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ORIGINAL RESEARCH ARTICLE

Formulation And Evaluation Of Zolpidem Tartrate Extended Release Matrix Tablets

M.Karthikeyan*[1],A.Arunachalam[2], N.Ravikiran[3],S.Ashutosh kumar[1], P.Eswaramma[4] , S.Manidipa[1]

1. Department of Pharmaceutics, AKRG College of Pharmacy, West Godavari, Andhrapradesh
2.Department of Pharmaceutics Sasikanth reddy College of Pharmacy, Nellore, Andhrapradesh
3. Department of Pharmaceutics, Dr.Reddy's Lab.Hyderabad, Andrapradesh.
4. Department of Pharmaceutics, Vaagdevi College of Pharmacy, Gurzala, Andhrapradesh.

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Abstract:

In the present study, to establish oral extended release tablets of Zolpidem tartrate using different polymers. The tablets were prepared using HydroxyPropyl Methylcellulose tartaric acid, cellulose, microcrystalline, lactose, anhydrous, magnesium stearate different polymers to impart extended release study. Tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, IR spectral analysis, *in vitro* release studies, and kinetic analysis of dissolution data, stability studies and pharmacodynamic activity. The present study concludes that extended release tablets of zolpidem tartrate can be a good way to increases the dissolution and bioavailability of zolpidem tartrate and also showed significant anti-ulcer activity in rats.

Keywords: Zolpidem tartrate, extended release tablets, *in vitro* Release study, Pharmcodymanic study.

INTRODUCTION:

The drug, zolpidem tartrate is a white to off-white crystalline powder. It is a non-benzodiazepine [1], sedative-hypnotic for the short-term treatment of insomnia. Although chemically unrelated to other hypnotics such as the benzodiazepines or barbiturates, zolpidem tartrate does share some pharmacological actions with these drugs. Unlike the benzodiazepines, zolpidem tartrate produces muscle relaxation and anticonvulsant effects only at doses much higher than the hypnotic dose [2-4]. Hence, at such higher doses, zolpidem tartrate is used in the treatment of antipsychotic induced Parkinsonism. It acts on benzodiazepine receptors. Although, zolpidem tartrate has a different structure and is said to be more selective in its action, it has similar effects to the benzodiazepines. The drug is rapidly absorbed and peak plasma levels are reached within 3h. First-pass metabolism reduces bioavailability to 70%. The liver also eliminates most of the drug with only 1% appearing unchanged in the urine. A lower dose is recommended for the elderly and patients with hepatic impairment. It has a half-life of 2h, but its hypnotic effect can last up to 6h. It has a rapid onset of action and should only be taken immediately before retiring. It has a short half-life and has no active metabolites, which reduces the possibility of residual next day effects from prolonged or excessive sedation. CNS depression with impairment of cognitive and motor function, commonly seen with barbiturates or long-acting benzodiazepines in the treatment for insomnia, is not common with zolpidem tartrate. In the present investigation extended release tablets of zolpidem tartrate were prepared by different polymers using HydroxyPropyl Methylcellulose tartaric acid, cellulose, microcrystalline, lactose, anhydrous, magnesium stearate. The aim of the work was to evaluate the effect of extended release properties and release characteristics of zolpidem tartrate tablets.

MATERIALS AND METHODS

Materials

Zolpidem tartrate was received as a gift sample from Fourrts (India) Pvt Ltd. Chennai. India.

***Corresponding Author:** M.Karthikeyan, **Email:** steaje@gmail.com, **Contact No:** 09989567617

HPMC 2208 [5-10] ,Pharmatose DCL121, Avicel pH102, were received as gift samples from Loba Chemie Pvt. Ltd; Mumbai, India. Metolose 90SH4000SR was purchased from Paxmy speciality chemicals, Chennai.India. Tartaric acid [11-15] was procured from S.d. fine chemical, Pvt., Ltd, Mumbai, India. Cellulose, microcrystalline [16-20] were purchased from S.D. fine – chem. Pvt., Ltd, Mumbai .India. All other ingredients were of laboratory grade.

