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Formulation and evaluation of immediate release tablet of zopiclone using wet granulation method

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ABSTRACT

Zopiclone, a cyclopyrolone, is a non-benzodiazepine derivative used as a hypnotic agent in the treatment of short term insomnia. The main objective of the present investigation was to formulate a pharmaceutically active stable and bioequivalent immediate release (IR) tablets of zopiclone using wet granulation method. The prepared formulations were evaluated using various physical parameters, equipment, dissolution study and drug release profile. The basic approach used in development of zopiclone IR tablets was that the use of superdisintegrants as like Corn starch (maize) and Sodium starch glycolate which provide instant disintegration after administration. *In-vitro* dissolution testing study was carried out for 1 hours using 0.1N HCl in a dissolution apparatus for evaluation of Drug release. On the basis of the dissolution profile, F3 gives a better result and were found 100 % release in just 20 minutes and also found that as the polymer ratio were increases the drug release rate also increased from the formulation.

Keywords: Hypnotic agent, immediate release, Wet granulation Method, Non-benzodiazepine derivative, Superdisintegrants, Zopiclone

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INTRODUCTION

Solid Oral Dosage Form

The oral route is the one most frequently used for drug administration. Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. The most popular oral dosage forms are tablets, capsules. Tablets are prepared by compression and contain drugs and formulation additives, which are included for specific functions, such as disintegrants which promote tablet break-up into granules and powder particles in the gastrointestinal tract, thereby facilitating drug dissolution and absorption. Tablets are often coated, either to provide a protection against environmental factors for drug stability purposes or to mask unpleasant drug taste, as well as to protect drugs from the acid conditions of the stomach [1].

Immediate Release Tablet:

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates i.e includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour [2]. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption.

In this context, the term "release" includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. For gastrointestinal tract release, the release is under pH conditions such as pH=1to3, especially at, or about, pH=1.

An immediate release pharmaceutical preparation offers: Improved compliance/added convenience, Improved stability, Allows high drug loading, Adaptable and amenable

to existing processing and packaging machinery and Cost-effective [3,4,5,6,7].

In vitro dissolution testing of solid dosage forms is the most frequently used biopharmaceutical, test method in formulation development. It is used from the start of dosage form development and in all subsequent phases [8]. Dissolution testing is a requirement for all solid oral dosage forms and is used in all phases of development for product release and stability testing. It is a key analytical test used for detecting physical changes in an active pharmaceutical ingredient (API) and in the formulated product. At early stages of development, *in-vitro* dissolution testing guides the optimization of drug release from formulations. Over the past 50 years, dissolution testing has also been employed as a quality control (QC) procedure, in R&D to detect the influence of critical manufacturing variables and in comparative studies for *in-vitro*/*in-vivo* correlation (IVIVC).The FDA guidance on dissolution testing for immediate release solid oral dosage forms includes the use of the Biopharmaceutics Classification System (BCS) guidelines for biorelevant dissolution tests, which is based upon API solubility and permeability. The FDA guidance on scale-up and post approval changes (SUPAC) for immediate release oral dosage forms recommends the use of *in-vitro* dissolution to justify post-approval changes [9,10,11,12] .

Zopiclone is used as a hypnotic agent in the short-term management of insomnia. Molecularly it is a pyrrolopyrazine derivative of cyclopyrrolone family. Cyclopyrrolone are distinct from benzodiazepines in structure, they have similar activity to that of benzodiazepines. Like diazepam, its actions are mediated by enhancement of the activity of gammaaminobutyric acid (GABA) in the brain. Zopiclone is reported to bind to the benzodiazepine receptor component of the GABA receptor complex but at a different site to the benzodiazepines. Its absorption time is approximately 2 hours with a bioavailability of 70% and the elimination half-life is 5 hours. It has a short duration of action. The usual oral dose is 7.5 mg before bed. In elderly patients, treatment should start with a dose of 3.75 mg before bed. Reduced doses are also recommended in patients with hepatic or renal impairment [13].

