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Original Article

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Preparation and In vitro Characterization of Alprazolam Extended- Release Tablets Using HPMC 4000cps

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Abstract

The main aim of this study was preparation and evaluation of extended - release system of the anxiolytic substance. Alprazolam is a short-acting benzodiazepine with general properties similar to those of diazepam. Our studies focused on development of extended drug delivery system based on Hydroxy Propyl Methyl Cellulose (HPMC 4000cps) as retard agent and Polyvinylpyrrolidone (PVP k30) as binder using factorial design. All prepared matrix tablets were considered for physicochemical evaluation and drug content. In vitro release study of matrix tablets for all formulations has shown that HPMC is the main component in retarding of alprazolam in dissolution medium. The optimum formulation (30% HPMC 4000 and 10% PVP) with suitable release profile according to criteria of United State Pharmacopoeia has selected for stability studies according to ICH guidelines.

Keywords: Alprazolam, Hydroxy Propyl Methyl Cellulose (HPMC 4000cps), Factorial design, Drug release

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Introduction

Alprazolam is a Triazolo analog of the 1, 4 Benzodiazepine class of central nervous system active compounds. Alprazolam is well absorbed from the gastrointestinal tract after oral doses, peak plasma concentrations being achieved within 1 to 2 hours of a dose. The mean plasma half-life is 11 to 15 hours. Alprazolam is 70 to 80% bound to plasma proteins, mainly albumin (Martindale, 2011). It is metabolized in the liver, primarily by the cytochrome P450 isoenzyme CYP3A4. Metabolites include α-hydroxyalprazolam, which is reported to be about half as active as the parent compound, 4-hydroxyalprazolam, and an inactive benzophenone. Plasma concentrations of metabolites are very low. Alprazolam is excreted in urine as unchanged drug and metabolites (Brayfield, 2011).

One way to achieve an oral extended release formulation is to mixing the active agent and the excipients with a hydrophilic polymer and compressing this into a matrix tablet. Moreover, Hydrophilic matrix sustained release dosage forms are drug delivery systems in which a therapeutic agent is dispersed in a compressed matrix made of water swellable polymers. When the tablet matrix exposed to aqueous medium, the surface of the polymer hydrates to form a viscous-gel layer. This gel layer formation and its stability, which defines the kinetics of drug delivery from matrix systems, are controlled by the concentration, viscosity and chemical structure of the polymer(s) (Varma et al. 2004). Hydroxy Propyl Methyl Cellulose (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. Controlled-release (CR) formulations have been introduced into drug therapy with two main purposes: to reduce the number of single doses per day that improving patient compliance of treatments and to decrease the fluctuations of plasma levels in order to obtain better therapeutic efficacy and lower toxicity (Aulton, 2007). Viriden et al. (2010) investigated the effect of substitution pattern of HPMC on polymer release from matrix tablets. These studies have shown that the compact components were domains of gel-like particles that at higher concentrations formed a more coherent network and thus would increase the viscosity. They suggested that a heterogeneous substitution pattern along the chain facilitates an amphiphilic behavior of the polymer, where more long-lived hydrophobic interactions between the chains can take place far below expected concentrations and precipitation temperatures for HPMC.

Model drug release from matrix tablets composed of HPMC with different substituent heterogeneity has studied (Viriden et al. 2010). The studies determined that batches with longer segments of low substituted regions and lower Hydroxypropoxylic content facilitated reversible gel-like structures that decreased the polymer erosion in matrix tablets. This lower erosion rate then decreased the drug release rate and released the drug by a more diffusion based release mechanism. This indicates that the gel-like structures might affect the robustness of the gel layer function in matrix tablets. Thus, it can be concluded from the present study that extensive polymer characterization is required to obtain predictable drug release rates from matrix tablets composed of HPMC batches.

Mahaguna et al. (2003) have investigated the influence of Hydroxypropyl methylcellulose polymer on in vitro and in vivo performance of controlled release tablets containing Alprazolam. In vivo clinical results indicated that molecular weight types and concentrations of HPMC did not influence in vitro or in vivo 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.

The purpose of this investigation was to develop controlled-release tablets of alprazolam by using HPMC 4000 cps as release retardant and Polyvinyl Pyrolydone (PVP k30) as binder using factorial design. Moreover, we decide to investigate the profile of release for different formulations

according to drug release monograph of alprazolam extended release tablet (USP 36).

