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Original Article

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Preparation of Alprazolam Extended- Release Tablets and In vitro Characterization

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Abstract

The main aim of this study was to prepare and evaluate the extended - release system of an anxiolytic substance. Alprazolam is a short-acting benzodiazepine with general
properties similar to those of diazepam. Our studies focused on the 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 formulations were prepared according to wet granulation method and were compressed after lubrication using 7.0 mm dip concave punch with tablet weight of 100 mg. The humidity of granules was selected below 3 percent for obtaining to suitable flowability and compression process. Physical tests such as weight variation, friability, hardness, and thickness tests were carried out.The variables were studied based on 22 factorial design procedure. All prepared matrix tablets were evaluated for physicochemical evaluation and drug content. In vitro release study of matrix tablets for all formulations has shown that HPMC was the main component in retardation of alprazolam in the dissolution medium. The optimum formulation (30% HPMC 4000 and 10% PVP) with suitable release profile according to criteria of United State Pharmacopoeia was selected for stability studies, according to ICH guidelines. For stability tests, the content of drugs did not show any change after 3 months during accelerated stability test. The release profile of this formulation was found acceptable as recommended by USP. The release studies have shown that swelling, swelling/erosion, and disentanglement/dissolution were the most important mechanisms that could affect the release profile.

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

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Introduction

Alprazolam is a derivative of the 1,4 benzodiazepine class, which functions in the central nervous system. Alprazolam, after consumption, can be absorbed from gastrointestinal tract. The mean plasma half-life is about 11 to 15 hours and the peak plasma concentrations can be obtained within 1 to 2 hours of a given dose. 70 to 80% of alprazolam can be bound to plasma proteins, especially albumin (Martindale, 2011). Alprazolam is metabolized in the liver by the cytochrome p450 enzymes CYP 3A4. There are three metabolites: -hydroxyalprazolam is half active as alprazolam, 4-hydroxyalprazoalm, and benzophenone which are inactive molecules. However, these metabolites have very low concentrations. The excretion of the alprazolam happens as unchanged drug and metabolites in urine (Martindale, 2011)

One method for formulating oral extended release is to mix the active agent and the excipients with a hydrophilic polymer and then compress it into matrix tablet. In this type of drug delivery system (hydrophilic matrix sustained release dosage forms), the therapeutic agent is dispersed in a compressed matrix made of water swellable polymers. By exposing the tablet matrix to the aqueous medium, the surface of the polymer hydrates and forms a viscous gel layer. The kinetics of drug delivery from matrix systems is defined by this gel layer formation and its stability. Moreover, the release is controlled by concentration, viscosity and chemical structure or the polymer(s) (Verma et al. 2004). One of the widely used polymers in controlled released matrix tablets is Hydroxy Propyl Methyl Cellulose (HPMC). HPMC is a nonionic cellulose ether polymer. Two important factors that the hydration rate of HPMC depends on are molecular structure and the degree of substitution. Controlled-release (CR) formulations have been prepared into drug therapy for two main goals: First, to reduce the number of single doses per day, to improve patient compliance of treatment and second, to decrease the fluctuation levels of plasma to obtain the better therapeutic efficacy with lower toxicity (Aulton, M.E, 2008). Viriden et al. reviewed how substitution pattern of HPMC affect the polymer release from matrix tablets (Viriden et al. 2010). According to this study, the compact components were domains of gel-like particles. These particles in high concentration formed a more coherent network and as a result, the viscosity increased. They suggested that amphiphilic behavior of the polymer was facilitated by heterogeneous substitution.

Viriden et al. studied the different substituent heterogeneity in model drug delivery release from matrix tablets composed by HPMC (Viriden et al.2010). The studies demonstrated that as a result of longer segments of low substituted regions and lower hydroxypropoxylic content in batches, reversible gel-like structures could be facilitated and the polymer erosion in matrix tablets would decrease. The drug release rate decreased by the lower erosion and it seems like the drugs were mainly released by a diffusion based release mechanism. This emphasized that the gel-like structures might have had an effect on the robustness of the gel layer function in matrix tablets. Moreover, this can be concluded that characterization of the extensive polymer was required to get predictable drug release rates from HPMC, composed of matrix tablets in batches.