MATERIALS AND METHOD

Materials

Zopiclone was received as a gift sample from Hetero Healthcare Ltd. Lactose monohydrate, Dibasic calcium phosphate, Corn starch(maize), Sodium starch glycolate, Magnesium stearate, Hypromellose(HPMC E-5), Ethyl cellulose, Diethyl phthalate, Talc, White opaspray K-1-7000-S(methanol,TiO2,HPMC15cps) and Iso propyl alcohol were procured from Central Drug House ltd., New Delhi and Loba Chemie Pvt. Ltd., Mumbai.

Method of preparation:

In this present work the formulation was prepared by wet granulation method.

Table 1: Formulation of zopiclone tablet

S.NO.	INGREDIENT	F1 (mg/tab.)	F2 (mg/tab.)	F3 (mg/tab.)
1	Zopiclone	7.50	7.50	7.50
2	Lactose monohydrate	30.80	30.80	30.80
3	Dibasic calcium phosphate	53.50	58.25	60.44
4	Corn starch(maize)	57.25	55.00	55.50
5	Corn starch(maize)	7.95	6.95	4.95
6	Purified Water	q.s.	q.s.	q.s.
7	Sodium starch glycolate	3.00	4.00	5.00
8	Magnesium stearate	5.00	2.50	1.70
9	Total Weight	165.00	165.00	165.00

Note- In the above formulation chart corn starch used two times as a binder and as a disintegrant in different ratios.

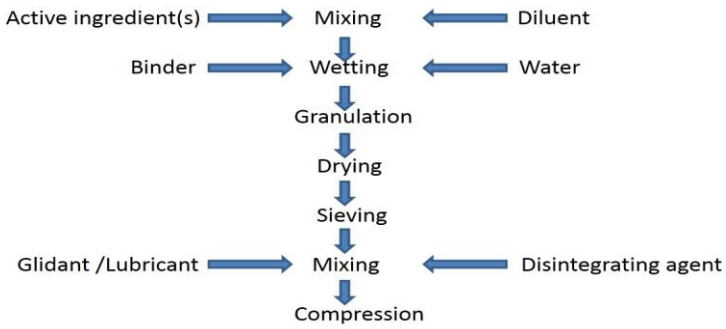
Table 2: Formulation chart for the coating solution of zopiclone tablet

S.N.	Ingredient	Quantity
1	Hypromellose(HPMC E-5)	2.825
2	Ethyl cellulose	0.925
3	Diethyl phthalate	0.775
4	Talc	1.625
5	White opaspray K-1-7000-S (Methanol,TiO2,HPMC15cps)	4.85
6	Iso propyl alcohol	q.s.
7	Water	q.s.

Wet Granulation Method:

Wet granulation is the process in which a liquid is added to a powder in a vessel equipped with any type of agitation that will produce agglomeration or granules. It is the oldest and most conventional method of making tablets. Although it is the most labor-intensive and most expensive of the available methods, it persists because of its versatility. The possibility of moistening powders with a variety of liquids, which can also act as carriers for certain ingredients, thereby enhancing the granulation characteristics, has many advantages. Granulation by dry compaction has many limitations. It does not lend itself to all tablet formulations because it depends on the bonding properties of dry powders added as a carrier to the drug thereby increasing the size of the tablet. In wet granulation, the bonding properties of the liquid binders available is usually sufficient to produce bonding with a minimum of additives. Wet granulation is a versatile process and its application in tablet formulation is unlimited [14, 15].

Wet granulation process[16]



Coating Process of tablet:

- Took IPA and water according to specification and mixed them, then add hypromellose and shaked for 30 min.

- Then add ethyl cellulose and mix for 10 min.

- After that add diethyl phthalate, talc, and white opaspray k-1-7000-s and shaked for 30 min [17].

