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Research paper

FORMULATION AND EVALUATION OF FAST DISSOLVING FILM OF ZOPICLONE

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Insomnia definitions could be generalized as rest condition. People who suffer with insomnia and or trouble in remaining sleeping even if there's chance are recognized to have the condition. Insomnia is serious disease so patients need to take medicine for preventive measure daily, now dosage form which don't need water and which can be consumed anywhere without water will make it easy for patient. Zopiclone is a non-benzodiazepine hypnotic agent with marked sedative effects widely used in the acute and chronic treatment of insomnia. In market, Zopiclone tablets available. The mouth dissolving film overcomes the shortfalls of conventional quick dispersing dissolving intraoral tablets. Fast dissolving film has got all advantages of tablets but in addition to it. It is easy to swallow and preferable for paediatric and geriatric patients (ease of application). The aim of present work is "Formulation and Evaluation of Fast dissolving film of Zopiclone" that attempt to formulate the drug in the form of fast dissolving films. The work done is summarized as follows the fast dissolving film of Zopiclone prepared by the solvent casting method and the prepared film was transparent with smooth surface without any drug excipients interaction.

Keywords - Zopiclone, Insomnia, HPMC 6cps, Maltodextrin

INTRODUCTION

Oral films also called oral wafers in the related literature are a group of flat films which are administered into the oral cavity. Although oral film systems the third class have been in existence for a number of years they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. Dissolvable oral thin films (OTFs) or oral strip (OS) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products.

Classification of Oral Film

There are three different subtypes

- Flash release
- Mucoadhesive melt-away wafer
- Mucoadhesive sustained-release wafers

Application of Oral Strip in Drug Delivery

- Topical applications
- Gastro retentive dosage systems
- Diagnostic devices

Introduction to Disease

Insomnia definitions could be generalized as rest condition. People who suffer with insomnia and/or trouble in remaining sleeping even if there's chance are recognized to have the condition. Insomnia is just a sign of a far more severe fundamental condition; it's not really illness by itself.

Classification of insomnia

Types of insomnia

Insomnia can be classified as transient, acute, or chronic.

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Transient insomnia lasts for less than a week. It can be caused by anotherdisorder by changes in the sleep environment, by the timing of sleep, severe depression or by stress. Its consequences – sleepiness and impaired psychomotor performance – are similar to those of sleep deprivation.

Acute insomnia is the inability to consistently sleep well for a period of less than amonth. Insomnia is present when there is difficulty initiating or maintaining sleep or when the sleep that is obtained is non-refreshing or of poor quality. Acute insomnia is also known as short term insomnia or stress related insomnia.

Chronic insomnia lasts for longer than a month. It can be caused by anotherdisorder, or it can be a primary disorder. People with high levels of stress hormones or shifts in the levels of cytokines are more likely to have chronic insomnia. They might include muscular fatigue, hallucinations, and/or mental fatigue. Some people that live with this disorder see things as if they are happening in slow motion wherein moving objects seem to blend together. Chronic insomnia can cause double vision.

DRUG PROFILE

- **Compound Name -** Zopiclone
- **Molar mass:** 388.80 gm/mol
- **Formula:** $C_{17}H_{17}ClN_6O_3$

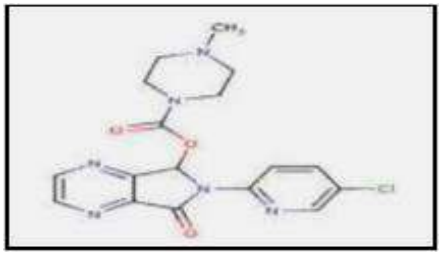

Fig. 1: Chemical structure of Zopiclone

- **Bioavailability:** 75-80%
- **Excretion:** Urine (80%)
- **Biological half-life:** ~5 hours (3.5–6.5 hours); ~7–9 hours for over 65

Mechanism of action

Zopiclone is a non-benzodiazepine hypnotic agent with marked sedative effects. Although unrelated chemically to the benzodiazepines, it produces similar pharmacological effects. Although the precise mechanisms have not been completely established, the activity of Zopiclone is believed to be related to its binding on the benzodiazepine receptor complex and facilitation of the gamma-aminobutyric acid (GABA) function. It does not appear to bind to sites corresponding exactly to benzodiazepine sites but rather to sites close by on the receptor complex. Enhanced binding of GABA to the GABA-chloride ionophore complex occurs to a greater extent with benzodiazepines as compared to Zopiclone. Zopiclone lacks affinity for the serotonin, GABA1 and GABA2 adrenergic and dopamine receptors.

