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Research Article

DEVELOPMENT AND EVALUATION OF FILM COATED EXTENDED RELEASE ZOLPIDEM TARTRATE TABLET BY DIRECT COMPRESSION TECHNOLOGY

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ABSTRACT

The goal of this study was to design and evaluate extended release system of the hypnotic agent Zolpidem (ZP) useful for the treatment of insomnia. The present work relates to development of extended drug delivery system based on polymers as a release retardant and film coaters to increase the overall bioavailability and patient compliance. Zolpidem tartrate was prepared by direct compression technique, using Carbopol 974 P NF (as release retardant) and Pharmacoat 603, PEG(as film coaters),and evaluated for various evaluation parameters. All the formulations showed compliance with pharmacopoeia standards. The in vitro release study of matrix tablets was carried out in 0.01 N HCl for 8 hrs. Among all the formulations, F-5 shows 99.32% better sustained release at the end of 8 hrs. The release mechanism from the matrix tablets of Zolpidem tartrate was non-Fickian diffusion and drug release from all formulations follows first order kinetics. The formulation F-5 shows drug release profile matched to the marketed product (Ambien CR). Stability studies were carried out according to ICH guideline which indicates that formulation F5 was stable.

Keywords: Zolpidem tartrate; Carbopol 974 P NF; Matrix tablets; Sustained release; HPMC

INTRODUCTION

Insomnia is one of the most common disorders in medical practice and, for its treatment, there are, nowadays, a lot of pharmacological agents.[1] In this regard, some benzodiazepines are the drugs of choice because they possess negligible side effects and toxicity. However, the long-term treatment of insomnia with benzodiazepines is problematic since it results in the development of tolerance and dependence.[2] Further improvement in the management of insomnia and other sleep disorders resulted after the recent introduction of non-benzodiazepine hypnotics such as zolpidem, zoplicone, and zaleplon.[1] In particular zolpidem, *N*,*N*-dimethyl-[2-(4-tolyl)-6-methylimidazo[2,1-*a*]pyridine- 3-yl] acetamide (ZP), exhibits strong hypnotic and sedative actions with negligible anxiolytic, muscle relaxant, or anticonvulsant properties, is widely prescribed for the treatment of the insomnia and sleep disorders.[3] In the management of short-term insomnia, ZP has a rapid onset of action but a short elimination half-life (about 2.5 h).[3] In this context, researchers have demonstrated that withdrawal of but not long-term exposure to ZP resulted in change of GABAA gene expressions.[4] Therefore, to elucidate the potential of ZP in the treatment of different insomnia categories, it could be useful to develop formulations enabling sustained-release of this drug.

The aim of the present work was to prepare extended release Zolpidem Tartrate (12.5 mg) tablets using Carbopol 974 P NF was investigated. Further film coating was done with HPMC (Pharmacoat 603) and PEG 400 Moreover, Direct compression is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations due to its simplicity and easy scale up. In recent years, direct compression has also been successfully employed in the development of CR formulations. Hence, the purpose of present investigation was to develop controlled release tablet of Zolpidem tartrate by using Carbopol 974 P NF as a matrixing agent, HPMC (Pharmacoat 603) and PEG 400 as a film coating agent respectively, which would release the drug for prolonged period of time in view to maximize therapeutic effect of the drug and in an effort to expand the coverage of sleep complaints and overcome the lack of efficacy in sleep maintenance.

MATERIALS AND METHOD

Materials

Zolpidem tartrate was procured from Tripada Pharmaceuticals Ltd., Ahmedabad, India. Carbopol 974 P NF was obtained from Indoco pharma, Mumbai, India. PEG 400 and HPMC (Pharmacoat) were obtained from S.D. Fine hemicals, Mumbai India. Lactose, Magnesium stearate, and talc were purchased from Shakti Chemicals, Mehsana, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Preparation of Zolpidem controlled-release tablets

Zolpidem Tartrate was shifted from mesh no.80 then Lactose DCL 15, Carbopol 974 P NF sifted through mesh no. 60 separately. All the sifted ingredients mixed thoroughly by using octagonal blender, for not less than 15 min, until to get uniformly mixed powder The resulting Blend was mixed with previously sifted Magnesium Stearate through sieve no. 60. And mixed thoroughly by using cone blender for not less than 15 min. to get uniform granules The lubricated granules were compressed into tablets using 8.0 mm dip concave punch with 8 station single rotary Rimek machine and keeping average weight of 250 mg. Simultaneously in process quality controls like weight variation, Friability, Hardness test were carried out, After compression dissolution and assay were carried out.