Preformulation studies

Before development of any formulation it is mandatory to carry out pre-formulation studies to determine any changes in the drug characteristics and suitability of a drug candidate for formulation development. Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Drug Characterization:

The drug was characterized and identified by spectroscopic analysis in the present study. The studies carried out include FT-IR, UV, Specific optical rotation, Sulphated ash, Assay, and Melting range.

Drug Solubility:

Solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous dispersion. The solubility of Zopiclone was studied in various aqueous and non-aqueous solvents. 10mg drug was taken in 10 ml of water, acetone, alcohol, methylene chloride, and dilute mineral at room temperature in screw-capped test tubes and shaken for 24 hours in wrist action shaker (York, India). The solubility was considered as soluble and what was insoluble.

Particle size analysis:

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution and chemical reactivity are directly affected by size, shape and surface morphology of the drug particles. The particle size analysis of Zopiclone involves the mechanical shaking of sample through a series of successively smaller sieves. Apparatus used for particle size analysis is mechanical shaker with vibratory motion.

Angle of Repose:

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The angle of repose calculated as:

Angle of repose = Tan^{-1} (h/r) (Where, h=height of pile, r = radius of pile)

Bulk Density Determination:

Weighed quantity of powder (W) was taken in a graduated measuring cylinder and volume (V_0) was measured. Bulk Density was calculated as:

Bulk Density = Weight of powder/ Volume of powder (g/ml)

Tapped Density Determination:

Weighed quantity of powder was taken in a graduated cylinder and the volume was measured (V_0). The graduated cylinder was fixed in the tapped densitometer and tapped for 500, 750, and 1250 times until the difference in the volume after consecutive tapping was less than 2%. The final reading was denoted by (V_F), the volume of blend was used to calculate the Tapped density, Hausner's ratio, and Carr's index. Taped Density calculated as:

Tapped density = Weight of powder/ Final Volume of powder (g/ml)

Hausner's Ratio:

Hausner's ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. Hausner's ratio calculated as:

Hausner's Ratio = Tapped density/ Bulk density ($H.R = V_F/V_0$)

Where, V_F = Final volume, V_0 = Initial volume.

Carr's Index:

Carr's index is also known as the compressibility index. It is directly related to the relative flow rate, cohesiveness and particle size. It is simple method of predicting powder flow. Carr's Index calculated as:

Carr's Index = (Tapped Density – Bulk Density)/ Tapped Density x 100

Preparation of Calibration curve of zopiclone:

100 mg of zopiclone was accurately weighed and transferred to previously dried 100 ml volumetric flask. Drug was dissolved in 0.1N HCl solution. The solution was suitably diluted with 0.1NHCl solution to get standard concentration of 2, 4, 6, 8, 10, 12, 14, and 16 µg/ ml. absorbance was measured at 303 nm UV visible spectrophotometer.

Pre-compression characterization

There were the primary requirements to determine whether the specific material was suitable for the targeted formulation or not and the aim was to formulate the tablet formulation with wet granulation method, so it was mandatory to know about the bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose as those were the necessary requirement while choosing any material for its dosage form and formulation. All the parameters as Bulk Density, Tapped Density, Carr's index, Hausner's ratio, Angle of Repose for various tablet formulation were evaluated and the result clearly indicates its suitability of the material to be selected for the formulation, results shown in **Table 3**.

Evaluation parameter of prepared immediate release tablet

Weight: Weight of formulated immediate release tablet was determined by weighing balance (Mettler Toledo).

Thickness: Thickness of tablets was measured by varnier caliper (Mitutoyo Corporation, Japan) and average was calculated.

Hardness: The hardness of the tablets from each batch was measured by using hardness tester (Dr. Schluniger).

Tablet friability: The friability of the tablets was measured in a Roche friabilator (Electrolab). Tablets of a known weight (W_0) or a sample of 20 tablets are de dusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

Determination was made in triplicate.

F = (W initial) - (W final)/ (W initial)×100

Where W initial = Initial weight of tablets.