Material and methods

Material and Equipment

Apparatus:

The High Performance Liquid Chromatography (HPLC) Younglin Acme 9000 HPLC was used for assay studies that were equipped with a 254-nm detector and a 4.6 mm x 15 cm;
5-μm packing L7 column. Peak identity was confirmed by comparison of spectra and retention time against of standard. Tablet hardness tester 5Y (Dr Schleuniger Pharmaton-USA), was used to measure the hardness of tablets. Tablet friability tester FR1000 (Dr. Schleuniger Pharmaton-USA) was used to determine the friability of the tablets. Tablet dissolution tester USP DT60 (Erweka-Germany) was used to do the release test and finally tablet compressing machine (Korsch-Germany) was used to press the tablets.

Chemicals:

Alprazolam and Hydroxy propyl methylcellulose 4000cps were provided as gifts by Hakim Pharmaceuticals Company, Iran. PVP k30, Lactose monohydrate, Magnesium stearate, Avicell PH102 and other materials used were obtained from faculty of pharmacy of Islamic Azad University.

Chromatographic conditions:

The mobile phase including Acetonitrile, water, and phosphoric acid with following ratios (350:650:1) was prepared. Standard and sample solutions were prepared according to assay method in USP monograph and injected to HPLC and the percentage of alprazolam based on the label claim, in the portion of tablets were calculated.

Methods

Preparation of Alprazolam extended release tablets

Alprazolam, Lactose monohydrate, HPMC (4000cps), half of Avicell PH 102, mixed not less than 15 minute. PVP was dissolved in 96º alcohol and then this solution was added to powder mixture to make a wet mass. The granules sifted to mesh No.14. The granules were dried and sifted with mesh No. 16. In next step, half of Avicell PH 102 and Magnesium stearate separately were added and mixed for 1-2 minutes.
The lubricated granules were compressed into tablets using 7.0 mm dip concave punch and keeping average weight of 100 mg. Tablets were obtained based on the 22 factorial design procedure that HPMC 4000cps concentration (X1) and PVP concentration (X2) were selected as independent variables (table 1) and the effect of these variables on drug release was also investigated.

Table I: Factors used in the factorial design experiment

Factor	Low level	High level
HPMC 4000 (%) (X1)	25	30
PVP (%) (X2)	5	10

The compositions of all model formulation are summarized in table 2. The percentage of drug release at 1, 4, 8 and 12 were selected (according to the USP 36 monograph) as response variables to detect the profile and ensure complete drug release. All formulations contain
2 mg of Alprazolam, 20% Avicell PH102, 1% magnesium stearate and X % of lactose monohydrate as filler to reach weight of each tablet to 100 mg.

Characterization studies:

Simultaneously in process quality controls such as weight variation, friability, hardness and thickness tests were carried out.

Table 2: The compositions of the model formulations

Formulations Ingredients	1 mg/tab	2 mg/tab	3 mg/tab	4 mg/tab	Function of each ingredient
Alprazolam	2	2	2	2	Active Ingredient
HPMC 4000 cps	25	30	25	30	Retarding Agent
PVP k30	5	5	10	10	Binder
Avicel PH102	20	20	20	20	Filler
Lactose Monohydrate	47	42	42	37	Filler
Mg Stearate	1	1	1	1	Lubricant

Drug release studies:

In vitro drug release of prepared alprazolam tablets was performed according to what described in United State Pharmacopoeia 36th, using apparatus I (100 rpm) at 37 C ± 0.5 in pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water; adjust with phosphoric acid). Samples were withdrawn in defined duration times and analyzed at wavelength 254 nm by HPLC that mentioned in USP monograph. The percentages of the labeled amount of Alprazolam released at the times specified was calculates that should be confirm to acceptance of USP monograph dissolution.

Stability studies:

The optimized formulation was subjected to stability studies according to ICH guideline (relative humidity (RH) of 75±5% and temperature 40±2 °C for 6 months as accelerated stability and RH of 60±5% and temperature 25±2 °C for 12 months as long-term stability).
The samples were taken at in determined intervals and were checked for physical changes, hardness, friability, drug content and drug release.

