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Original Article

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Formulation and Evaluation of Extended- Release Tablet of Zolpidem Tartrate by Wet Granulation Technique

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Abstract

The goal of this study was to design and evaluate extended - release system of the hypnotic agent, Zolpidem tartrate usefulness for the treatment of insomnia. The half-life of this drug is about 1.9 - 3 hours that indicating it a candidate for the extended release formulation. Our investigation relates to development of extended drug delivery system based on Hydroxy propyl methyl cellulose (HPMCK4M) as release retardant, polyvinyl pyrrolidone (PVP k30) as binder and Magnesium Stearate using Factorial design. In vitro release study of matrix tablets was carried out in 0.01N HCl for 2 hours. All prepared matrix tablets were evaluated for physicochemical evaluation and drug content. The formulation that had release profile according to United State Pharmacopoeia selected for stability study according to ICH guidelines.

Keywords: Zolpidem tartrate, Wet granulation, Hydroxy propyl methyl cellulose (K4M), Factorial design, ICH guideline

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Introduction

Controlled-release (CR) formulations have been introduced into drug therapy with two main purposes: to reduce the number of single doses per day 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). Zolpidem is a non-benzodiazepine analogue of Imidazopyridine class. Zolpidem tartrate is a GABA agonist (sedative and hypnotic) used in the treatment of insomnia dosing ranging from 5 to 12.5 mg. The half-life of the drug is about 1.9 to 3 hr. and oral bioavailability is 72 ± 7 % (Goodman & Gilman, 1966). Because of short half-life, Zolpidem tartrate has indication for treatment of Insomnia characterized by difficulties with sleep onset (Karwa & Kasture, 2011). Thus extended release form of Zolpidem tartrate can be helpful for having extended sleep and be fresh on the next morning in comparison with benzodiazepine (Kirkwood et al. 2007).

Wet granulation of powder is primarily carried out to improve the flow and compatibility of a tablet compression mix, and it is probably the most common means of tablet production. The reason for its popularity is that just about any drug of any dose can be processed successfully by wet granulation (Chein, 1992).

The purpose of this investigation was to develop controlled-release tablets of Zolpidem tartrate by using Hydroxy propylmethyl cellulose (HPMC K4M) as release retardant, Polyvinyl Pyrolydone (PVP k30) as binder and Magnesium stearate using factorial design. We use this method to understand the effect of these three components in release profile of Zolpidem tartrate tablets.

Material and methods

Material and Equipment

Apparatus:

The High Performance Liquid Chromatograph (HPLC) Younglin Acme 9000 HPLC was used for assay studies and was equipped with a 240- nm detector and an 4.6- mm × 15- cm column that contains 5μmm packing L1. The HPLC was performed at room temperature. Peak identity was confirmed by comparison of spectra and retention time with those of standard. Tablet hardness tester 5Y (Schleuniger Pharmaton-USA), was used to measure the hardness of tablets. Tablet friability tester FR1000 (Schleuniger Pharmaton- USA) was used to determine the friability of the tablets. Tablet dissolution tester USP DT60 (Erweka-Germany) was used to measure the release, and finally tablet compressing machine (Lorsch-Germany) was used to press the tablets.

Chemicals:

Zolpidem tartrate was obtained from Osveh Pharmaceuticals Company, Iran. Hydroxy propyl methylcellulose K4M was obtained from Darupakhsh Pharmaceutical co., 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 was consisted of Acetonitrile, methanol and Buffer* with following ratios (4:5:11).

*Buffer: 3.3 mL of phosphoric acid in 1 L of water, pH adjustment with triethylamine at 5.5.

The mobile phase, Buffer and sample solution were always filtered using 0.45μm membrane filters. The flow rate and run time were 1ml/min and about 13 minutes, respectively.

Methods

Preparation of Zolpidem controlled release tablets

Zolpidem tartrate, Lactose monohydrate, HPMC (K4M), half of Avicell PH 102, mixed not less than 15 minute. The binder solution consists of water and PVP k30 made our mixed powder to granules. Our granules sifted to mesh no.14. After giving time to our granules to get dry, sifted them to mesh no. 16. Adding extra granular components (half of Avicell PH 102 and Magnesium stearate) separately and mixing them was at this step.