W final = Final weight of tablets

Disintegration test: Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. In disintegration test, measured using tablet disintegration test apparatus (Electrolab, India) using distilled water without disk at room temperature (37±2˚C).

Weight variation test: Twenty tablets were selected randomly and weighed individually. Average weight of tablets were calculated and compared with that of the individual tablets. Weight not more than two of the individual weight deviate from the average weight by more than the percentage shown in table.

Content Uniformity: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia .The content uniformity test is mandatory for tablets whose average weight is below 50mg. This test is performed by preparing standard solution of pure drug and sample solution solution of prepared formulation.

Standard solution: Weighed accurately about 50 mg of standard zopiclone, dissolved and diluted to 100ml with 0.1 N HCl. Diluted 3 ml of this solution to 100 ml with 0.1 N HCl.

Sample solution: One tablet of zopiclone 7.5mg transferred in to a 100ml volumetric flask and add 80 ml of 0.1 N HCl, placed in an ultrasonic bath for 10 minutes until total disintegration of powder, makes up with HCl 0.1 N, shaked and filtered. Diluted the 5 ml of this solution to 25 ml with 0.1N HCl.

Procedure: Determined the absorbance of standard and sample solution at 303nm against 0.1 N HCl as a blank. Then calculate the content of zopiclone in the sample with the data obtained.

***In-vitro* drug release**

In the present study dissolution profiles of Zopiclone tablets were determined using the Dissolution Test apparatus USP-2 set with a paddle speed of 50rpm. Dissolution was tested in 0.1 N HCl, Dissolution was performed in 500 ml, at 37±0.5°C; 5 ml aliquot was withdrawn, at the 5, 10, 15, and 20 min with 5minutes interval, and filtered through Whatmann filter paper. From these samples, 1ml taken into test tube volume made up with the same medium up to 10 ml and the drug solution absorbance was analyzed at 303nm in 1cm cuvette using UV-Visible spectrophotometer (Shimadzu-1800, Japan).

Limit- Not less than 80% of labeled amount of zopiclone was dissolved after 15min.

RESULT AND DISCUSSION

Drug Characterization

Identification by IR: The infrared absorption spectrum of a sample should concordant with working standard spectrum of zopiclone.

Identification by UV absorbance: The solution shows absorption maximum at 303nm and specific absorbance at the maximum is 340 to 380.

In the above study of drug characterization different parameters of drug were carried out including identification, related substance(0.17%), sulphated ash (0.04%),optical rotation (-0.05°to+0.05°), assay (99.51%), and melting point(177.2°C) by different method and the result was found to be acceptable.

Further this was characterized for drug solubility study in the different solvent including water, acetone, alcohol, methylene chloride, and dilute mineral. Later after it was observed that zopiclone was soluble in methylene chloride and dilute mineral, sparingly soluble in acetone, and insoluble in water and alcohol.

Particle size analysis of zopiclone was performed using vibratory shifter and the result was found to be within limit and had more fines that were determined to be 91.885%. Bulk characterization was carried out to observe the flow property of active drug that have great effect during formulation process. This includes bulk density (0.66gm/ml), tapped density (0.86gm/ml), Hausner's ratio (1.30), Carr's index (23.25%), and angle of repose (26°). The result of bulk characterization was found to be acceptable and had good flow property.

The drug-excipient interaction was carried out by preparing different ratios of drug and excipient, and it was determined on the different temperature and relative humidity condition to find out the interaction and related impurities, water content and appearance of the drug and excipient. It was observed that at different condition all parameter was within limit and found to be compatible.