Methods

Preparation of Floating Tablets of Zolpidem tartrate:

Table: 1.Compositoion of Zolpidem tartrate Tablets

	Dry mixing mg/ tablet				
Ingredients used	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Zolpidem tartrate	6.305	6.305	6.305	6.305	6.305
Pharmatose DCL121	60.00	60.00	60.00	60.00	66.00
Avicel pH102	34.595	40.195	45.195	49.195	52.195
Tartaric acid	12.60	12.00	12.00	12.00	12.00
Metolose 90SH 4000SR	35.00 (23%)	30.00 (20%)	25.00 (16%)	21.00 (14%)	18.00 (12%)
Magnesium stearate	1.5	1.5	1.5	1.5	1.5

Average Weight of the tablet = 150 mg

The composition of different formulations of zolpidem tartrate floating tablets is shown in Table **1**. Five Trial formulations of extended release tablets of zolpidem tartrate using polymers such as Pharmatose DCL121, Avicel pH102, Metolose 90SH 4000SR , Magnesium stearate were prepared by Dry mixing method. Metolose90SH4000,Pharmatose DCL21 and AvicelpH102 act as a Release controlling Polymer and Diluents, Avicel pH102 tartaric acid, HPMC 2208 through 40 mesh sieve Sift magnesium stearate through 60 mesh sieve and Load the sifted materials into hexagonal double cone Blender and mix zolpidem tartrate with pharmatose . Geometrically with Pharmatose DCL21 and Avicel pH102 and min for 5 minutes at slow speed Add HPMC 2208 and mix it for 10 minutes add tartaric acid and mix it for 5 minutes , Add Sifted magnesium stearate and Mix for 2 minutes at fast speed. Then Compress the lubricated blend in a cadmach Compression machine with 7.1mm N/C Plain punches

Dissolution rate studies:

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900ml pH 7.4, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5^o C and rpm of 50. One zolpidem tartrate tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Samples measuring 10ml were withdrawn after every 1 hour up to 10 hours using 10 ml pipette. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with pH7.4 and analyzed at 265 nm using pH7.4 as blank. The percentage drug release was calculated and shown in Figure.1, 2.

Stability studies:

Stability studies were aimed at determining the result of aging and storage under various conditions on the formulated extended release tablets. It was carried out to evaluate the stability of zolpidem tartrate in formulated tablets after storing at different temperatures for 45 days. The prepared tablets were kept at three different temperatures 4^o C ±2 ^{o} C, 27^o C ±2^o C and 45^o C ±2^o C for 45 days at RH 75±5%. At 15 days intervals the tablets was evaluated for all physical parameter. The results are showed in table 7.

RESULTS AND DISCUSSION:

The bulk density [21-23] of all formulations was measured by using measuring cylinder. The bulk density was found in the range of 0.26 – 0.31 gm/cm^3. The tapped density was found in the range of 0.30 – 0.35 gm/cm^3. The angle of repose of all the formulations was within 30^{o}C. The CI of all the formulations exist in the range between 8.08-18.59%.It indicates that the granules showed good flow character. The result of the hausner ratio of all the formulations is between 1.08-1.147. The result indicates that all formulations show good flow property. The values are showed in table 2.

Evaluation of ER Zolpidem tartrate Tablets

The formulated extended release tablets were evaluated for various physico chemical parameters. The formulated tablets were evaluated for organoleptic characters. The tablets are circular in shape white in color, with no characteristic odour. All the tablets showed elegance in appearance. Oral tablets normally have a hardness of 4-10kg/cm^2. The hardness of the tablets of the all formulations was within the range of 4-5kg/cm^2. The percentage deviation is ±7.5% for more than 130mg tablet.The results are presented in Table 3. The result showed that the percentage of zolpidem tartrate in all formulations was ranging from 95-99%. It revealed that the drug is uniformly dispersed in the formulations and confirms the homogeneous mixing of the drug and the polymer.

DRUG-EXCIPIENTS COMPATABILITY STUDIES

The active ingredient (Zolpidem tartrate) with various excipients in 1:1 and 1:10 and 1:0.25 ratio were taken in glass vial and kept at various conditions (40^{0}C/75%RH and 60^{0}C/80%RH) in stability chamber (Newtronic walkin Humidity chamber, India).The study is carried out in open and closed glass vials for a period of 1Month. The samples were withdrawn at intervals of 7, 15 and 30 days and characteristic like colour change, water content and Related substances was recorded. Finally the compatible mixtures were selected for formulation. At the each week the samples were withdrawn and analyzed for any color change. Chemical compatibility was confirmed by FT-IR spectrometry.