The lubricated granules were compressed into tablets using 7.0 mm dip concave punch and keeping average weight of 150 mg. The composition of all prepared formulations is summarized in Table 1 and 2.

Table 1: Composition of different formulations. series A

Ingredients (%)	Formulation code							
	c(A4)	b(A3)	a(A2)	1(A1)	bc(A7)	ac(A6)	ab(A5)	abc(A8)
HPMC (K4M)	7.5	7.5	15	7.5	7.5	15	15	15
PVP (k30)	2.5	5	2.5	2.5	5	2.5	5	5
Mg-St	4	2	2	2	4	4	2	4

Table 2: Composition of different formulations. series B

Ingredients (%)	Formulation code							
	1(B1)	a(B2)	b(B3)	c(B4)	ab(B5)	ac(B6)	bc(B7)	abc(B8)
HPMC (K4M)	5	7.5	5	5	7.5	7.5	5	7.5
PVP (k30)	2.5	2.5	5	2.5	5	2.5	5	5
Mg-St	2	2	2	4	2	4	4	4

All formulations contained 6.25 mg of Zolpidem tartrate, 30% Avicell PH102 and X% of Lactose monohydrate as filler to reach 150 mg (the weight of each tablets).

Characterization studies:

Simultaneously in process quality controls like weight variation, friability, hardness and thickness test were carried out.

Dissolution studies:

In Vitro Dissolution study of prepared Zolpidem tablets was performed according to what described in United State Pharmacopoeia 35thed., using apparatus I (100 rpm) at 37 ° C ± 0.5 in HCl 0.01 N as medium for 2 hours in test 3 of drug monograph. Samples were withdrawn and analyzed at wavelength 237 nm with spectrophotometer. Percentage drug release was calculated using an equation obtained from calibration curve which is developed in the range of 2 to 15 μg/ml.

Assay studies:

The percentages of the Zolpidem tartrate in best formulation were analyzed by HPLC method. To prepare assay stock, 8 tablets were transferred to a suitable volumetric flask and 70% of the flask volume, mixture of alcohol and hydrochloric acid 0.01 M with ratios of 5:2 was added. The mixture was diluted with alcohol to volume. Finally sample solution

prepared with 0.1 mg/mL of Zolpidem tartrate from above solution in Mobile phase. Standard solution also prepared with 0.1 mg/mL of USP Zolpidem tartrate RS in Mobile phase.

Stability studies:

The optimized formulation was subjected to stability study according to ICH guideline (relative humidity (RH) of 75±5% & temperature 40±2 for 6 months: Accelerated Stability and RH of 60±5 & Temp. 25±2 for 12 months: Long-term Stability). The samples are taken at intervals of 3 months and check for physical changes, hardness, friability, drug content and drug release.

Result and discussion

Physicochemical characteristic

The result of physicochemical tests are summarizes in Table 3 and 4.All formulations passed weight variation limit of 150 mg ±7.5%.

Table 3: Physicochemical properties of series A ,s formulations.

Parameters	Thickness(mm.)	Hardness(kp)	Friability(%)
1 (A1)	3.09± 0.12	9.13±0.43	0.23
a (A2)	3.08±0.13	8.25± 0.42	0.18
b (A3)	3.04± 0.06	9.65± 0.57	0.3
c (A4)	3.07±0.08	9.15± 0.47	0.41
ab (A5)	3.09± 0.07	10.55± 0.49	0.22
ac (A6)	3.04± 0.05	9.4± 0.51	0.31
bc (A7)	3.02± 0.04	10.2± 0.46	0.28
abc (A8)	3.04±0.08	9.2± 0.42	0.28

Table 4: Physicochemical properties of series B ,s formulations.