In vitro and in vivo performance studies have been done to observe the influence of hydroxypropyl methylcellulose polymer of controlled release tablets containing alprazolam by Mahaguna et al (Mahaguna et al.,2003). In vivo, clinical studies have shown that molecular weight types and concentrations of HPMC had no significant effect on the performance of controlled release tablets, which contains lipophilic alprazolam. Bioequivalent results in both fed and fasted states have been done by different HPMC

polymer types and concentrations of controlled release tablets.

The aim of this study was to develop controlled-release tablets of alprazolam by using HPMC 4000 cps as release retardant and Polyvinyl Pyrrolidone (PVP K30) as binder using factorial design. In addition, we investigated the drug release profile of alprazolam extended-release tablet according to 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 the 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 were mixed for more than 15 min. 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 1: Factors used in the factorial design of experiment

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

The compositions of all model formulation were 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 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:

Simultaneous 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 the description in United State Pharmacopoeia 36th, using apparatus I (100 rpm) at 37 C ± 0.5 in phosphate buffer with a pH of 6.0 (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water; adjusted with phosphoric acid). Samples were withdrawn in the defined duration of time and analyzed at a wavelength of 254 nm by HPLC, mentioned in USP monograph. The percentage of the labeled amount of alprazolam release, at specific times, was calculated according to the confirmed 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 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 did not require any changes in the ratio of excipients in formulations. The pressed tablets were smooth, shiny and did not require coating for experimental purpose (for patient compliance and palatability, the aqueous polymer coating can be used). The result of

physical tests was summarized in Tables 3-6. All formulations passed weight variation limit of 100 mg ±7.5%.

The friability for all of the formulation didn't exceed 0.5% and it has shown that the tablets could be coated without any damage to 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 was obtained by assay procedure according to the USP monograph (data was 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 formulation 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 5: Physical properties of formulation series 3 (n=3)

Factor Formulation	Humidity of granules (%)	Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)
1(1)	1.2	103	2.5	13.5	0.23
1(2)	1.8	99	2.5	12.6	0.34
1(3)	2.5	104	2.5	15.4	0.28

Table 6: Physical properties of formulation 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 Figure1-4. The responses of these formulations are summarized in Table 7.

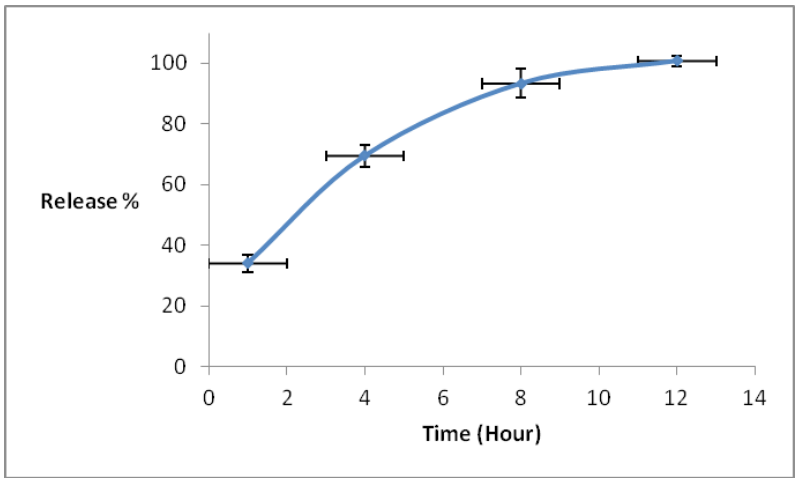

Figure1: Release profile of alprazolam in 1st formulation series versus time (n=3)

