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Formulation and *In Vitro* Evaluation of Sustained Release Matrix Tablet of Zolpidem Tartrate

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Abstract: In this present study, matrix tablet of Zolpidem tartrate was prepared by direct compression technique, using Carbopol 974 P NF as release retardant. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. All the formulations showed compliance with pharmacopeial standards. The *in vitro* release study of matrix tablets was carried out in 0.01 N HCl for 4 hrs. Among all the formulations, F-5 shows 99.32% better sustained release at the end of 4 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.
Key words: Zolpidem tartrate, Carbopol 974 P NF, Matrix tablets, Direct compression, Sustained release.

Introduction

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy, for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1] Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects.[2] Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug.[3]

Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class used for the treatment of insomnia. The biological half-life of Zolpidem tartrate is 2.9 hours.[4] Sustained release delivery systems for oral dosing are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration which eliminate rapidly.[5] Carbopol 974 P NF is less water permeable and hydrophobic property utilization in the preparation of sustained release matrix tablets for water soluble drug such as Zolpidem tartrate. In the present investigation sustained release tablets of Zolpidem tartrate were prepared by different concentrations of Carbopol 974 P NF. The aim of the work was to evaluate the effect of sustained release properties and release characteristics of Zolpidem tartrate tablets.

Material and Methods

Materials

Zolpidem tartrate obtained from Aarti Drugs Ltd. Carbopol 974 P NF was procured from
Research Lab Fine Chem. Industries Mumbai.. All other ingredients used were of analytical grade.

Formulation and Preparation of Matrix Tablets

Matrix tablets were prepared by direct compression method. The composition of various formulations is given in Table 1. Zolpidem tartrate, Lactose DCL 15 and Carbopol 974 P NF were mixed in a polybag and the mixture was passed thourgh mesh no. 60. The resulting blend was mixed with previously shifted magnesium stearate through mesh no. 60 in polybag for 5 min. to get uniform granules. Tablets were compressed at 300 mg weight on a 10-station rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 8.0 mm dip concave shaped punches. Five different formulas, having different concentrations of Carbopol 974 P NF (2%, 3%, 4%, 5% and 6%), were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Evaluation of Granules

The angle of repose was measured by using funnel method, which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= weight of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in Table 2.[6,7]

Evaluation of Tablets

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 3.[6,7]

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 the solution was filtered through 0.45 µ membranes. The absorbance was measured at 237 nm after suitable dilution.

in vitro Drug Release Study

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electrolab, Mumbai, India) at 100 rpm. The dissolution medium consists of 500 ml of 0.01 N HCl, maintained at 37 $\pm$ 0.5^0C. The drug release at different time intervals was measured using an UV spectrophotometer (Labindia, Mumbai, India) at 237 nm. The study was performed in triplicate.

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.[8]

Table 1: Composition of different formulations

Ingredients (mg/tablet)	Formulation code				
	F1	F2	F3	F4	F5
Zolpidem tartrate	12.5	12.5	12.5	12.5	12.5
Lactose DCL 15	279.25	276.25	273.25	270.25	267.25
Carbopol 974 P NF	6	9	12	15	18
Magnesium stearate	2.25	2.25	2.25	2.25	2.25

Table 2: Granule properties of formulations F1 to F5

Parameters	F1	F2	F3	F4	F5
Angle of repose (°)	29.54 ± 0.12	31.94 ± 0.24	31.74 ± 0.32	32.64 ± 0.34	32.64 ± 0.38
Bulk density (g/ml)	0.594 ± 0.018	0.582 ± 0.04	0.564 ± 0.01	0.572 ± 0.03	0.575 ± 0.05
Tapped density (g /ml)	0.732 ± 0.02	0.737 ± 0.01	0.722 ± 0.08	0.724 ± 0.02	0.752 ± 0.12
Compressibility index	18.8 ± 0.12	21.0 ± 0.16	21.8 ± 1.08	20.9 ± 0.23	23.53 ± 0.29

Results and Discussion

FTIR Spectroscopy

The pure drug Zolpidem tartrate and the solid admixture of drug and various excipients used in the preparation of sustained release tablet formulations were characterized by FT-IR spectroscopy to know the compatibility. As shown in figure 1-3, there was no significant difference in the FT-IR spectra of pure Zolpidem tartrate and optimized formulation.