Parameters	Thickness(mm.)	Hardness(kp)	Friability(%)
1 (B1)	3.12± 0.01	9.4± 0.41	0.33
a (B2)	3.2± 0.03	8.25± 0.42	0.23
b (B3)	3.14± 0.01	10.7± 0.38	0.21
c (B4)	3.02± 0.02	9.6± 0.51	0.5
ab (B5)	3.21± 0.02	9.65± 0.57	0.3
ac (B6)	3.23± 0.01	9.15± 0.47	0.41
bc (B7)	3.02± 0.12	10.8± 0.6	0.24
abc (A8)	3.01± 0.03	10.2± 0.46	0.28

Dissolution studies:

The results of release profiles are shown in Table 5, 6. Figures 1 and 2 illustrate the release profiles of all formulations and with consideration on Table 7, the best formulation that fit with USP35 limits, were selected.

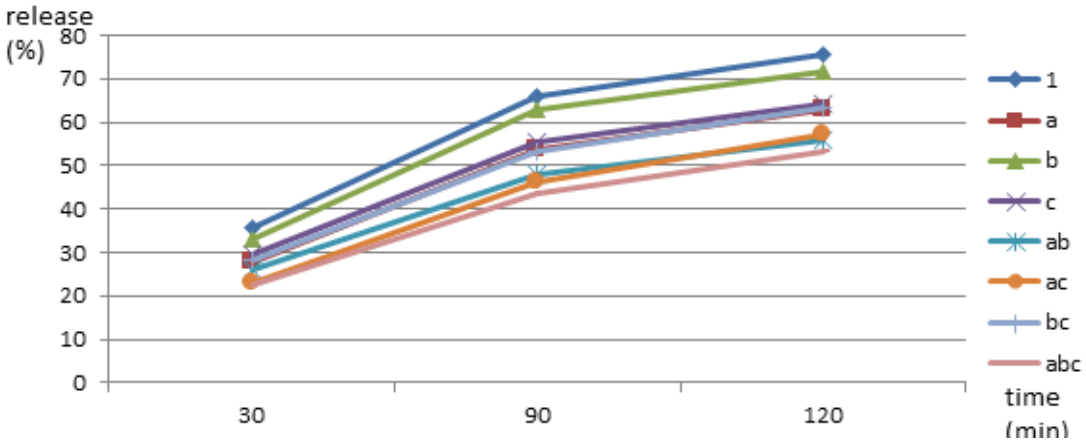

Figure 1: Release profile of Zolpidem tartrate in series A ,s formulations versus time at wavelength 237 nm.

Table 6: Percentage of drug release versus time in series B ,s formulations.

Time (min.) Release (%)	0	30	90	120
1 (B1)	0	43.57± 1.18	77.01± 0.82	87.07± 1.89
a (B2)	0	35.51± 2.01	65.94±0.18	75.70± 1.09
b (B3)	0	38.03± 1.01	71.05± 0.89	82.33± 1.9
c (B4)	0	35.47± 0.76	66.36± 0.78	76.35± 1.1
ab (B5)	0	32.91± 0.91	62.91± 0.67	71.71± 1.07
ac (B6)	0	29.54± 0.86	55.48± 0.81	64.08± 0.67
bc (B7)	0	32.31± 0.91	63.38±0.29	72.56± 0.8
abc (B8)	0	28.26± 1.03	53.03± 1.8	63.34±1.1