Result and discussion

Physicochemical characteristic

Tablets were compressed without any problem and do not require any change in ratio of excipients

in formulations. The pressed tablets were smooth, shiny and do not require coating as for experimental purpose (for patient compliance and palatability, aqueous polymer coating can be used). The result of physical tests are summarizes in tables 3 to 6. All formulations passed weight variation limit of 100 mg ±7.5%.

The friability for the all of formulation was not exceeded of 0.5% and it has shown that the tablets could be coated without any damage in tablet appearance. The limit of hardness was selected between 8-20 kp and all the tablet formulations were compressed in this limit without any sign of capping, chipping or lamination. The humidity of granules was selected below 3 percent for obtaining to suitable flowability and compression process. Mean drug content value for all formulations were obtained by assay procedure according to the USP monograph (data has not shown).

Table 3: Physical properties of formulations series 1 (n=3)

Factor Formulation	Humidity of granules (%)	Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
1(1)	2.5	98	2.5	12.9	0.23
1(2)	1.4	103	2.5	11.5	0.18
1(3)	2.9	105	2.6	13.5	0.13

Table 4: Physical properties of formulations series 2 (n=3)

Factor Formulation	Humidity of granules (%)	Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
1(1)	1.9	105	2.5	11.9	0.19
1(2)	2.3	102	2.6	15.6	0.27
1(3)	2.1	101	2.6	14.7	0.31

Table 4: Physical properties of formulations series 2 (n=3)

Factor Formulation	Humidity of granules (%)	Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
1(1)	1.9	105	2.5	11.9	0.19
1(2)	2.3	102	2.6	15.6	0.27
1(3)	2.1	101	2.6	14.7	0.31

Table 6: Physical properties of formulations series 4 (n=3)

Factor Formulation	Humidity of granules (%)	Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
1(1)	2.3	105	2.5	14.5	0.31
1(2)	1.9	103	2.5	16.6	0.29
1(3)	2.2	101	2.6	11.4	0.32

Dissolution studies:

The dissolution profiles of all model formulations required by the factorial design were shown in figure1 to figure 4. The responses of these formulations are summarized in Table 7.

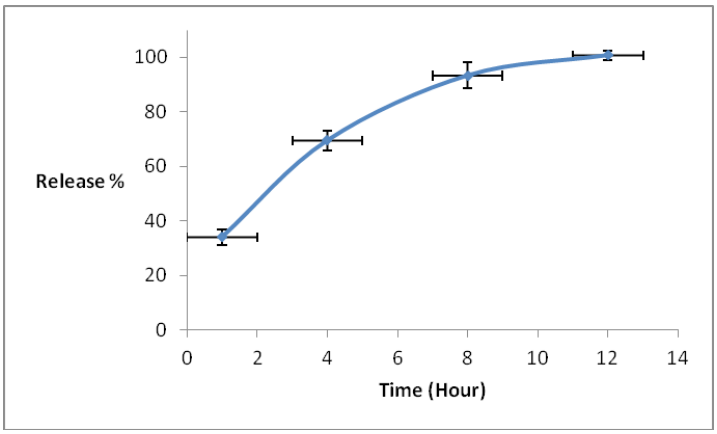

Figure 1: Release profile of alprazolam in series 1 formulations versus time (n=3)

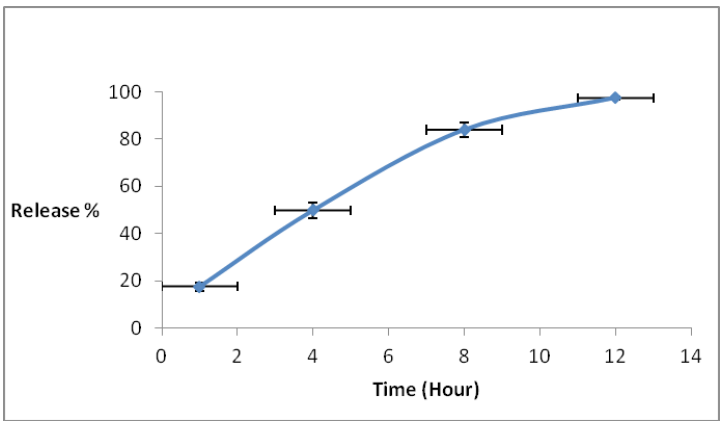

Figure 2: Release profile of alprazolam in series 2 formulations versus time (n=3)