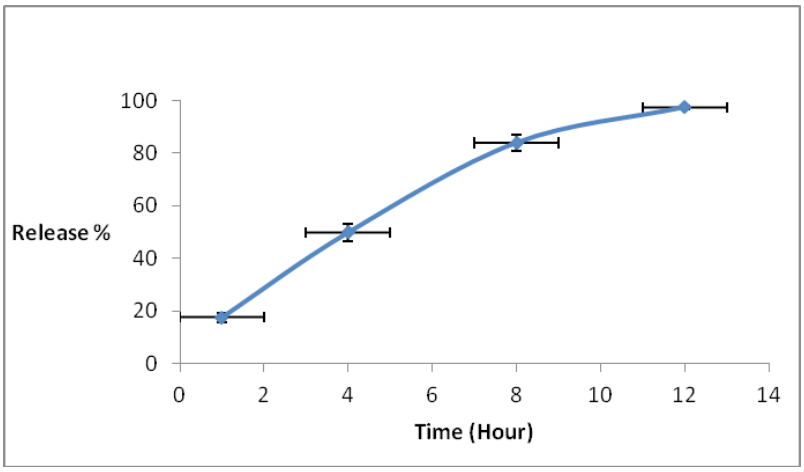

Figure2: Release profile of alprazolam in 2nd formulation series versus time (n=3)

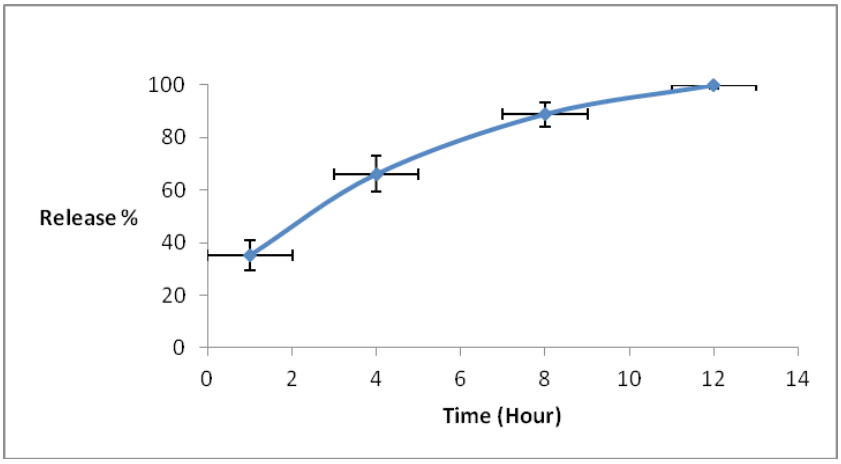

Figure3: Release profile of alprazolam in 3rd formulation series versus time (n=3)

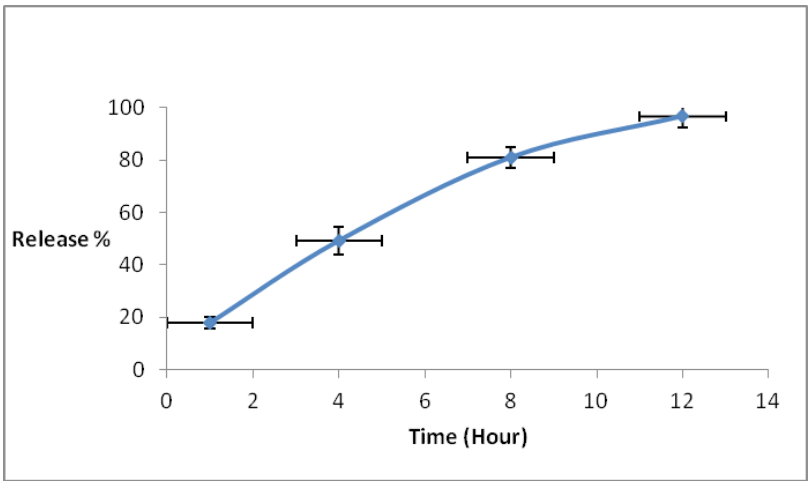

Figure4: Release profile of alprazolam in 4th formulation series versus time (n=3)

