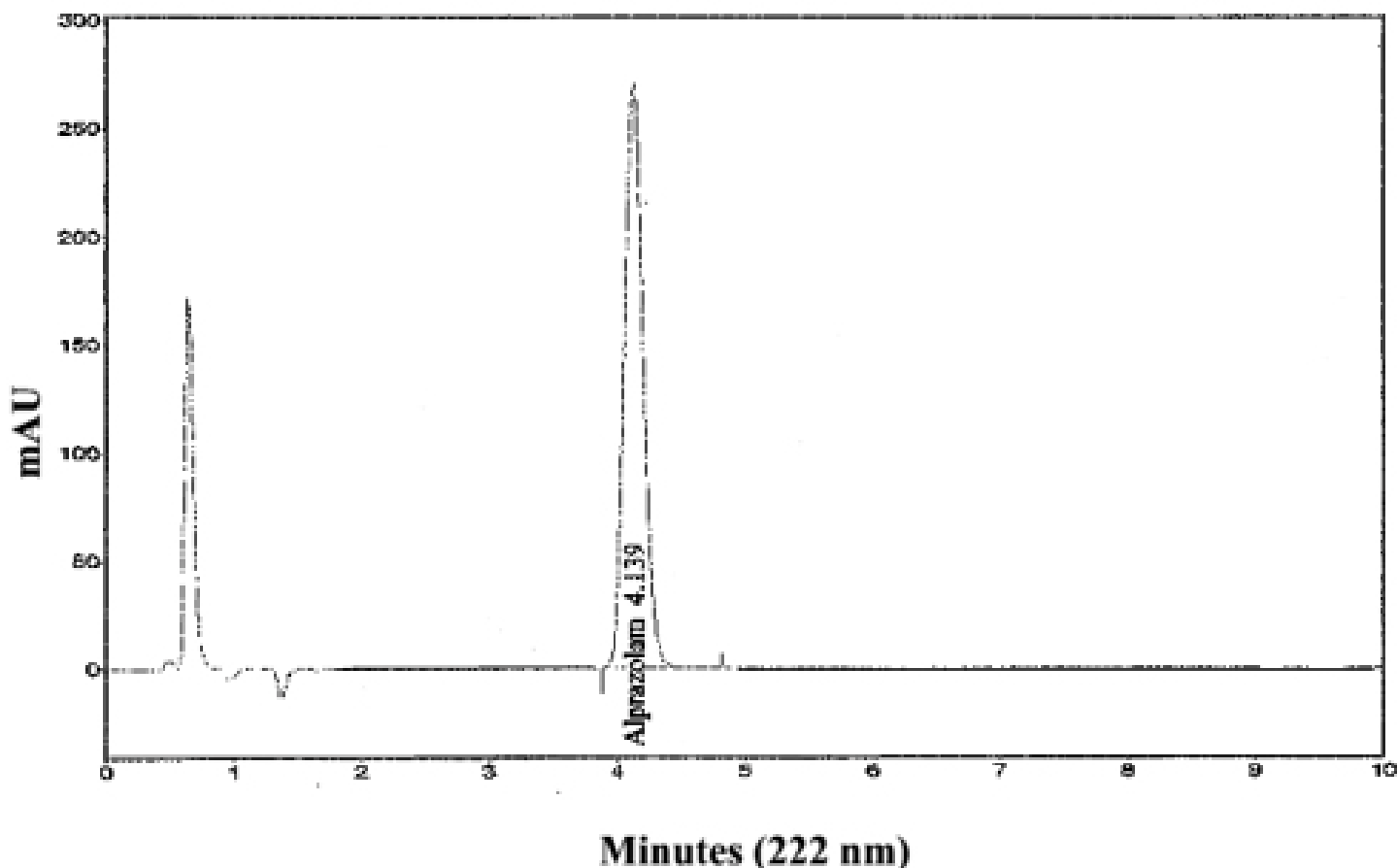


Figure 2. A typical high-performance liquid chromatographic chromatogram of alprazolam in a tablet or powder blend containing hydroxypropyl methylcellulose polymer.