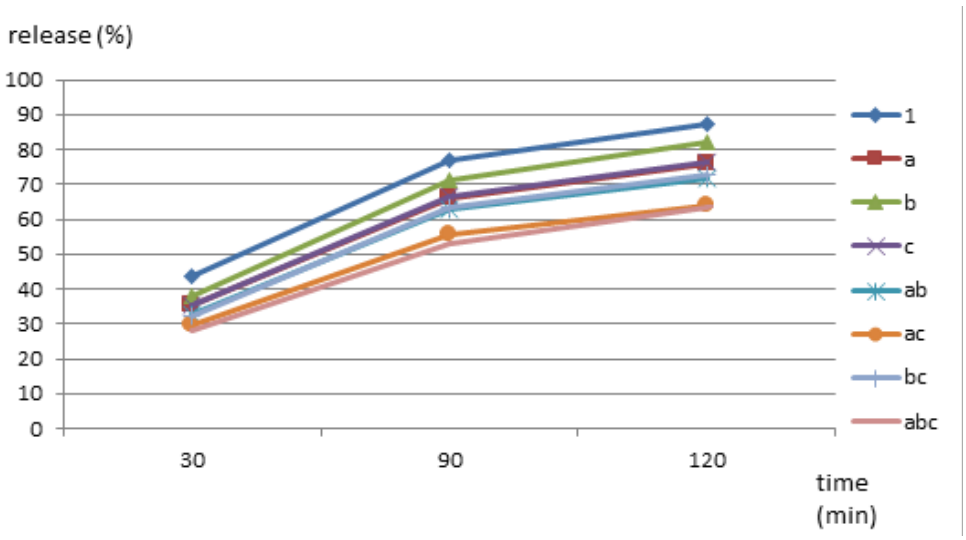

Figure 2: Release profile of Zolpidem tartrate in series B ,s formulations versus time at wavelength 237 nm.

Table 7: Percentage of drug release versus time at test 3 of Zolpidem tartrate extended release monograph in United State Pharmacopeia 35th ed (USP, 2012).

Time (min.)	Release (%)
30	25-45
90	65-85
120	NLT80

The situation of test 3 has described in method section. According to the dissolution results, B1formulation successfully passed test 3 rules, thus chosen for Stability studies.

Assay Studies:

According to USP35 Zolpidem tartrate extended-release tablet contained not less than 90% and not more than 110%. Assay studies were carried out on B1formulation and the results showed acceptable drug contents (99.33%).

Stability studies:

Table 8 indicates the drug content of B1 formulation during accelerated stability test for Zolpidem tartrate. After accelerated stability test, dissolution tests were done and the results were satisfactory and according to the guidelines. Table 9 represents the release percentages of drug and Figure 3 shows release profile of B1 formulation after accelerated stability studies in sixth months.

Table 8: The result of assay test of B1 formulation during accelerated stability test.

Time (month)	Onset	First month	Third month	Sixth month
Active ingredient content	99.33%	108%	104.1%	105.5%

Table 9: Percentage of drug release versus time from B1formulation after six month under accelerated stability studies conditions.

Release (%) Time (min.)	First month	Sixth month
30	43.57± 1.18	44.37± 0.89
90	77.1± 0.82	80± 1.8
120	87.07± 1.89	89.19± 1.1

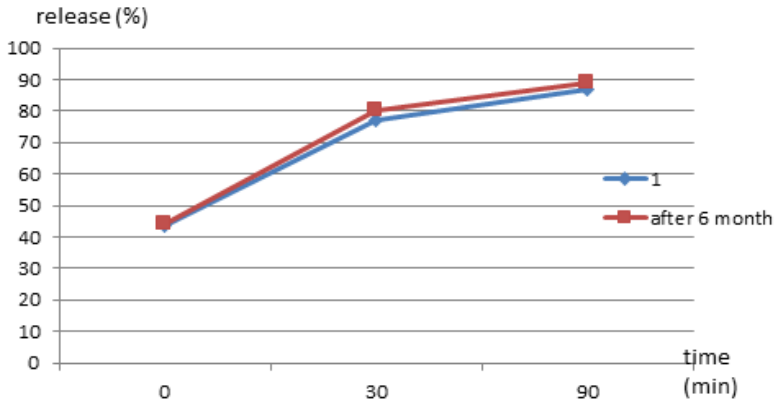

Figure 3: Release profile of Zolpidem tartrate from B1 formulation before and after stability studies.

Conclusion

This study revealed that HPMC K4M can extent release of drug to 4 hours in our 3concentrations. The formulation contain PVP, mg-st and HPMC all in high level have lower percentage of release. The effect of HPMC is more than mg-st and mg-st is more than PVP k30 in drug release. Weight variation for different formulations found to be 150±7.5% that is in range of USP pharmacopeia. Hardness measured according to official methods and friability was below 1% for all the formulations that indicating good mechanical resistance. The percentage of drug content of the selected formulation was 99.33±0.21%. The B1formulation passed all physicochemical, dissolution, assay and stability test. The content of drugs did not change after 6 months during accelerated stability test. The release profile of this formulation was found acceptable as recommended by USP.

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