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R E S E A R C H A R T I C L E

Formulation and Evaluation of Fast dissolving film coated tablets of Zopiclone

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A B S T R A C T

The objective of the present investigation was to formulate and evaluate fast dissolving film coated tablets of Zopiclone by solvent casting technique. Zopiclone is a non-benzodiazepine hypnotic agent, with marked sedative effects. Nine formulations of fast dissolving tablets were prepared using solvent casting method various polymers like PVA, Maltodextrins, HPMC 5cps and HPMC 6cps were used to prepare the FDFs of Zopiclone. Plasticizer (glycerin) at 150 mg concentration of total polymer weight gave excellent results in preliminary work. The evaluation results revealed that all formulations comply with the specification of official pharmacopoeias and/or standard reference with respect to general appearance, content uniformity, hardness, friability and dissolution. Out of all the formulation developed, Formulation 3 has been found that HPMC 6cps with 400 mg gave good results as compared to PVA and HPMC5cpsm and Maltodextrin. Different concentrations of the glycerin (90,120and 150 mg of dry polymer weight) were used as a plasticizer during film formation. Hence, developed fast dissolving film formulation can be a new era of drug delivery in future.

Key words: Zopiclone, Solvent casting technique, Polymers, Formulation, HPMC5cpsm and Maltodextrin.

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C O N T E N T S

1. Introduction

Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. There are multiple fast-dissolving OTC and prescription drug products in the market worldwide, most of which have been launched in the past 3 to 4 years. There has also been significant increase in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

Fast dissolving oral films:

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. Companies with experience in the formulation of polymer coatings containing active pharmaceutical ingredients (APIs) for transdermal drug delivery capitalized on the opportunity to transition this technology to OTF formats.

Drug profile:

Zopiclone is a non-benzodiazepine hypnotic agent, with marked sedative 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.

2. Materials and Methods

Materials:

The following chemical and instruments are used to formulation and evaluation of Zopiclone tablets.

Table 1: List of Chemicals

Name of materials	Name of company
Zopiclone	Astron Lab Pvt. Ltd., Ahmedabad, India.
Maltodextrin	Lincoln Pharma Ltd, India.
Aspartame	Himedia Laboratory Pvt Ltd, Mumbai, India
HPMC 5 cps	Acme Pharma Ltd., Ganpat Vidhyanagar,
HPMC 6 cps	Acme Pharma Ltd., Ganpat Vidhyanagar,
Citric acid	Finar Chemicals Ltd, Ahmedabad, India
Ammonium acetate	Finar Chemicals Ltd, Ahmedabad, India.
Potassium dihydrogen ortho phosphate	Finar Chemicals Ltd, Ahmedabad, India
Sodium Hydroxide	Finar Chemicals Ltd, Ahmedabad, India

Table 2: List of Instruments

Name of instruments	Model name and company
Digital weighing balance	Sartorious electronic balance BT 124 S
Magnetic stirrer	Remi service Pvt Ltd.
Sonicator	FS-5 ultrasonic cleaner
UV Spectrophotometer	Shimadzu 1800UV/Vis double beam
Differential Scanning Colorimeter(DSC)	Shimadzu DSC-60,C304544
Hot air oven	Prototech service Ltd, Mumbai.
Fourier transform infrared	FTIR8400S, Shimadzu
Thermo stability chamber	Thermo lab Pvt Ltd.
Dissolution test apparatus	TDT-O6T (Lab India ltd.)
Tensile strength machine	Eureka techno service Ltd.
Scanning electron microscope	Philips XL-30 environment
Digital micrometer	Mitutoya corporation, Japan.

Methods

Preformulation study:

Characterization of drug:

By checking its visualappearance, odour and solubilities in various solvents according to description in monograph in British Pharmacopeia etc. (Karabey Y et al 2003)

Drug-Excipient compatibilitystudy

DSC study:

Assessment of possible incompatibilities between an active drug substance and different excipient forms an important part of the Preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC TA- 60WS) allows the fast evaluationof possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermo grams of pure drug, other excipients and optimized film were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 100C/min over a temperature range of 400C to 3000C. DSC study was performed for Zopiclone and physical mixture of all ingredients of optimized film. (HPMC 6cps+Citric Acid+ Aspartame+ Drug).

FTIR Study: The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR- 8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400cm-1.