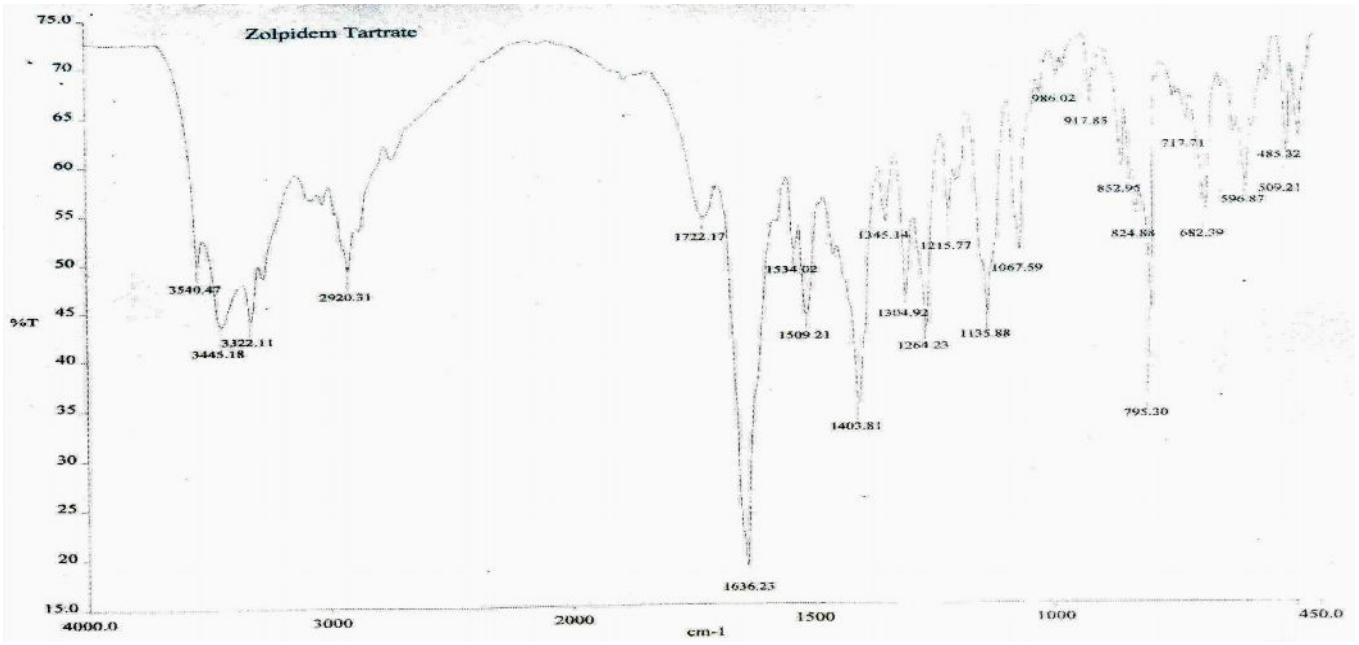

Figure 1: FTIR Spectroscopy of pure drug

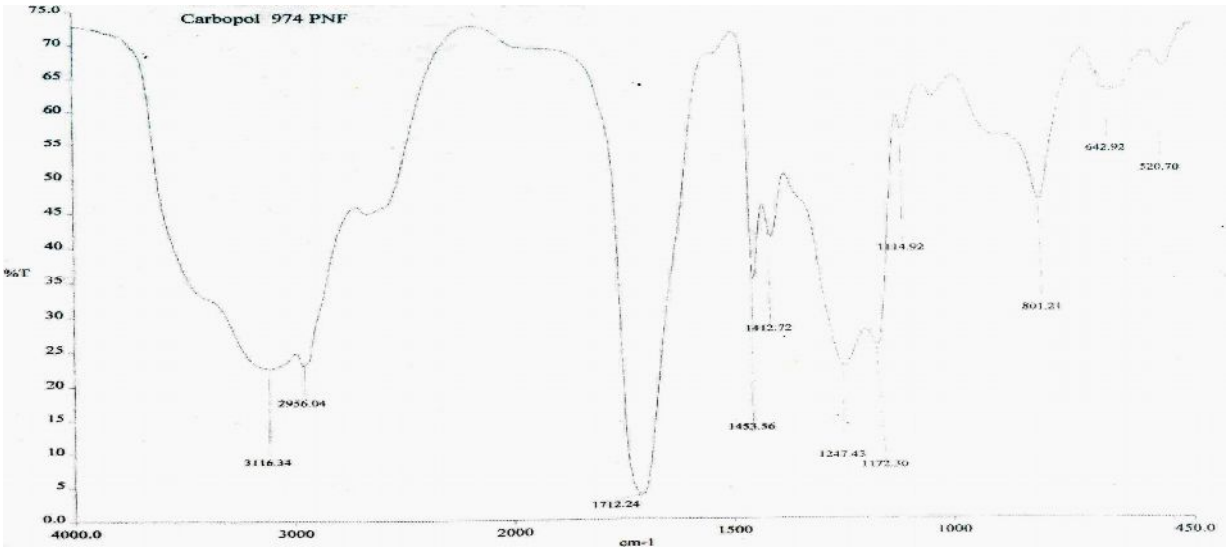

Figure 2: FTIR Spectroscopy of Carbopol P NF

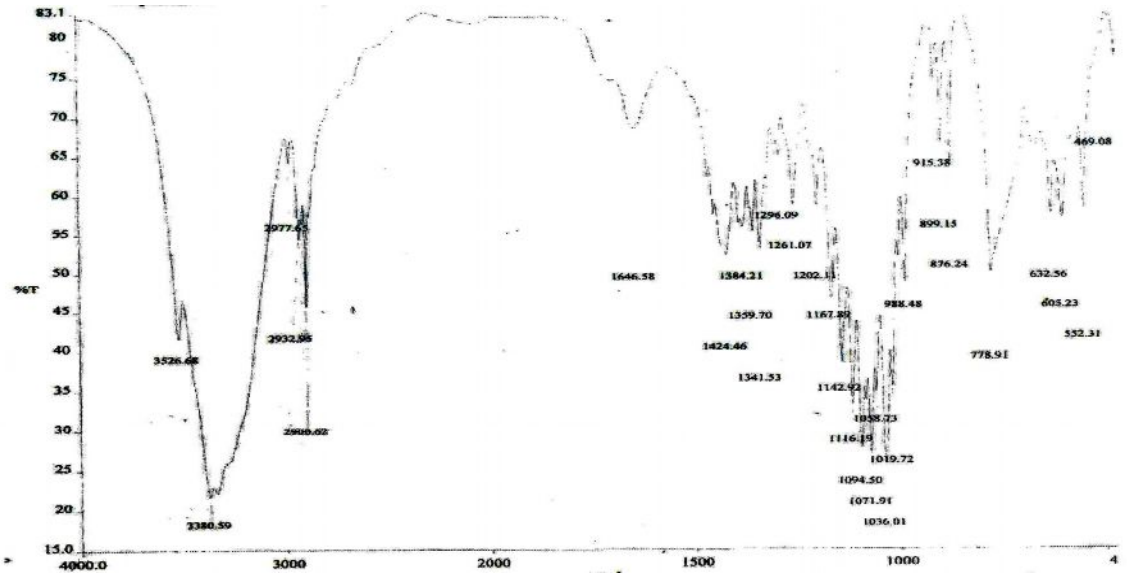

Figure 3: FTIR spectra of formulation F-5

Table 3: Tablet properties of formulations F1 to F5

Parameters	F1	F2	F3	F4	F5
Thickness (mm)	5.51 ± 0.03	5.52 ± 0.01	5.51 ± 0.01	5.53 ± 0.01	5.52 ± 0.04
Hardness (kg/cm^2)	7.4 ± 0.02	7.2 ± 0.12	7.1 ± 0.17	7.3 ± 0.04	7.5 ± 0.06
Friability (%)	0.193	0.206	0.228	0.209	0.242
Drug content (%)	99.24 ± 0.35	98.93 ± 0.38	98.05 ± 0.92	100.1 ± 0.29	98.32 ± 0.35

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.

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^2. 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 specifications.

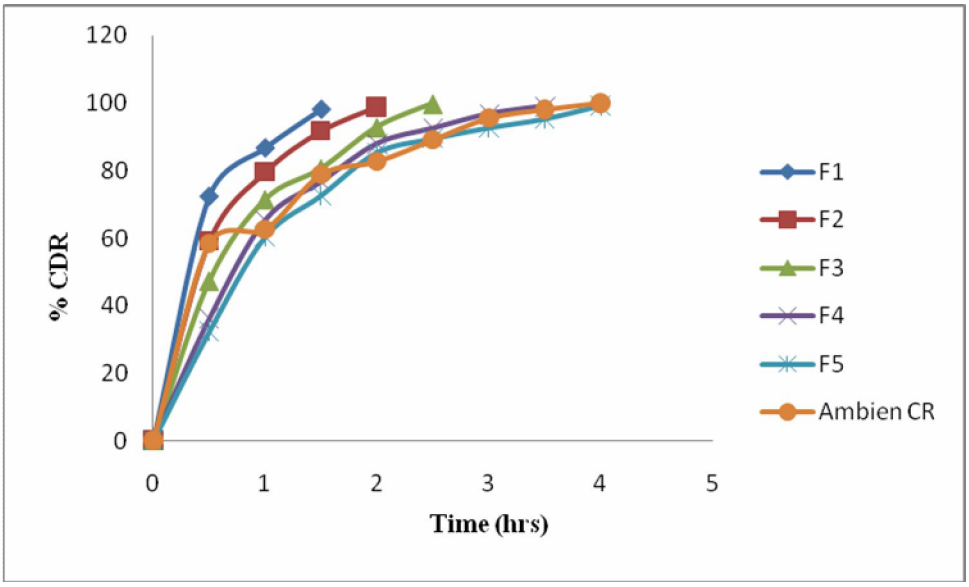