AIM AND OBJECTIVE

Aim

Insomnia affects 1.1 million US residents. It is more common in blacks and Native Americans. Zopiclone is the drug of choice in insomnia. Zopiclone is a nonbenzodiazepine hypnotic agent used in the treatment of insomnia. it is a cyclopyrrolone, which increases the normal transmission of the neurotransmitter gamma-aminobutyric acid in the central nervous system, as benzodiazepines do, but in a different way. It works by causing a depression or tranquilization of the central nervous system. The activity

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METHODOLOGY

MATERIAL USED IN THE PRESENT INVESTIGATION

Table: 1 Materials used in the present investigation

Name of materials	Name of company
Zopiclone	Ipca Ltd. Ratlam
Maltodextrin	Central drug house, New Delhi
Aspartame	Central drug house, New Delhi
HPMC 6 cps	Kalpana polymer pvt. Ltd.
Citric acid	Central drug house, New Delhi
Ammonium acetate	Central drug house, New Delhi
Potassium Di Hydrogen Ortho phosphate	Central drug house, New Delhi
Sodium Hydroxide	Central drug house, New Delhi

INSTRUMENT USED IN PRESENT INVESTIGATION

Table: 2 Instrument used in present investigation

Name of instruments	Model name and company
Digital weighing balance	Citizen
Magnetic stirrer	Instrumental india
UV Spectrophotometer Doublbeam	Shimadzu Japan
Hot air oven	Labtech.
Fourier transform infrared	Shimadzu Japan
Vernier Caliper	LabTech.

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METHODS

Preformulation study

Preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Preformulationstudy is the backbone of pharmaceutical formulations, which gives the basic information for selection of ingredients and process Increasing demand or cost effective formulation development needs accurate selection of excipients and projection of risk involved during bioequivalence and stability study. As shown in table 6 different polymers (HPMC5cps, HPMC 6cps, PVA, and Maltodextrin) are used to check the solubility in the solvent system (methanol, Isopropyl alcohol, Dichloromethane) for selection of polymer.

Preliminary Trials (Polymers)

Table: 3 Preliminary trials (polymers)

Polymer (600mg)	E1	E2	E3	E4
HPMC 5cps	√			
HPMC 6cps		√		
PVA			√	
Maltodextrin				√
Methanol	√	√	√	√
Isopropyl alcohol	√	√	√	√
Dichloromethane	√	√	√	√

Selection Of Plastisizer

Preparation of trial batches using HPMC 6cps with different plasticizers.

Table: 4 Preliminary trials (Polymers)

Components	P1	P2
HPMC 5cps(mg)	600	-
HPMC 6cps(mg)	-	600
Glycerin(mg)	90	90
Methanol(ml)	5	5
Isopropyl alcohol(ml)	5	5
Dichloromethane(ml)	10	10

Table: 5 Preparation of trial batches using HPMC 6cps with different plasticizers.

Components(mg)	R1	R2	R3	R4	R5	R6
Zopiclone	74	74	74	74	74	74
Hpmc 6cps(mg)	600	600	600	600	600	600
Dibutylphthalate(mg)	90	120		--	--	--
Peg(mg)	--	--	90	120	--	--
Glycerin(mg)	--	--	--	--	90	120
Methanol(ml)	5	5	5	5	5	5
Isopropyl alcohol(ml)	5	5	5	5	5	5
Dichloromethane(ml)	10	10	10	10	10	10

As shown in table 8, different plasticizers were checked out by optimized polymer (HPMC 6 cps).there were two concentration of plasticizers viz. 90 mg and 120 mg were used. Polymer conc. was same in all batches viz. 600 mg with 74 mg of drug (Zopiclone).

Preparation Of Final Trial Batch With Hpmc 6cps And Glycerin

Table: 6 Preparation of final trial batch with HPMC 6cps and glycerin

Components	V1	V2	V3
Zopiclone(mg)	74	74	74
HPMC 6cps(mg)	400	600	800
Glycerin(mg)	90	90	90
Methanol(ml)	5	5	5
Isopropyl alcohol(ml)	5	5	5
Dichloromethane(ml)	10	10	10

As shown in table 10 optimized film was taste masked by use of combination of sweetener and flavor. For taste mask of film aspartame was used as a sweetener. As compared to other sweetener (sodium saccharin, sucrose, fructose) only aspartame was soluble in solvent system (methanol, IPA and DCM). Aspartame shows

Preliminary Trials (Sweetener)

Table: 7 Preparation of film with sweetener

Ingredients	C1	C2	C3
Zopiclone (mg)	74	74	74
HPMC 6cps (mg)	400	400	400
Glycerin(mg)	90	90	90
Aspartame(mg)	30	60	90
Methanol(ml)	5	5	5
Isopropyl alcohol(ml)	5	5	5
Dichloromethane (ml)	10	10	10

greater taste masking effect with combination of flavor. Here different conc. of aspartame was used viz. 30 mg, 60 mg, 90 mg. but it shows greater taste masking effect in conc. of 60 mg.