Preparation of Fast Dissolving Films (FDFs):

The solvent casting method was used for the preparation of the films. The required amount of film forming polymer

was allowed to hydrate using minimum amount of DCM for about 3-4 hours and then uniformly dispersed to get clear solution of film forming polymer. After that the required amount of plasticizer was added to film forming solution. Other ingredients including drug, sweetener, saliva stimulating agent and green color were dissolved one by one in previously prepared film forming solution with constant stirring to form clear aqueous solution. The aqueous solution was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass petridish having area of 78 cm^2 and was dried at room temperature. The petridishes were put on the leveled surface during drying toavoid variation in the thickness. The film took approximately 24 hours to dry at room temperature. The dried film was carefully removed from the mould and was cut into size required for testing. The films were stored in airtight plastic bags till furtheruse.

Evaluation of the Fast dissolvingfilm:

Fast dissolving film should be stiff, flat and should not curl on the edges. The fast dissolving film strip must be robust enough to be removed from the unit-dose packaging and to be handled by the consumer without breaking. The film must also dissolve readily in order to deliver the active agent rapidly when placed in the oral cavity. Mechanical property of fast dissolving film plays an important role in deciding all these things. Therefore, the mechanical property of fast dissolving film is as importantasits solubility rate.

3. Results and Discussion

Characterization of Drug:

Drug was found to be freely soluble in chloroform andmethelyne dichloride, so solvent casting method can be used using solvent. Drug is known to be slightly bitter. So, it can be made palatable by using sweeteners and flavors.

DSC Study: The DSC curves of pure drug (Zopiclone) and physical mixture of final optimized film formulation containing drug (Zopiclone), HPMC 6cps, aspartame and citric acid. Zopiclone showed endothermic peak at 179.100c corresponding to its melting point. Physical mixture of final optimized film formulation except glycerin and solvent show same intact endothermic peak at 183.620c but peak intensity was less since amount of drug was very low as compared to other excipients. These results indicate that the drug did not interact with the excipients used in the film formulation.

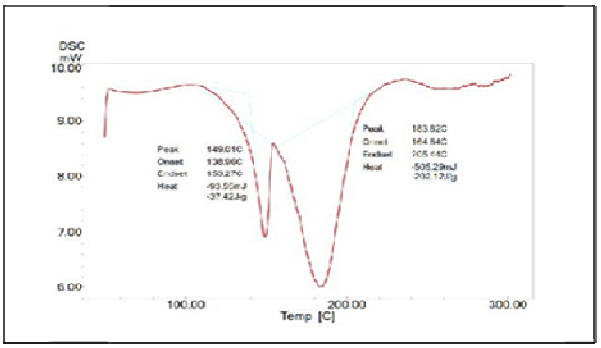

Fig 1: DSC Thermograms (a) Pure drug (Zopiclone) (b) Physical mixture of Optimized film formulation

FT-IR Study:

From FTIR spectra of pure Zopiclone 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. In case of physical mixture of final optimized film formulation containing Drug, HPMC6cps, aspartame and citric acid also show same FTIR wave numbers peak as pure Zopiclone, so these results suggest that there is no any functional group changes of Zopiclone in case final formulation of film. So all ingredients are chemically compatible with each other's in film.

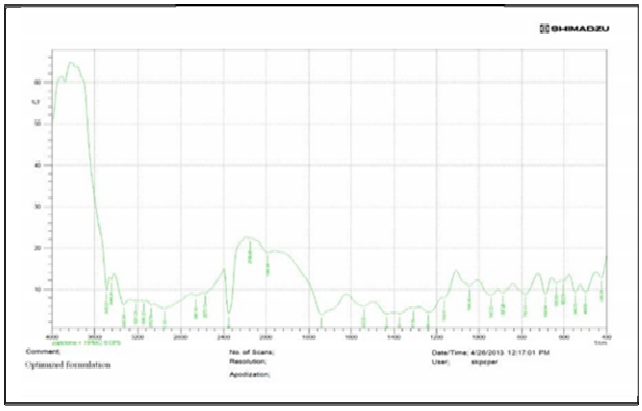

Fig 2: FTIR spectra of physical mixture of film formulation

UV Spectrophotometric Analysis (BP 2010):

The UV calibration curve of Zopiclone was constructed in phosphate-buffered saline (PBS) at pH 6.8 (2.38 g Na2HPO4, 0.19 g KH2PO4, and 8.00 g NaCl / 1L of distilled water). 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, UV-1800 PC, Japan) 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 =0.997.