- **Sample preparation method I**

Using ACN alone as the extraction solvent, samples A and B were prepared using the same sample preparation method, but a different method of incorporating the alprazolam. For sample A, alprazolam was dissolved in ACN and then added as a solution, whereas alprazolam powder was used in sample B. The percent recoveries of alprazolam from samples A and B were $100.54 \pm 1.83\%$ and $86.81 \pm 2.45\%$, respectively (Table 4). Similar to sample B, drug recoveries from samples C and D using alprazolam powder and different orders of addition were low, $95.11 \pm 1.80\%$ and $91.59 \pm 2.38\%$, respectively (Table 4). These low drug recoveries occurred because the gelation rate of the HPMC polymer was faster than the dissolution rate of alprazolam powder in the extraction solvent, ACN. HPMC was poorly soluble in ACN, but gelled on exposure to ACN; therefore, drug was trapped within the swelling gel layers of HPMC polymer before it could be completely dissolved. Also, ACN, at temperatures of -20°C to 5°C , was used as the extraction solvent for samples E-J (Table 1). These methods were performed to minimize the solubility of HPMC in ACN at low temperatures and to increase drug recovery. Drug recoveries from samples prepared from alprazolam powder were significantly low ($P < 0.05$; except sample I), and ranged from 90% to 96% (Table 4), regardless of the sample preparation method used and the order of addition of drug and placebo powder blend containing HPMC (samples E, F, G, H, and J; Table 1). However, sample I, which was prepared from the alprazolam stock solution using cold ACN at -10°C as a solvent had $99.10 \pm 1.53\%$ drug recovery, was similar to the recovery found for sample A using ACN at 22°C as a solvent (Tables 1 and 4). Therefore, the solvent temperature did not improve the recovery of alprazolam. Some drug particles were trapped within the gel layers of HPMC before complete dissolution in the extraction solvent. The results indicated that it is necessary to dissolve HPMC before dissolving the drug substance to prevent entrapment of drug particles and incomplete dissolution as the HPMC swells and gels on contact with ACN. Therefore, sample preparation method II was investigated to identify a cosolvent system capable of dissolving both drug and polymer.

Table 4. Recovery of Alprazolam from Powder Blends Using Different Sample Preparation Methods

Sample	Theoretical Assay		% Alprazolam Recovery
	Amount of Alprazolam (mg/mL)	Amount of Alprazolam (mg/mL)	
<i>Sample Preparation Method I: Acetonitrile Alone</i>			
A (K4M)	0.02000	0.02011	100.54 ± 1.83
B (K4M)	0.04960	0.04306	86.81 ± 2.45
C (K4M)	0.05040	0.04793	95.11 ± 1.80
D (K4M)	0.04970	0.04552	91.59 ± 2.38
E (K4M)	0.05200	0.04997	96.09 ± 1.49
F (K4M)	0.05260	0.05036	95.74 ± 1.08
G (K4M)	0.05040	0.04835	95.94 ± 1.55
H (K4M)	0.05550	0.05272	94.99 ± 2.34
I (K4M)	0.04000	0.03964	99.10 ± 1.53
J (K4M)	0.05450	0.04939	90.62 ± 1.13
<i>Sample Preparation Method II: Acetonitrile/Water</i>			
K (K4M)	0.05030	0.05056	100.52 ± 2.41
L (K100LV)	0.05010	0.05090	101.60 ± 1.59

- **Sample preparation method II**

In sample preparation method II, ACN was used as the extraction solvent for alprazolam, and water was used as the solvent for HPMC. Water was a poor solvent for alprazolam because the aqueous equilibrium solubility at 37°C was 0.045 mg/mL , as determined in this study. Therefore, stronger solvents were still necessary to enhance the dissolution of alprazolam. Recovery of alprazolam from sample K, which was prepared by swelling HPMC in hot water ($\sim 90^{\circ}\text{C}$) and dissolving HPMC in cold water ($\sim 5^{\circ}\text{C}$) before extraction of the drug in ACN at 22°C was $100.52 \pm 2.41\%$, even though drug powder was used in the preparation (Table 4). After the HPMC polymer was completely dissolved in the aqueous solution, its gelling and hydrating properties did not influence drug dissolution. This method was shown to achieve complete recovery of alprazolam from matrix placebo blends. This method was employed for investigating formulation compositions (samples K-P), as discussed in the next section.