Table 7: Drug release from different extended release alprazolam formulations at 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 (at a high HPMC level) was lower than drug release in formulations

1, and 3. Since the drug release of formulation 2 was lower than the other two formulations, it could be concluded that when HPMC 4000cps be at a high level, the release of the drug would decrease significantly, comparing to PVP as a binder. It seems like HPMC 4000cps was the main parameter as rate limiting factor in release profile. Ravi et al., have investigated the designation of lamivudine oral controlled release tablets. In this study, HPMC4000 was used as the retarding agent. The studies have shown that this polymer was able to retard the release of active agent from matrix tablet by increasing the viscosity of the polymer (high grade HPMC), so that the slow release of lamivudine was observed (Ravi et al., 2007). 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 would decrease kinetic constant,so that it would decrease release rate of a drug from HPMC matrices. The effect of HPMC concentration is also related to the solubility and molecular volume of a drug. Kiortsis et al., have studied about drug release from tableted wet granulations comprising cellulosic (HPMC or HPC) and hydrophobic component (Kiortsis et al., 2005). The result of this investigation has shown that there is a significant interaction between drug solubility and type of cellulosic polymer that enables alteration in the swelling of HPMC, 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 the effect of various restriction degrees of 4-aminopyridine release from HPMC matrices on the mechanism, controlling the process, was conducted by Martinez-Gonzalea et al., (Martinez-Gonzalea et al., 2003). The studies have shown that a swellable hydrophilic matrix restricted drug release through formulation variables such as 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. provides the maximum potency of HPMC 4000 used in the various dosage form and current patent status review of HPMC as a release controlling polymer in extended release matrix systems (Phadtare et al., 2014). The data has shown that many diverse techniques have been used to study the mechanism of drug release from HPMC matrices; 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 was done by Erfani (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 the 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 a drug, and hydrophilic polymer (HPMC), the release should follow three steps. In the first stage, the outer surface of extended release tablet start to adsorb to the aqueous medium and the gelling structure is formed due to the swelling mechanism. For the drugs that have good solubility, this process may be in company

with rapid releases of the active agent. After a while, the gelling layer will be thicker and produce a diffusion layer for diffusion. In the second step, the integrity of gelling layer will be destroyed and the outer surface will erode leading to drug release. Dissolution is the third mechanism for drugs with different solubilities. Furthermore, an active agent with good solubility pretends to get released more than the other substances that have a weak solubility in the dissolution medium. Moreover, the polymer hydration occurs in the following steps: 1) swelling 2) swelling/erosion and 3) disentanglement/dissolution. Regarding 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 contains 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 desirable according to the monograph criteria. Data has shown no significant changes for the third month and the retained 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 successfully was developed by using HPMC 4000 cps. We used different percents of the polymer by 22 factorial design to retard the drug release and to reach an optimum drug release profile (30% HPMC and 10% PVP are used in this formulation). This study demonstrated that HPMC 4000 cps were able to extend the release of alprazolam to 12 hours according to USP monograph. The result has indicated that the formulation which contains PVP and HPMC 4000 cps all at high levels, show the minimum percentage of release. Moreover, the effect of HPMC as a retarding agent is more than PVP in drug release. According to the result and obtained data in physiochemical tests such as hardness, friability, weight variation, assay and drug release, formulation 2 contains 30% HPMC 4000 and 10% PVP was selected as modified and superior formulation.

According to accelerated stability tests, we didn't observe any changes in the content of drugs after 3 months. So the release profile of this formulation was found acceptable according to release test mentioned in USP.

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