Table1: Composition of different formulations

Ingredients	Formulation code				
	F1	F2	F3	F4	F5
Zolpidem tartrate (mg/tablet)	12.5	12.5	12.5	12.5	12.5
Lactose DCP 15	230	228.74	227.5	226.25	225
Carbopol 974 P NF	5.0	6.25	7.5	8.75	10
Magnesium stearate	2.5	2.5	2.5	2.5	2.5

Preparation of film coating solution

In warm purified water dissolve Indigo carmine and add Pharmacoat 603 (HPMC) slowly in it. Then add previously sifted through 80 # titanium dioxide, were stirred for 15 min. then add PEG 400 (polyethylene Glycol) to that solution and mixed well. Finally added IPA and mixed well, and homogenized for 15 min to get the desired solution. Coating pan was cleaned with distilled water and then washed with isopropyl alcohol and air dried at about 40 – 50 ^{0}C. Tablets were to be coated, placed into that cleaned, dried pan and dried about 40 ^{0}C for around 10 mins. Prepared film coating solution was then allowed to spray (4 kg / cm^3) and was to be continued until to get the proper coating and polished by talc. Finally tablets were dried at around 45 ^{0}C for some time and then transferred into a clean dried plastic drum and send for packing.

Table2: Coating formula for 1000 tabs

Ingredients	Quantity (gm)
Pharmacat603(HPMC)	3.750
Titanium dioxide	1.860
Indigo Carmine	0.200
PEG 400(polyethylene Glycol	0.370
Iso propyl alcohol	0.145
Water	0.065

Table3: instrumental parameters for tablet manufacturing.

Specification	Film coated
Coating pan	Bectochem
Pan rpm	25rpm
Atomizing air pressure	4 kg/cm^{2}s
Inlet air temperature	58^{0}C
Out air temperature	45 ^{0}C
Bed temperature	55 ^{0}C
Pre drying in pan	10 mins, 40 ^{0}C
Final drying in pan	10 mins, 40^0 – 50 ^{0}C
Post drying in pan	5mins 80 ^{0}C
Relative Humidity	75 %

Fig. 1: Film coated tablet

EVALUATION

Characterization of powder blend

Granules prepared for compression of controlled release tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range of 29.54 ± 0.12º to 32.64 ± 0.38º which indicates better flow of the powder for all formulations. The bulk density of the granules formulation was in the range of 0.564 ± 0.01 to 0.594 ± 0.018 gm/ml; the tapped density was in the range of 0.722 ± 0.08 to 0.752 ± 0.12 gm/ml, which indicates that the powder was not bulky. The Compressibility index was found to be in the range of 18.8 ± 0.12 to 23.53 ± 0.29%, indicating compressibility of the tablet blend is good. These values indicate that the prepared granules exhibited good flow properties.

Table 4: Granule properties of formulations F1 to F5

Parameters	F1	F2	F3	F4	F5
Angle of repose(°)	29.53±0.10	31.92±0.21	31.72±0.31	32.64±0.32	32.64±0.38
Bulk density(g/ml)	0.592±0.02	0.583±0.01	0.564±0.01	0.573±0.03	0.576±0.0
Tapped density(g/ml)	0.733±0.01	0.736±0.02	0.723±0.07	0.725±0.02	0.754±0.12
Compressibility index	18.7±0.13	21.0±0.15	21.8±0.08	20.9±0.22	23.54±0.29

Evaluation of Tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods.

Physical Characterization

The fabricated tablets were characterized for weight variation (n = 20), hardness (n = 6) Pfizer hardness tester (Janki Instrument Ltd, Ahmadabad, India), thickness using a screw-gauge micrometer (Campbell Electronics, Mumbai, India), and % friability (n = 20, Roche friabilator, Electrolab, Mumbai, India).

Physicochemical evaluation of sustained release tablets

The controlled release Zolpidem tartrate tablets were off-white, smooth, and concave shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of controlled release tablets were measured by vernier caliper and were ranged between 5.51 ± 0.01 and 5.53 ± 0.01 mm.