Drug -Excipient Compatibility Study

The primary objective of this investigation was to identify a stable storage condition for zopiclone in solid state and identification of compatible excipients for its formulation.In this method, different excipients were selected and mixed separately with drug in proportion generally used in the formulation

Formulation of Zopiclone Fast dissolving film

Table: 8 Different Formulation of Zopiclone -

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Zopiclone (mg)	74	74	74	74	74	74	74	74
HPMC 6 cps(mg)	400	400	400	600	600	600	800	800
Glycerin(mg)	90	120	150	90	120	150	90	120
Citric acid(mg)	50	50	50	50	50	50	50	50
Aspartame(mg)	60	60	60	60	60	60	60	60
Methanol(ml)	5	5	5	5	5	5	5	5
Isopropyl alcohol(ml)	5	5	5	5	5	5	5	5
Dichloromethane(ml)	10	10	10	10	10	10	10	10

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RESULT AND DISCUSSION

Preformulation Study

Organoleptic Properties

On organoleptic evaluation zopiclone was found white to gray-white, crystalline powder, odourless, sparingly soluble in water, freely soluble in chloroform.

Table: 9 Organoleptic properties of zopiclone

Test	Observation
Description	White to gray-white, Crystalline powder
Odour	Odourless

Detection of Melting Point Range

Melting point of zopiclone was performed using Digital Programmable Melting Point apparatus and the melting point was found to be **172⁰ C** which which was in the

Table: 10 Melting point Range of Zopiclone

Drug	Specification	Observation
Zopiclone	177⁰ C	172⁰ C

range as prescribed in Indian Pharmacopoeia, so the drug was found to be of standard prescribed purity and quality.

Partition Coefficient

The partition coefficient of zopiclone was calculated from the ratio between the concentration of zopiclone in oil (n- octanol) and aqueous phase (water). The ratio between the concentration of zopiclone in oil (n-octanol) and aqueous phase (water) was determined and the partition coefficient of zopiclone (log P) was found to be 0.8 which was in the range as prescribed in Indian pharmacopeia so the drug was found to have standard prescribed hydrophobic character**.** The DSC curves of pure drug (Zopiclone) is show in figure 11 Zopiclone showed endothermic peak at 179.10⁰c corresponding to its melting point.

FT-IR Spectrum

From FTIR spectra of pure Zopiclone in figure 12 indicate that four principle peaks observed at wave numbers 1606, 1487, 1342 and 1111 cm^{-1} according to mentioned in Zopiclone protocol these wave numbers match with the standard drug wave numbers.

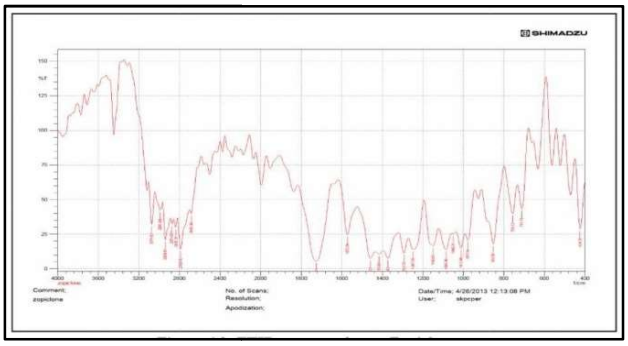

Figure: 7 FTIR spectra of pure Zopiclone.

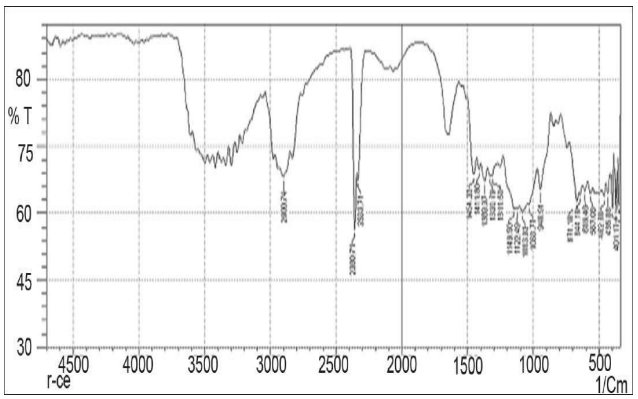

Figure: 8 FTIR spectra of HPMC

Determination of absorption maxima

A solution of 10µg/ml of zopiclone was scanned in the range of 200 to 400 nm. The drug exhibited the λ_{max} at 303 nm in phosphate buffer saline has good reproducibility graph.