ASSAY:

Preparation of Standard Solution:

Weigh accurately 0.062g of Zolpidem tartrate working standard into a 100 ml volumetric flask, add 70 ml of mobile phase, shake and sonicate to dissolve the content and make up the volume with mobile phase. Pipette 5ml of resulting solution to 50 ml volumetric flask and make up the volume with mobile phase. Filter the solution through 0.45µm membrane filter.

Table: 2.Evaluation of Zolpidem tartrate Granules with Different Polymers

PHYSICAL PARAMETER	TRIAL1	TRIAL2	TRIAL3	TRIAL4	TRIAL5
Angle of Repose	33^0.28’	30^0.30’	28^0.10’	27^0.45’	28^0.50’
Bulk density In g/ml	0.269	0.272	0.284	0.306	0.318
Tapped density in g/ml	0.331	0.308	0.326	0.333	0.352
Compressibility Index	18.59%	11.71%	12.85%	8.08%	9.43%
Hausner’s ratio	1.228	1.132	1.147	1.08	1.104
Flow	Fair	Good	Good	Excellent	Excellent

*All values are average of 5 determinations.

Preparation of Sample solution:

Weigh and powder 20 tablets. Weigh accurately about 6.25g of powdered tablet equivalent to about 6.25 mg of Zolpidem tartrate into a 100 ml volumetric flask, add 70 ml of mobile phase sonicate and shake for 10 minutes to dissolve the contents and make the volume with mobile phase. Filter the solution through whatman no: 41 filter paper. Collect the filtrate after discarding the first 20 ml of the filtrate. Pipette out 5 ml of resulting solution to 50 ml volumetric flask and make up the volume with mobile phase. Filter the solution through 0.45µm membrane filter. Collect the filtrate.

Procedure:

Separately inject 20µm of filtered portion of the standard preparation and sample preparation into the chromatograph. Record the chromatogram and measure the response for all the major peaks. Calculate the content of Zolpidem tartrate in mg per tablet.

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Stability studies [24-25]

Zolpidem tartrate extended release tablets (all 5 formulations) were stored at refrigerated temperature ($4^o \pm 2^oC$), room temperature ($27^o \pm 2^oC$) and in programmable environmental test chamber ($45^o \pm 2^oC$) for 30 days. At the end of 3 months of storage, the extended release tablets were observed for changes in physical appearance, analyzed for drug content and subjected to Dissolution studies and the result are present in Table.4, 5.

STABILITY STUDIES:

The formulation was tested for 3 months at the storage conditions of room temperature and 40^0 C at 75 % hr, was analyzed for their drug content including physical parameters. The residual drug contents of formulations were found to be within the permissible limits as shown in the Table - 4, 5. No appreciable changes were found in their physical parameters. The tablets showed satisfactory physical stability at room temperature and 40^0 C at 75 % rh. The physical appearance did not change considerably.

TEST	Limits	INITIAL	1 Month	2 Months	3 Months
Appearance	White, circular, biconvex, uncoated extended release tablets	Satisfactory	Satisfactory	Satisfactory	Satisfactory
Average weight	About 150mg	151mg	151	150 mg	150 mg
Hardness	3-7 kg/cm^2	5 kg/cm^2	4.5kg/cm^2	4.5 kg/cm^2	4.5/cm^2
Dissolution					
1st hour	Between 40-60%	55.2%	52.2%	50.2%	47.2%
2th hour	Not less than 60%	80..5%	75..5%	73.5%	70.5%
4th hour	Not Less Than 80%	98.5%	95.5%	935%	90.5%
Related substance Individual impurity Total impurity	Not more than 0.5% Not more than 1.0%	Below detectable limits	Below detectable limits	Below detectable limits	Below detectable limits
Assay : Each tablet Contains:	5.625mg to 6.785 mg (90.0%-110% of the	6.32mg (101.2%)	6.30mg (100.9%)	6.26 (100.1%)	6.26 (100.1%)
Zolpidem tartrate Remarks	labeled amount)	Complies	Complies	Complies	Complies