Influence of polymer molecular weight (viscosity) on drug recovery

Table 4 shows the percent alprazolam recoveries from samples K and L prepared from placebo blends containing different grades of HPMC polymer ($100.52 \pm 2.41\%$ and $101.60 \pm 1.59\%$,

respectively). Sample K contained a high molecular weight (high-viscosity) grade of HPMC (Methocel K4M, 4126 cPs apparent viscosity as a 2% aqueous solution), and sample L contained a low molecular weight (low-viscosity) grade of HPMC (Methocel K100LV, 107 cPs apparent viscosity as a 2% aqueous solution). Both HPMC grades possess similar degrees of methoxyl substitution (19%-24% methoxyl), hydroxypropyl substitution (7%-12% hydroxypropyl), and similar gelation rates. However, they are different in terms of degree of polymerization resulting in different molecular weight distribution, which is reflected in the viscosity of an aqueous solution [2]. Although sample K contained HPMC with molecular weight distribution or viscosity about 40 times greater than sample L, the percent drug recoveries were similar at about 100% using sample preparation method II. This indicated that the molecular weight distribution or viscosity of the polymer did not influence the dissolution of the lipophilic drug using sample preparation method II because HPMC was completely dissolved before alprazolam.

Influence of excipient type on drug recovery

The results shown in Table 5 describe the influence of excipient type on the recovery of alprazolam from matrix powder blends using sample preparation method II. The percent recovery of alprazolam from samples containing water-soluble excipients, sucrose and dextrose, was $100.26 \pm 1.92\%$ and $97.60 \pm 0.79\%$, respectively. Similar results were obtained for samples containing water-insoluble excipients, dicalcium phosphate anhydrous and calcium sulfate dihydrate, ($98.90 \pm 1.36\%$ and $102.68 \pm 2.03\%$, respectively). The chromatogram shown in Figure 2 is characteristic of the chromatogram obtained for each of the investigated excipients. The results indicated that the excipients comprising the matrix tablet formulations did not influence the recovery of alprazolam.

Sample preparation method II allowed for complete recovery of alprazolam from matrix powder blends containing HPMC and different types of tableting excipients.

Table 5. Alprazolam Recovery from Powder Blends Containing Different Types of Excipients Using Sample Preparation Method II

Sample	Excipient Type	Theoretical	Assay	% Alprazolam Recovery
		Amount of Alprazolam (mg/mL)	Amount of Alprazolam (mg/mL)	
M	Sucrose	0.05070	0.05083	100.26 ± 1.92
N	Dextrose	0.05010	0.04890	97.60 ± 0.79
O	Dicalcium phosphate anhydrous	0.05040	0.04985	98.90 ± 1.36
P	Calcium sulfate dihydrate	0.05020	0.05155	102.68 ± 2.03

Determination of drug content in a matrix tablet

Sample preparation method II was used to determine the content uniformity and composite assay of 2 lots of tablets. Two tablet formulations containing different grades of HPMC (K4M or K100LV) and lactose monohydrate as the excipient (Table 3) were tested. For content uniformity results of each tablet formulation, the mean alprazolam level of 10 tablets for formulation Q (K4M) and formulation R (K100LV) was $101.90 \pm 3.41\%$ (3.35% RSD) and $98.80 \pm 2.16\%$ (2.18% RSD) of label claim, respectively. For both formulations, the alprazolam content in each tablet was uniform as indicated by the low magnitude of the RSD. The results obtained for the composite assay of 10 tablets from formulations Q and R were $99.35 \pm 2.06\%$ and $97.98 \pm 1.92\%$, respectively. Therefore, the results from the drug content uniformity indicated that sample preparation method II achieved complete recovery of alprazolam from the tablets.

CONCLUSIONS

A method to recover alprazolam from tablets containing HPMC was developed. The method, which consisted of using hot water to swell the HPMC polymer, followed by adding cold water to completely dissolve HPMC, and then adding a strong solvent-ACN-to dissolve the alprazolam and extract the drug from the HPMC solution, was shown to be the most efficient and least variable method of achieving complete recovery of alprazolam from powder blends and tablets containing different excipient types and different

grades of HPMC. This method may be useful to recover other lipophilic drugs from hydrophilic matrix tablets containing HPMC.

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