Weight variation for different formulations were found to be 300.3 ± 0.903 to 300.7 ± 1.379 mg, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the controlled release tablets were measured by Monsanto tester and controlled between 7.1 ± 0.17 and 7.5 ± 0.06 kg/cm. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F6 was found to be in between 98.05 ± 0.92 to 100.1 ± 0.29 % of Zolpidem tartrate it complies with official specification. The results are shown in table 5.

Drug Content

Five tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with 0.01 N HCl and followed by phosphate buffer (pH 6.8; 900 mL) the solution was filtered through 0.45 µ membranes. The absorbance was measured at 237 nm after suitable dilution. The results are shown in table5

Table5: Tablet properties of formulation F1 to F5

Parameters	F1	F2	F3	F4	F5
Thickness(mm)	5.52±0.01	5.52±0.03	5.52±0.03	5.54±0.01	5.54±0.02
Hardness(kg/cm2)	7.4±0.01	7.2±0.11	7.3±0.02	7.1±0.18	7.5±0.05
Friability (?)	0.194	0.205	0.226	0.208	0.243
Drug content	99.23±0.31	98.92±0.37	98.04±0.90	100.1±0.19	98.33±0.3

***In Vitro* Dissolution Study**

The *in vitro* dissolution study of Zolpidem tablets (n = 3) was performed as described in Indian Pharmacopoeia 2010 using USP apparatus II (model TDT-08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at 37 ◦ C ± 0.5 ◦ C using simulated gastric fluid (pH 1.2; 900 mL) as a dissolution medium for first 2 hours and followed by phosphate buffer (pH 6.8; 900 mL) for remaining hours. At the predetermined time intervals, 10-mL samples were withdrawn and analyzed at 238 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative

Percentage drug release was calculated using an equation obtained from a calibration curve which is developed in the range of 2–16 μg/ml for 0.1 N HCl and pH-6.8 phosphate buffer.

Stability Studies

The optimized formulation was subjected to stability study at 40 ± 2ºC and 75 ± 5% RH for 90 days. The samples were withdrawn at intervals of fifteen days and checked for physical changes, hardness, friability, drug content and percentage drug release.

FT-IR spectrum

The IR spectrum of the Zolpidem Tartrate tablet shows the peaks at following values which are characteristic of the drug. 3380 cm^{-1}- O-H stretching, 1646 cm^{-1}- C=O stretching for carbonyl, 2900 cm^{-1} aliphatic C-H stretching. The IR spectrum of the Carbopol 974 P shows the peaks at following values which are characteristic of the polymer. 3116 cm^{-1}- O-H stretching, 1712 cm^{-1}- C=O stretching for carbonyl, 2956 cm^{-1} aliphatic C-H stretching,1247 cm^{-1} C-O stretching for carboxylic acid

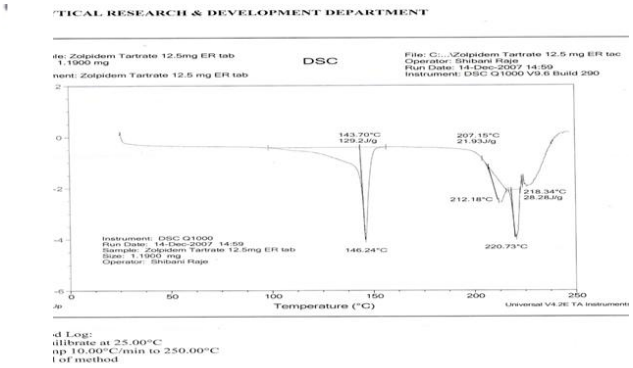

Fig 2: Dissolution Profiles of developed matrix tablets f1 to f5 and comparison with Ambien Cr