Table:3 : COMPARITIVE *IN-VITRO* RELEASE STUDIES

S. NO	TIME HOURS)	LIMIT(%DRUG RELEASE)	TRIAL-1	TRIAL-2	TRIAL-3	TRIAL-4	TRIAL-5
1	1	Between40-60%	25.4	30.6	34.2	45.2	54.4
2	2	Not less than 60%	45.7	49.8	54.5	58.4	70.3
3	4	Not less than 80%	54.2	59.9	65.7	78.2	100

Figure: 1: COMPARITIVE *INVITRO* RELEASE STUDIES

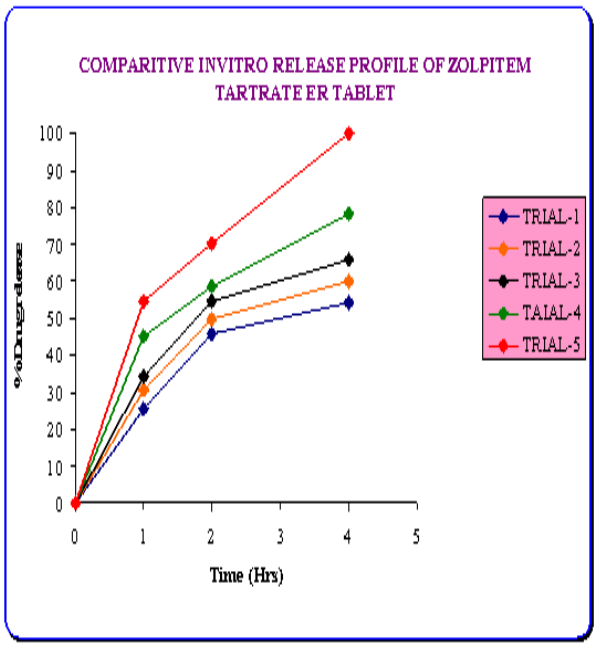


Table: 5. Drug content estimation after storing at Different Temperatures

TEST	LIMITS	3 Months
Appearance	White, circular, biconvex, uncoated extended release tablets About 150mg	Satisfactory
Average weight	5.0kg/cm^2	150 mg
Hardness	Between 40-60%	4.5/cm^2
Dissolution 1st hour 2th hour 4th hour Related substance Individual impurity	Not less than 60% Not Less Than 80% Not more than 0.5% Not more than 1.0% 5.625mg to 6.785 mg	47.2% 70.5% 90.5% Below detectable
Total impurity	(90.0%-110% of the	limit
Assay : Each tablet Contains: Zolpidem tartrate	labeled (amount)	6.26 (100.1%)

*All values are expressed as mean ± standard deviation, n =5

TABLE-7 Assay of Zolpidem Tartrate

Materials	Area	Percentage found
Standard sample	2635111	
Test sample	2621736	99.58%
Trial No:1	2672341	6.184(98.94%)
Trial No:2	2612843	6.210(99.36%)
Trial No:3	2532145	6.162(98.59%)
Trial no:4	2652312	6.190 (99.04%)
Trial no:4	2632122	6.224 (99.58%)