Figure 4: Dissolution profiles of developed matrix tablets F1 to F5 and comparison with Ambien CR

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 2%, 3% and 4% 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, 2.5 hrs and 3.5 hrs, respectively. Marketed formulation Ambient CR released 98.66% of drug at the end of 4 hrs. Formulation F5 sustained drug release 99.32% at the end of 4 hrs. It was found that the cumulative percentage of drug release decreases with increase in the polymer concentration.

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.[9] The first-order equation describes the release from systems where dissolution rate is dependent on concentration of the dissolving species.[10] 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.[11] 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.[12] 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^2) 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 4: Kinetic values obtained from different plots of formulations F1 to F5 and Ambien CR

Formulations	Zero order plots◘	First order plots▪	Higuchi's plots●	Korsmeyer et al's plots□	
	R^2	R^2	R^2	R^2	Slope(n)
F1	0.815	0.966	0.972	0.998	0.525
F2	0.838	0.946	0.985	0.991	0.595
F3	0.872	0.914	0.993	0.984	0.578
F4	0.83	0.973	0.972	0.934	0.522
F5	0.82	0.93	0.965	0.925	0.569

◘Zero order equation, $C=K_0 t$, First order equation, Log C=log C□-Kt/2.303, ●Higuchi's equation, Q= Kt½, □Korsmeyer et al's equation, Mt/Mα= 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 4 hrs. Among all the formulations, F5 showed 99.32% release at the end 4 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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