***In vitro* release study**

In vitro dissolution studies of all the formulations of Zolpidem tartrate sustained release tablets were carried out in 0.01 N HCl. The study was performed for 24 hrs. The higher initial drug release was observed in tablets containing various concentrations of Carbopol 974 P NF. This showed that in less concentration Carbopol 974 P NF hydrated more rapidly in the presence of 0.01 N HCl. The variation in drug release was due to different concentrations of polymer in all the 5 formulations. When % drug release was plotted versus time (figure 4), it was observed that for increase in polymer concentration from 2%-6%, a decrease in the release rate. The results of the dissolution studies for formulations F1, F2, F3, F4, F5 and marketed formulation Ambient CR are shown in the figure-4. Formulations F1, F2, F3 and F4 released 98.13%, 98.96%, 99.79% and 99.02% of drug at the end of 1.5 hrs, 2 hrs, 4 hrs and 6 hrs, respectively. Marketed formulation Ambient CR released 98.66% of drug at the end of 8 hrs. Formulation F5 sustained drug release 99.32% at the end of 8 hrs. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration

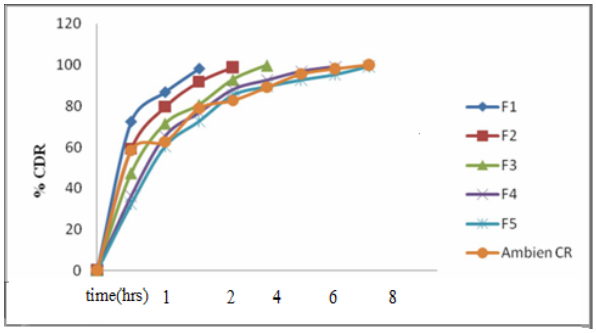

Fig 3: *In Vitro* drug release profile

Kinetics

In order to describe the kinetics of release process of drug in all formulations, various equations were used, such as the zero-order rate equation, which describes the systems where the release rate is independent of concentration of dissolved species.[5] The first-order equation describes the release from systems where dissolution rate is dependent on concentration of the dissolving species.[6] The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to rate of drug diffusion.[7] The Korsmeyer-Peppas equation is used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release phenomena could be involved.[8]

The applicability of all these equations was tested in this work. The kinetic data for all the formulations were shown in Table 4 The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of the drug release (Table 4). The regression coefficient (R) obtained from first-order kinetics were found to be higher (R^2 : 0.914 to 0.976) when compared with those of zero-order kinetics (R^2 : 0.815 to 0.872), indicating that the drug release from all the formulations followed first-order kinetics. All the formulations in this investigation could be best expressed by Higuchi's classical diffusion equation, as the plots showed high linearity (R^2: 0.965 to 0.993) indicates that the drug release follows diffusion mechanism. To confirm the diffusion mechanism, the data were fitted into Korsmeyer–Peppas equation. All the formulations showed good linearity (R^2 : 0.925 to 0.998) with slope (n) values ranging from 0.522 to 0.595, indicating that non-Fickian diffusion (anomalous) was the predominant mechanism of drug release from all the formulations. Hence, diffusion coupled with erosion might be the mechanism for the drug release from Carbopol 974 P NF based sustained release matrix tablets

Table 6: Kinetic values obtained from different plots of formulations F1 to F5 and Ambien

Formulations	Zero order Plot	First order plot	Higuchis plot	Korsmeyer et al's plot	
	R^2	R^2	R^2	R^2	R^2
F1	0.815	0.966	0.972	0.997	0.525
F2	0.838	0.946	0.984	0.992	0.596
F3	0.872	0.914	0.994	0.985	0.578
F4	83	0.973	0.973	0.935	0.528
F5	82	0.93	0.966	0.926	0.569

Zero order equation, C=K t, First order equation, Log C=log C-Kt/2.303, ●Higuchi's equation ; Q= Kt½, □Korsmeyer etal's equation, Mt/Ma= Ktn.

CONCLUSION

Matrix tablets containing Zolpidem tartrate can be prepared successfully by using direct compression technique. The matrix tablets were found to be effective in sustaining the drug release up to 8 hrs. Among all the formulations, F5 showed 99.32% release at the end 8 hrs. The formulation F-5 shows the release profile closer to that of Ambient CR The drug release follows first order kinetics and the mechanism was found to be diffusion coupled with erosion. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable. FT-IR studies revealed that there was no interaction between Zolpidem tartrate and other excipients used in the tablets. The results suggest that the developed sustained release tablets of Zolpidem tartrate could perform better than conventional dosage forms, matched with the Ambien CR, leading to improve efficacy and better patient compliance. Thus, the aim of this study was achieved.

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