Figure: 2 PEAK AREA PLOT OF ZOLPIDEM TARTRATE STANDARD

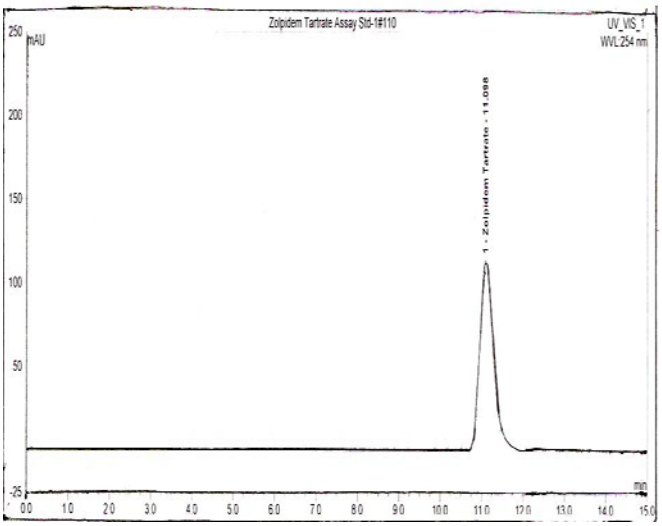
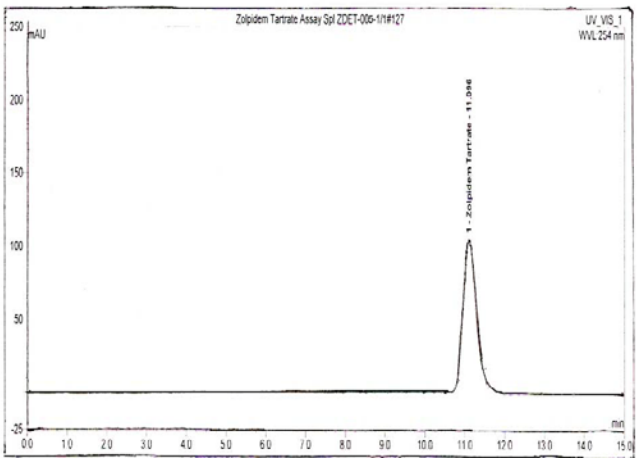


Figure: 3 PEAK AREA PLOT OF ZOLPIDEM TARTRATE SAMPLE



***Corresponding Author:** M.Karthikeyan, **Email:** steaje@gmail.com, **Contact No:** 09989567617

Teble:8. Stability studies:

S. No.	Drug+ Excipients	Ratio	Initial (Dry Aqueous Non-Aqueous)	Conditions			
				40^0C/75%RH		30^0C/60%RH	
				7 days	14 days	30 days	comments
1	Zolpidem tartrate+pharmatoseDCL21	1:10	A white or almost white crystalline powder	No change	No change	No change	compatible
2	Zolpidem tartrate +avicel pH102	1:10	A white or almost white crystalline powder	No change	No change	No change	compatible
3	Zolpidem tartrate+ dicalcium phosphate	1:10	A white or almost white crystalline powder	No change	No change	No change	compatible
4	Zolpidem tartrate+ maize starch	1:10	A white or almost white crystalline powder	No change	No change	No change	compatible
5	Zolpidem tartrate+ METOLOSE 90SH4000SR	1:1	A white or almost white crystalline powder	No change	No change	No change	compatible
6	Zolpidem tartrate+ HPMC6CPS	1:1	A white or almost white crystalline powder	No change	No change	No change	compatible
7	Zolpidem tartrate+ tartaric acid	1:1	A white or almost white crystalline powder	No change	No change	No change	compatible
8	Zolpidem tartrate+ citric acid	1:1	A white or almost white crystalline powder	No change	No change	No change	compatible
9	Zolpidem tartrate+ Magnesium stearate	1:0.25	A white or almost white crystalline powder	No change	No change	No change	compatible
10	Zolpidem tartrate+ Zinc stearate	1:0.25	A white or almost white crystalline powder	No change	No change	No change	compatible
11	Zolpidem tartrate+ Talc	1:0.25	A white or almost white crystalline powder	No change	No change	No change	Compatible

Result: According to the physical Drug-Excipient compatibility study it was found that the polymer as well as the excipients selected were compatible with the drug zolpidem tartrate. So the excipients and polymers were selected for formulation.

Assay- by HPLC method The assay was carried out according to the procedure given. The peak area plot of Zolpidem tartrate standard is given Zolpidem tartrate optimized formulation (Trial 5)

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CONCLUSION:

Zolpidem tartrate extended release systems prepared by using direct compression as showed good tabletting properties like weight variation, thickness, diameter and hardness, friability.All Controlled released systems showed good extended elease property of the drug .Especially pharmatoseDCL21,avicel pH102,dicalcium phosphate, maize starch, and METOLOSE 90SH4000SR containing extended release systems may be considered to release zolpidem tartrate even up to acceptable limits. Thus the excipients and the relative proportions of them used in this experiment are proved successful and effective in designing extended release systems.

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