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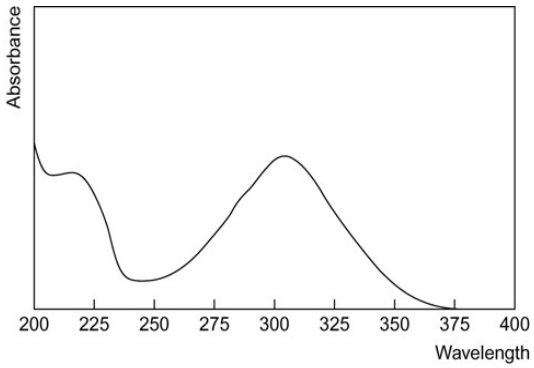

Figure: 9 Absorption maxima of Zopiclone

Solubility Study On solubility studies it was found that

Table: 11 Solubility Studies of Zopiclone in different solvent

Solvent	Saturation solubility (µg/ml)
Distilled water	115
	195
Glycerine	300
Methanol	440
Dichloro methane	460

zopiclone is sparingly soluble in distilled water and freely soluble in glycerine, methanol dichloro methane.

Calibration Curve

The UV calibration curve of Zopiclone was constructed in phosphate-buffered saline (PBS) at pH 6.8 (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl / 1L of distilledwater). Stock solutions were prepared by dissolving 10 mg Zopiclone in 100 ml of phosphate-buffered saline (PBS). Serial dilutions of the stock solutions were prepared and their absorbance values were measured using an ultraviolet–visible (UV-VIS) spectrophotometer (Shimadzu) at λmax 303 nm. No interference from excipients used was noticed at that wavelength. Linearity was observed over a concentration range of 10-30 µg/ml, with an R2 = 0.930. The absorbance values of different concentration of Zopiclone in 6.8 buffer solution at 303 nm wavelength are given in Table 15

Table: 12 Calibration data of Zopiclone in 6.8pH buffer solution at 303 nm

Concentration(µg/ml)	Absorbance
0	0
10	0.343
15	0.401
20	0.478
25	0.534
30	0.597

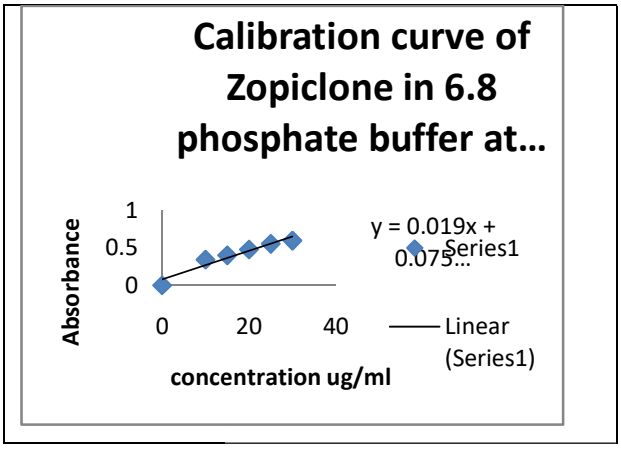

Figure: 10 Calibration curve of Zopiclone in 6.8 phosphate buffer at 303 nm.

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SELECTION OF POLYMER AND PLASTISIZER

EVALUATION OF FILM PREPARED BY DIFFERENT POLYMER:

Table: 13 Evaluation of film prepared by different polymer

BATCH NO.	POLYMERS USED	APPEARANCE CAPACITY	FILM FORMING
E1	HPMC 5cps	+++	Transparent
E2	HPMC 6cps	++++	Transparent,non, Sticky
E3	PVC	++	Transparent
E4	Maltodextrin	++	Sticky

Where ++ Poor, +++ Good, ++++ Very Good

EVALUATION OF TRIAL BATCHES OF SELECTED POLYMER

Table 14: Evaluation of trial batches of selected polymers

Batch Code	Polymer Used	Film forming capacity	Appearance	Disintegration time (sec)
P1	HPMC 5cps	Good	Semitransperant	37
P2	HPMC 6cps	Very Good	Transperant	31

As shown in table 16 HPMC 6cps had good film forming property and appearance than other polymers. Film formed by Maltodextrin was very sticky, so there was a problem to scrap out the film from the pt.dish. PVA had low film forming property as compare to HPMC grade polymers and there was also a sticky problem, so HPMC grade two polymers (HPMC 5cps and HPMC 6cps) were carring out for further study.

From results shown in table 16 and table 17 the HPMC 5 cps and HPMC 6 cps polymeric films shows that these two polymer at 600 mg concentration with 90 mg plasticizer (glycerol) concentration give good results interms of physical properties (for example, appearance) and disintegration time. Physical appearances provided by these films were as good as compare to other previous film formers. All films prepared with HPMC had very nice clearity and transparency, without any grittiness. They differed only in case of *in vitro* disintegration and dissolving criteria, so according to our aim to achieve disintegration as possible as low HPMC. 6cps (polymer) was optimized

.

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