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Original Article

DEVELOPMENT AND EVALUATION OF SUBLINGUAL TABLET OF ZOLPIDEM TARTRATE AN ANTIPSYCHOTIC DRUG

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ABSTRACT

Objective: The present work aims to develop and evaluate sublingual tablets of Zolpidem Tartrate used for the short-term treatment of insomnia.

Methods: The tablet of Zolpidem Tartrate was prepared by direct compression technique using two classes of super disintegrates represented by Crospovidone and Sodium Starch Glycolate (SSG) and the efficiency of these super disintegrants in the tablets was compared with various tests like disintegration time, waiting time, water absorption ratio, *in-vitro* dissolution profile and stability study.

Results: The disintegration efficiency of Crospovidone is better than SSG. Fourier Transform Infrared (FT-IR) spectrum of pure drug and the mixture of drug polymers revealed no chemical interaction. The pre-compression study indicated good flow properties of the bulk powder. *In-vitro* drug release from the formulations was studied using buffer pH 6.8. From the entire formulations, F5 and F6 containing 4 % and 5 % of Crospovidone conceded as an optimized formulation which is showing the drug release of 102.00±0.21 % and 103.10±0.42 % in 30 min considerably.

Conclusion: The results indicated that delivery of Zolpidem Tartrate into the systemic circulation via the sublingual route to improving its bio-availability and circumvent the first-pass effect. The optimized formulations were also found to be stable during stability studies conducted for 3 mg as per ICH guidelines.

Keywords: Insomnia, Zolpidem Tartrate, Crospovidone, Sodium Starch Glycolate, *In-vitro* disintegration, *In-vitro* drug release, Sublingual tablet

INTRODUCTION

In the current scenario, there is an increased incidence of sleep disorder due to several reasons. Sleep disorders (somnipathies) are conditions characterized by disruptions of sleep quality or of sleep pattern. They can involve difficulty falling asleep (prolonged sleep onset latency); difficulty staying asleep (disturbance of sleep maintenance), sleep of poor quality (unrefreshing), or combinations of these and can lead to poor health and quality of life problems [1]. In medical practice, insomnia is one of the most common disorders and, for its treatment a lot of pharmacological agents are available. 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. Further improvement in the management of insomnia and other sleep disorders resulted after the recent introduction of non-benzodiazepine hypnotics such as zolpidem, zopiclone, and zaleplon. In particular Zolpidem, the active moiety of Zolpidem Tartrate is chemically, N, N, 6-trimethyl-2-p-tolylimidazo [1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1) that exhibit strong hypnotic and sedative actions with negligible anxiolytic, muscle relaxant, or anticonvulsant properties and is widely prescribed for the short-term treatment of insomnia [2]. Zolpidem Tartrate [1, 3-5] is a white to off-white crystalline powder and is slightly soluble in water, sparingly soluble in alcohol, propylene glycol, practically insoluble in methylene chloride, freely soluble in 0.1N sulfuric acid and inorganic solvents like acetonitrile, methanol. Zolpidem Tartrate acts by GABA-A Receptor Agonists and causes Sedative and Hypnotic action. For adults, the recommended initial dose is 5 mg for women and either 5 or 10 mg for men.

Sublingual route is one of the oral mucosal drug delivery systems, where the placement of the drug under the tongue and drug reaches directly into the blood stream through a ventral surface of the tongue and the floor of the mouth. The drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained into systemic circulation [6]. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes [7-9].

Presently EDLUAR (5 and 10 mg) and INTERMEZZO (1.75 and 3.5 mg) are the Zolpidem Tartrate products marketed for the treatment of insomnia as a sublingual tablet, and no generics are available in the market. In this study, we tried to develop Zolpidem Tartrate sublingual tablets as an alternate formulation of the available products.

MATERIALS AND METHODS

Materials

Zolpidem Tartrate gift sample from Medreich, Bengaluru, India, Crospovidone, Microcrystalline Cellulose, Poloxamer 188 and Aspartame was purchased from Sigma-Aldrich Corporation, Bengaluru, India. SSG, Disodium hydrogen phosphate, Magnesium stearate and Sodium hydroxide pellets were purchased from S. D. Fine Chemical Limited, Mumbai, India. Potassium dihydrogen phosphate and potassium bromide (IR grade) were purchased from Merck, Mumbai, India. Mannitol was purchased from Roquette Pharma, Bengaluru, India.

FT-IR spectroscopic study

This was carried out to find out the compatibility between the drug Zolpidem Tartrate and the polymers such as Crospovidone, SSG, Microcrystalline cellulose, Poloxamer, Aspartame. The prepared pellet was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in Perkin Elmer FT-IR spectrophotometer. The spectra obtained were compared and interpreted for the functional group peaks.