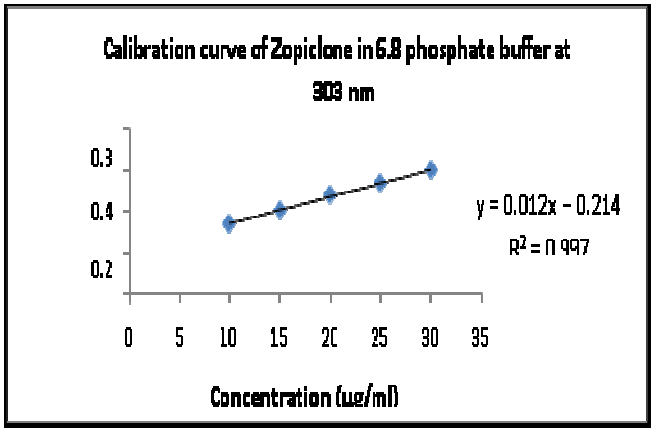

Fig 3: CalibrationcurveofZopiclonein6.8phosphate bufferat303nm

Evaluation of Selected Polymers:

From results 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 in terms 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 clarity 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.

Optimization of HPMC 6cps and glycerin by 3^2 factorial designs:

HPMC 6cps and glycerin concentration optimization were carried out by taking these two variable at three level and dependent variables like tensile strength,% elongation, Q3min and folding endurance results obtained from these batches are shown in table 6.

Stability Study results of optimized batch films:

The films stored under accelerated conditions did not show any changes with respect to content uniformity thus no problem of drug dose variation in these prepared film formulation. In case of physical appearance of film that were stored accelerate condition (75% RH and 400C) clear homogeneous film remained throughout 30 days of film formulation so films were stable in accelerate condition. Results of in vitro DT and folding endurance also suggest that as temperature increase amount of moisture in the film that remain less and due to insufficient amount of moisture presence it will diminish the film forming properties of HPMC, so hard and brittle film formed. That also results into more DT time. By this way final formulation was stable in accelerate condition.

Process Parameters Optimization for Optimized Film Formulation:

Optimizations of process parameters are mandatory for any dosage formulation preparation at large scale. Here solvent casting technique was used so optimization of drying time and drying temperature considered as crucial parameter to be checked. Nine batches results for in vitro DT time (seconds), Q3 min (%), tensile strength (N/mm 2) and % elongation and f2 value were calculated as deciding the desired value for these four response Results of . f2 value of nine batches (P1-P9) were also shown in table 9.Drying time play very major role in mechanical property like thickness, tensile strength, folding endurance, and % elongation, *in vitro* disintegration and also *in vitro* drug release after 3 minute of film that is shown in table 6.19 since again same theory of mass transfer of water from film due to more and more heat energy provided by longer drying time at fixed temperature. Drying time also decided the manufacturing speed of film formulation and thus production cost. So, film prepared at room temperature (30^0c) and 20 hrs dried had well in terms of all properties those were desired in fast dissolving film of Zopiclone. In case of these experiment results suggest that 20 hrs drying at 30^0C gave good film formulation. So, it was optimized processing condition amongst other selected processing condition for fast dissolving film of Zopiclone.

Validity of Regression Equations of 3^2 full factorial design (Check point batch):

Full factorial design gives regression equation for response for selected variables within range selected for those variables. But validity of these equation are confirmed within those selected range by taking one or more check point batches at particular value of those selected variables. Here we found that relative error was less than 2% for all responses like tensile strength, % elongation and amount of drug released at 3 minute for both level {(Drying temp., drying time)}. So equations obtained for selected responses are validated in selected range of variables. Thus these regression equations are further useful for deriving the desired response from selected range of variables.

4. Conclusion

The fast dissolving film of Zopiclone obtained by the solvent casting method showed acceptable mechanical properties and satisfactory drug release after 3 minute. The prepared film was transparent with smooth surface without any drug excipients interaction. The multiple regression analysis of the results led to be equations that describe adequately the influence of the selected variables concentration of HPMC 6cps and concentration of glycerin on the responses under study.In preliminary work various polymers like PVA, Maltodextrins, HPMC 5cps and HPMC 6cps were used to prepare the FDFs of Zopiclone. It has been found that HPMC 6cps with 400 mg gave good results as compared to PVA and HPMC5cps and Maltodextrin. Different concentrations of the glycerin (90,120 and 150 mg of dry polymer weight) were used as a plasticizer during film formation. Plasticizer (glycerin) at 150 mg concentration of total polymer weight gave excellent results in preliminary work. Further optimization of HPMC 6cps and glycerin wascarried out using32 full factorial design as well as overall desirability criteria. Previous work done enumerated that stability is major issue in FDFs so stability study in accelerated condition (400c and 75%RH) was performed for optimized batch F3.In nutshell, fast dissolving film of Zopiclone was successfully developed with good in-vitro characteristics at laboratory scale. Hence, developed fast dissolving film formulation can be a new era of drug delivery in future.