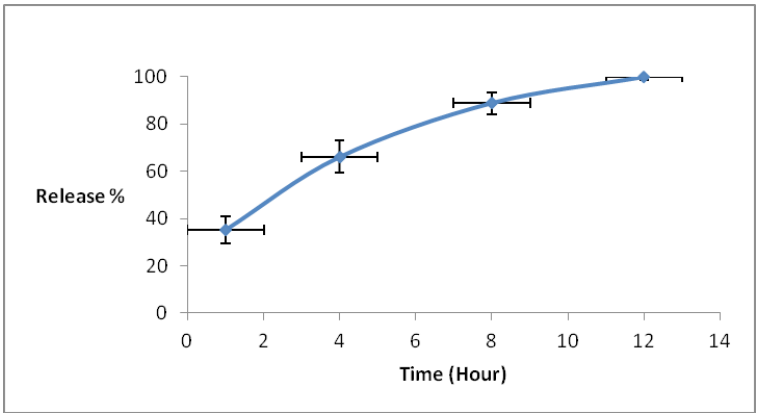

Figure 3: Release profile of alprazolam in series 3 formulations versus time (n=3)

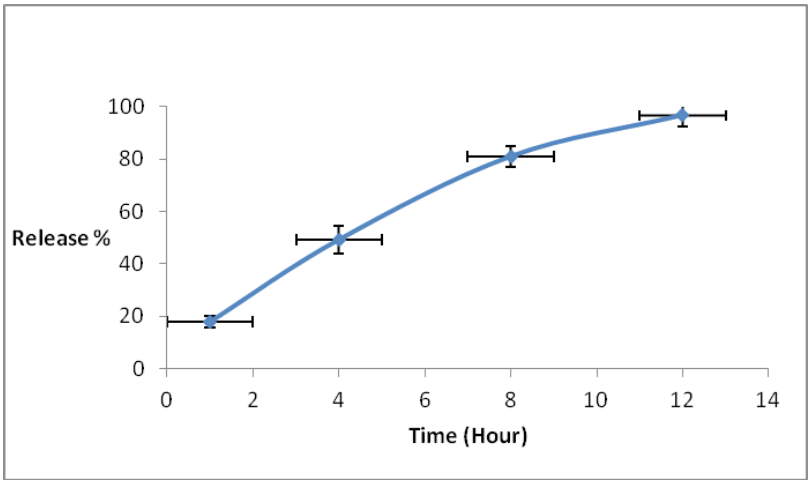

Figure 4: Release profile of alprazolam in series 4 formulations versus time (n=3)

Table 7: Drug release from different extended release of alprazolam formulations in defined times

Release (%) Time(hour)	1	2	3	4
1	33.97±2.79	17.63±1.69	35.23±5.77	17.87±2.03
4	69.47±3.76	49.82±3.23	66.10±6.83	49.20±5.29
8	93.3±4.77	83.83±3.09	88.87±4.67	80.93±3.79
12	100.73±1.80	97.33±0.77	99.90±1.08	96.67±4.53

By reviewing the drug profiles, it can be explained that the rate of drug release as well as the burst effect was decreased with an increase in the tablet content of HPMC4000 cps. Moreover drug release in formulation 2 (with HPMC at high level) is lower than drug release in formulations 1, and 3. Since the drug releases of formulation 2 is lower than the other two formulations, it

can be concluded that when HPMC 4000cps is at high level, the release of drug will be reduce significantly comparing to PVP as binder. It seems that HPMC 4000cps was the main parameter as rate limiting factor in release profile. Ravi et al. (2007) have investigated the design and study of Lamivudin oral controlled release tablets. In this study, HPMC4000 was used as retarding agent. The studies has shown that this polymer is able to retard the release of active agent from matrix tablet, as well by increasing the viscosity of polymer (high grade of HPMC) the slow release in Lamivudin would observed. In another study the prediction of drug release from HPMC 4000cps matrices was conducted by Fu
et al., (Fu et al., 2004). This investigation has shown that increasing HPMC concentration will decrease kinetic constant, so decrease release rate of a drug from HPMC matrices. The effect of HPMC concentration is also related with the solubility and molecular volume of a drug. Kiortsis et al. (2005) have studied about drug release from tableted wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component. The result of this investigation has shown that there is significant interaction between drug solubility and type of cellulosic polymer that able to alteration in the swelling of HPMC is caused by the drug solubility. Similarly, for the release rate, the most significant effect is that of drug solubility, followed by the type of the cellulosic polymer, the weight ratio of cellulosic–hydrophobic component, the mixing method and the drug mass fraction. The study of effect of varying the restriction degree of 4-aminopyridine release from HPMC matrices on the mechanism controlling the process was conducted (Martinez-Gonzalea et al. 2003). The studies have shown that a swellable hydrophilic matrix restricts drug release through formulation variables that include enlargement of the diffusion path length and reducing the drug diffusivity through the matrix. For a given polymer matrix its drug permeability increases as a function of time due to increasing polymer hydration. Moreover, every increase in the exposure to an aqueous environment increases hydration and dissolution of the polymer forming the matrix. Furthermore, the HPMC 4000cps dissolution rate increases with the time of exposure to the aqueous environment.