Calibration curve of zopiclone was prepared. In this the absorbance of standard solution of zopiclone at 0-16 µg/ml were plotted as absorbance v/s concentration which gave almost a straight line passing from the origin with regression-coefficient o.989. So it followed Beer's and Lambert's law at the concentration range of 0-16 µg/ml. (Shown in figure no. 1)

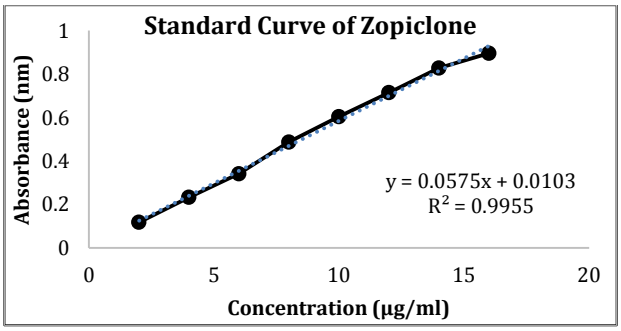


Figure 1: Standard curve of zopiclone

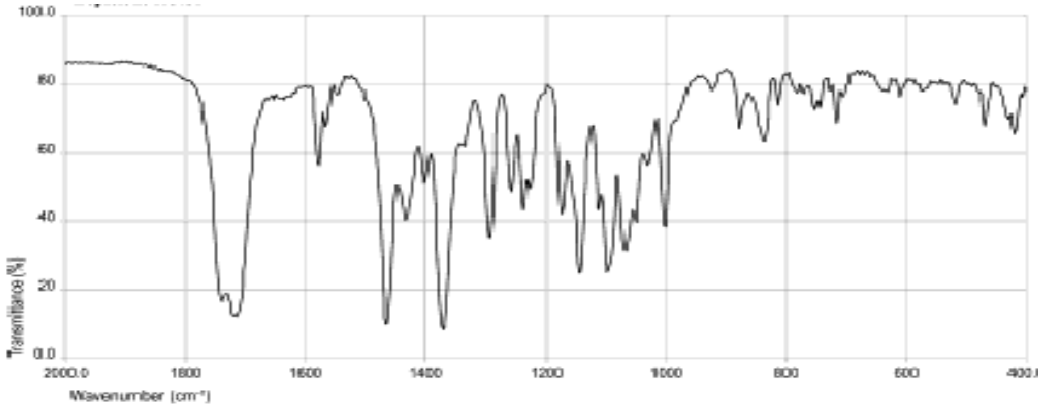


Figure 2: FTIR spectra of zopiclone

In the study of pre- compression characterization there were all the parameter as bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose were determined and found (shown in table no.3). Particle size analysis was also performed (shown in table no. 4). Here all parameter were found to be within limit and suitable for the further process of formulation.

Table 3: Pre-compression characterization

S.No.	BulkDensity (gm/cm³)	TappedDensity (gm/cm³)	Carr'sIndex	Hausner'sRatio	Angleof Repose
F1	0.676±0.12	0.789±0.05	12.768±1.0%	1.163±0.05	32.24°±0.08
F2	0.649±0.06	0.781±0.08	16.883±2.0%	1.203±0.03	32.00°±0.06
F3	0.612±0.08	0.769±0.06	20.408±3.0%	1.256±0.06	29.19°±0.05

n=3

Table 4: Particle size analysis of granules

S. No.	Sieve No.				
	20#	**40#**	**60#**	**80#**	**100#**
F1	18.16%	7. 32%	11.325%	4.78%	38.642%
F2	16.29 %	6.425%	13.268%	6.42%	41.66%
F3	17 %	5.36%	14.48%	7.36%	50.32%

Post-compression characterization was performed and the parameter evaluated were average weight, thickness, hardness, friability,disintegration, and weight variation, the drug content, and all these parameter were found to be within limit and formulation F3 gave best result as per the objective of this project. (Shown in table no. 5)