Formulation of zolpidem tartrate loaded sublingual tablets

Separately sift the Zolpidem Tartrate, Crospovidone XL, Mannitol (Pearlitol DC400), SSG, Microcrystalline cellulose, Poloxamer,

Aspartame through #30 mesh and Magnesium stearate through #60 mesh and collected individually in a double-lined polyethylene bag. Then, mix the Zolpidem Tartrate, Mannitol (Pearlitol DC400), Crospovidone XL, SSG, Microcrystalline cellulose in different concentration as given in (table 1 and 2) by using mortar and pestle for 10 min. To the premixed blend, Aspartame and Poloxamer 188 was added and thoroughly mixed for 15 min. As a lubricant add Magnesium stearate to the above blend. Then tablets were prepared by direct compression by 12 station tablet compression machine manufactured by Rimek, India (I. P/B. P/U. S. P. Standard) of 6 mm Flat Faced Bevel Edged (FFBE) punches. The total weight of the tablet was made up to 100 mg.

Table 1: Composition for the preparation of zolpidem tartrate sublingual tablets

Name of the ingredients	Quantity/Unit dose (mg)					
	F001	**F002**	**F003**	**F004**	**F005**	**F006**
Zolpidem Tartrate	*5.00*	*5.00*	*5.00*	*5.00*	5.00	5.00
Mannitol (Pearlitol DC 400)	60.00	60.00	57.00	-	56.00	55.00
Mannitol (Parteck M-200)	-	-	-	57.00	-	-
Croospovidone XL	1.00	2.00	3.00	3.00	4.00	5.00
Sodium Starch Glycolate	-	-	-	-	-	-
Microcrystalline Cellulose	28.00	28.00	30.00	30.00	30.00	30.00
Poloxamer 188	1*.00*	1.00	1.00	1.00	1.00	1.00
Aspartame	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium Stearate	3.00	3.00	2.00	2.00	2.00	2.00
Average weight of tablets (mg)	100.00	100.00	100.00	100.00	100.00	100.00

Table 2: Composition for the preparation of zolpidem tartrate sublingual tablets

Name of the ingredients	Quantity/Unit dose (mg)					
	F007	**F008**	**F009**	**F010**	**F011**	**F012**
Zolpidem Tartrate	*5.00*	*5.00*	*5.00*	*5.00*	5.00	5.00
Mannitol (Pearlitol DC 400)	60.00	60.00	-	-	-	60.00
Mannitol (Parteck M-200)	-	-	57.00	60.00	65.00	-
Croospovidone XL	-	-	-	-	-	-
Sodium Starch Glycolate	1.00	2.00	3.00	4.00	5.00	5.00
Microcrystalline Cellulose	29.00	28.00	30.00	26.00	20.00	25.00
Poloxamer 188	1*.00*	1.00	1.00	1.00	1.00	1.00
Aspartame	2.00	2.00	2.00	2.00	2.00	2.00
Magnesium Stearate	3.00	2.00	2.00	2.00	2.00	2.00
Average weight of tablets (mg)	100.00	100.00	100.00	100.00	100.00	100.00

Evaluation of zolpidem tartrate compressed tablets [10, 11]

Pre-compression parameters

Pre-compression parameters Bulk Density (Db), Tapped Density (Dt), Compressibility index (Carr's Index) (CCI), Hausner's Ratio and Angle of Repose were carried out.

Post-compression parameters [12-14]

Thickness of prepared tablets

The thickness and diameter of the tablet were measured using Vernier calipers. It is measured in mm.

Friability (F)

The friability was determined by using Roche friabilator. The percentage friability was calculated for each batch by using the following formula

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Where,

$W_{initial}$ = initial weight of the tablets

W_{final} = Final weight of tables

Weight variation test

20 tablets were selected at random from a lot, weighed individually, and the average weight was determined. The percent deviation of each tablet weight against the average weight was calculated. The test requirements are met; if not more than two of the individual weight deviates from the average weight of not more than existing 5 %.

Uniformity of drug content

The prepared tablets were tested for their drug content. 20 tablets of each formulation were finely powdered; weight equivalent to 100 mg of powder was accurately weighed, and the drug Zolpidem tartrate was completely extracted with methanol and the solution was filtered. 1 ml of the filtrate was suitably diluted using phosphate buffer of pH 6.8 and analyzed for Zolpidem tartrate content by a UV spectrophotometer at 241 nm.

Wetting time [13]

The tablets wetting time was measured by a procedure modified from that reported by Bi *et al.* The tablet was placed at the center of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablets was then recorded using a stopwatch.

Water absorption ratio [13]

A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio (R), was determined using the following equation.

$$R = 100 \times Wa–W_b/Wa$$

Where,

Wa = Weight of tablet after water absorption.

W_b = Weight of tablet before water absorption.

***In-vitro* disintegration time [15]**

In-vitro disintegration study of Zolpidem Tartrate was carried out by using Disintegration Tester (USP) ED2L model. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless steel screen (mesh no. 10) was immersed in a water bath at 37±2 °C. The time required for the complete disintegration of the tablet in each tube was determined.