Table-3: Formulation composition of 3^2 full factorial design batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zopiclone (mg)	74	74	74	74	74	74	74	74	74
HPMC 6 cps(mg)	400	400	400	600	600	600	800	800	800
Glycerin(mg)	90	120	150	90	120	150	90	120	150

Citric acid(mg)	50	50	50	50	50	50	50	50	50
Aspartame(mg)	60	60	60	60	60	60	60	60	60
Pineapple flavour	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Methanol(ml)	5	5	5	5	5	5	5	5	5
Isopropyl alcohol(ml)	5	5	5	5	5	5	5	5	5
Dichloromethane(ml)	10	10	10	10	10	10	10	10	10

Table 4: Preformulation data of Zopiclone

Tests	Results of analysis
Description	White to gray-white, crystalline powder
Solubility	Sparingly soluble in water, freely soluble in chloroform and methelyne dichloride
Odour	Odorless

Table 5: Evaluation of selected polymers

Batchcode	Polymer used	Film forming capacity	Appearance	Disintegration time (sec)
P1	HPMC 5cps	Good	Semitransparent	37
P2	HPMC 6cps	very good	Transparent	31

*All batches contain 74 mg of Zopiclone

Table 6: Results of 32 full factorial design Batches

Batch Code	Tensile strength (N/mm2)	% Elongation	Q3min (%)	*f2* value
F1	4.02	82.43	96.02	96.73
F2	4.57	85.50	96.85	98.73
F3	4.99	87.34	97.11	99.19
F4	5.23	89.65	93.71	89.69
F5	5.56	92.45	94.33	91.61
F6	5.67	94.23	95.05	93.86
F7	5.87	95.25	83.27	67.88
F8	5.98	97.45	84.94	70.33
F9	6.17	98.34	88.11	75.82

Table 7: Results of 3^2full factorial design Batches

Batch Code	In vitro D.T time (sec)	Thickness (mm)	Content uniformity (%)	Palatability grade
F1	42	0.08	97.11	A
F2	41	0.07	98.97	B
F3	39	0.08	99.33	A
F4	42	0.09	95.96	A
F5	47	0.11	96.60	A
F6	45	0.09	95.74	A
F7	44	0.09	94.57	B
F8	45	0.15	96.80	A
F9	49	0.12	94.03	A

Table 8: Results of stability data for F3 batch

Stability condition	Sampling time	Observations			
		Folding endurance	In vitro DT	Visual appearance	Drug Content
Accelerated Condition (40 ± 2^{0C} and 75±5% RH)	Initial (0 day)	>100	39	Clear homogeneous film	95.60
	After 10 days	>100	40		95.45
	After 20 days	>100	43	Slightly hazy film	95.94

	After 30 days	>100	41	Slight recrystallization	94.89

Table 9: Results of process parameters study

Batch	*In vitro* D.T(Sec)	% Elongation	Y3min (%)	Tensile strength (N/mm2)	*f2* value
P1	37	90.34	97.45	6.45	95.56
P2	39	89.15	95.54	5.98	99.72
P3	39	85.34	93.66	5.76	98.50
P4	41	81.45	92.3	5.43	94.87
P5	41	78.23	90.14	5.22	88.21
P6	42	70.78	88.12	5.01	82.67
P7	45	64.67	87.22	4.89	80.49
P8	47	59.12	85.97	4.54	77.72
P9	49	50.43	82.13	4.23	70.75

Table 10: Results of Thickness, content uniformity, folding endurance and Physical appearance of P1-P9 batch

Batch code	Thickness (mm)	Content uniformity	Folding endurance	Physical Appearance
P1	0.08	95.86	21	Sticky and soft film
P2	0.07	96.14	>50	Very good clear film
P3	0.08	96.09	>50	Good film, less flexibility
P4	0.09	95.57	>50	Good film with bubbling
P5	0.11	93.67	22	Good film, bubbling, brittle
P6	0.09	91.26	12	brittle and bubbled film
P7	0.09	93.89	>50	Air bubble, flexible
P8	0.15	88.82	19	Brittle film with air bubble
P9	0.12	90.34	13	Brittle with air bubble

Table 11: Check point batch results

	Parameter	Predicted value	Experimental value	Relative Error %
Batch C1 (Drying temp. 31.20^{0}c and Drying time 17.34 hrs)	Tensile Strength	5.99	6.10	1.83
	% elongation	84.32	85.82	1.77
	Y3 min (%)	94.99	95.97	1.03
	D.T.(sec)	38.81	39	0.49

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