Table 5: Post-compression characterization

PARAMETER	FORMULATION		
	F1	**F2**	**F3**
Avg. Weight(Mg)	174±3.2	174±3.7	176±3.9
Thickness (mm)	3.66±0.4	3.85±0.7	3.65±0.9
Hardness(N)	151±10.1	147.4±8.2	149.36±8.5
Friability(%W/W)	0.424±0.02	0.567±0.04	0.437±0.03
Disintegration time(Min-Sec)	3.00±0.17	2.50±0.13	2.40±0.16
Weight Variation(%)	2.84±0.25	3.97±0.30	3.40±0.27
Content Uniformity(%)	99.18±0.37	100.08±0.35	105.32±0.29

n=3

In the present work *in-vitro* studies were performed and observed that in formulation F1 when used 3% superdisintigrant the drug release was to be found 72.36±0.3% after 15 min. and was below the limit. Further increased the concentration of superdisintegrant in the formulation F2 by 4% and the release of drug were found to be 75.39±0.5% after 15 min. and 99.51±0.7% after 20 min. and this was also not satisfactorily. At last in the formulation F3, 5% of superdisintegrant was used and found to be 82.06±0.5% after 15 min. and 100.02±0.6% after 20 min. and this was denoted as the best and final formulation. After dissolution studies it was observed that on increasing the content of superdisintigrant the release of drug was also increased. Since Zopiclone is acidic in nature and its absorption window is stomach, so it released the drug in the stomach. The Drug Release Profile of Immediate Release Tablet of zopiclone was shown in figure no. 3.

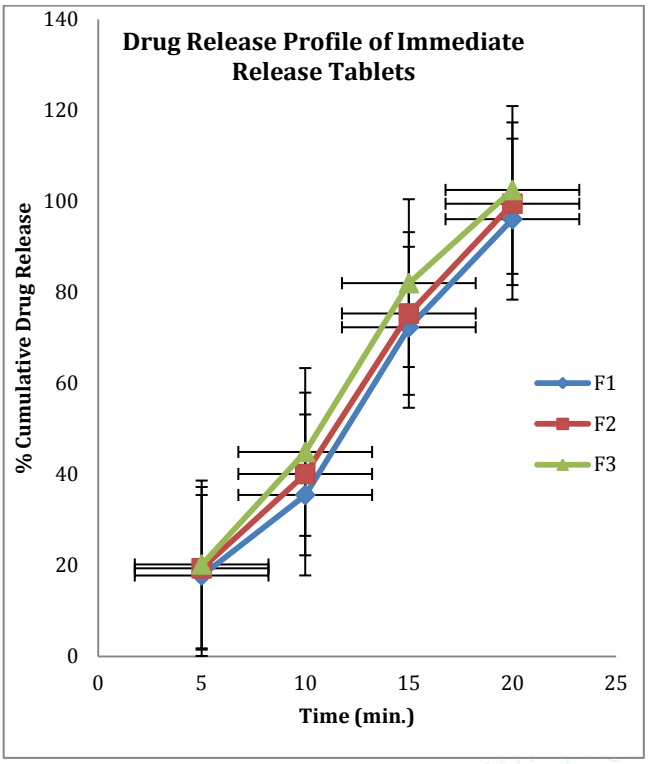


Figure 3: Drug release profile of immediate release tablet

SUMMARY AND CONCLUSION

In the present work, the tablet was prepared by wet granulation method using the superdisintegrant in the ratio of 3%, 4%, 5%. There were three formulation prepared using material lactose monohydrate, dibasic calcium phosphate, corn starch (maize), sodium starch glycolate, magnesium stearate. The granules were prepared and subjected to pre- compression analysis. Later Pre-compression analysis was found and tablet was compressed using 7.00 mm round shape, plain both side, standard concave Punches by 12 station compression machine (Rimek). The manufactured tablets were evaluated for post-compression parameters. After observation we found that formulation F1 gave less release, so further trail was taken by changing the concentration of binder and the final formulation F3 was found to be satisfactorily on increasing the concentration of superdisintegrant. At last the formulation was coated by film coating.

After preparing the formulation of zopiclone immediate release tablet, there were found the great effect of superdisintegrant on release of drug. The increased ratio of polymer increased the dissolution profile of drug and released the drug in less time.

According to the found result it was concluded that immediate release tablet of zopiclone prepared on the above ratio is the best formulation in the treatment of short term therapy of insomnia.

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