Phadatre et al. (2014) provides the maximum potency of HPMC 4000 used in various dosage form and current patent status review of HPMC as a release controlling polymer in extended release matrix systems. The studies data has shown that many diverse techniques have been used to study the mechanism of drug release from HPMC matrices and HPMC can be selected as the controlled release polymer of choice.

Formulation, release and stability study of Bupropion sustained release 150 mg us¬ing HPMC 4000 has done (Erfani et al. 2012). Bupropion sustained release matrix tablet was prepared successfully using HPMC 4000cps polymer by a 23 factorial design to retard the drug release and achieve an optimum dissolution profile. The results of this study showed that HPMC was the main determining factor in drug release and can be used for extended tablet preparation.

All the presented articles have shown that HPMC 40000cps is able to retard the release of active agent from matrix tablet and consequence, increasing HPMC 40000cps concentration will decrease kinetic constant, so decrease release rate of a drug from HPMC matrices that confirm our studies.

According to our investigation and the result of release profiles in matrix-tablet comprising drug, and hydrophilic polymer (HPMC), the release should follow three steps. In the first stage the outer surface of extended release tablet start to adsorption the aqueous medium and the gelling structure is formed due to swelling mechanism. For the drugs that have good solubility, this process may be in company with rapid releases of active agent. After a while, the gelling layer will be thickener and produce a diffusion layer for diffusion. In second step the integrity of gelling layer will be destroy and the outer surface will involve to erosion that cause to drug release. Dissolution is the third mechanism for drugs with different solubilities. Furthermore, active agent with good solubility pretends to release more than the other substanc-

es have weak solubility in dissolution medium. Moreover, the polymer hydration occurs in the following steps: 1) swelling 2) swelling/erosion and 3) disentanglement/dissolution. Regarding to alprazolam solubility (practically insoluble in water) each of above-mentioned mechanism may be involved in drug release that needs more tests to determine the rate limiting factor.

Assay Studies:

According to USP36, alprazolam extended-release tablet contained not less than 90% and not more than 110%. Assay studies were carried out on formulation 2 and the results showed acceptable drug contents (102.2%, data has not shown).

Stability studies:

Table 8 indicates the alprazolam assay of formulation 2 during accelerated stability test for Alprazolam. The accelerated stability test was done according to ICH guideline and the results of dissolution tests were satisfactory according to the monograph criteria. Data has shown for the third month and the samples were in chamber stability and the samples would take and test after the sixth month of stability.

Table 8: The result of assay test for formulation 2 during accelerated stability test

Time (month)	Onset	First month	Third month
Alprazolam assay	102.2%	99.3%	104.1%

Conclusion

Alprazolam sustained release matrix tablet was prepared successfully using HPMC 4000cps polymer by a 22 factorial design to retard the drug release and achieve an optimum drug release profile (formulation contains 30% HPMC and 10% PVP). This study revealed that HPMC 4000cps are able to retard the alprazolam to 12 hours according to USP monograph. The result has shown that the formulations contain PVP and HPMC 4000cps all in high level show the minimum percentage of release. Furthermore, the effect of HPMC as retarding agent is more than PVP in drug release. According to data and result of physicochemical tests such as hardness, friability, weight variation, assay and drug release, formulation 2 contains 30% HPMC 4000 and 10% PVP was selected as superior formulation.
For stability tests, the content of drugs did not show any changes after 3 months during accelerated stability test. The release profile of this formulation was found acceptable as recommended by USP.

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