In-vitro dissolution study [15]

The *in-vitro* dissolution studies of prepared Zolpidem Tartrate were carried out for the formulations using phosphate buffer of pH 6.8 for 30 min in USP apparatus type II. The samples were measured by UV Spectrophotometer at 241 nm for Zolpidem Tartrate against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time. Calibration cure for Zolpidem Tartrate, in phosphate buffer of pH 6.8, was linear from 2 to10 µg/ml (r^2>0.99)

Stability study [16]

The selected formulations were packed in the strip packaging Alu-Alu, which was placed in the cardboard box and labeled. They were then stored at 40 °C/75 % RH and kept for three months and evaluated for their Hardness, drug content, and drug release at specific intervals of time as per ICH Guidelines.

Statistical analysis

The *in-vitro* release data obtained were statistically analyzed by one-way ANOVA followed by Tykey method. A probability value of p<0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

Pre-formulation studies

Organoleptic properties of zolpidem tartrate were found to be normal.

FT-IR spectroscopic study

The IR spectrum of the pure drug and the pure drug with used excipients is given in table 3 and fig. 1, 2, 3, 4, 5, 6, 7, 8 and 9. It concludes that Zolpidem Tartrate is compatible with all the excipients used in the formulation.

Table 3: Compatibility studies of zolpidem tartrate

Excipients	Drug/Excipients ratio	Physical description initial	40 °C/75 % RH		
			1st week	2nd week	3rd week
Drug	1:1	White amorphous powder	*	*	*
Drug+Mannitol	1:1	White amorphous powder	*	*	*
Drug+Crospovidone	1:1	White amorphous powder	*	*	*
Drug+SSG	1:1	White amorphous powder	*	*	*
Drug+Poloxamer	1:1	White amorphous powder	*	*	*
Drug+MCC	1:1	White amorphous powder	*	*	*
Drug+Aspartame	1:1	White amorphous powder	*	*	*
Drug+Magnesium stearate	1:1	White amorphous powder	*	*	*

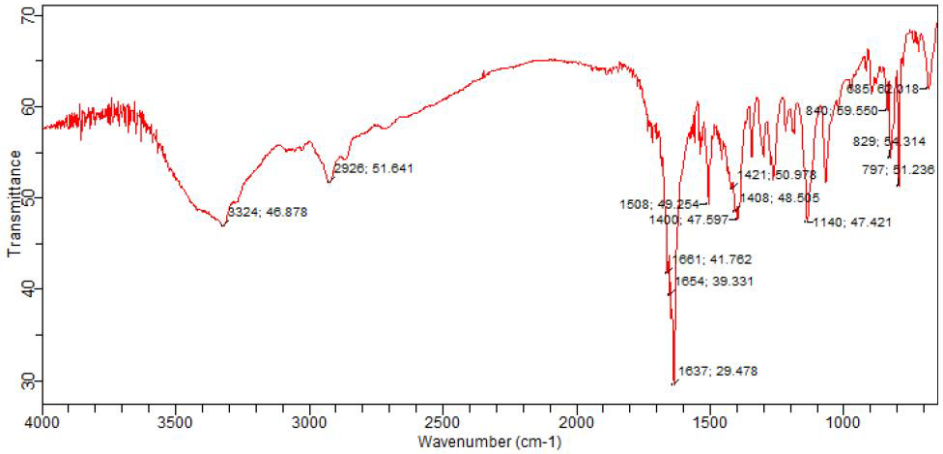

Fig. 1: FTIR spectra of zolpidem tartrate

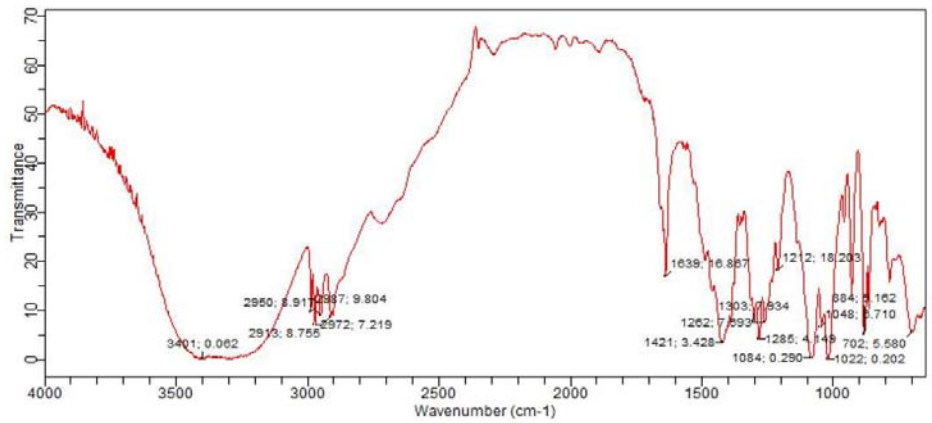

Fig. 2: FTIR spectra of zolpidem tartrate with pearlitol DC 400

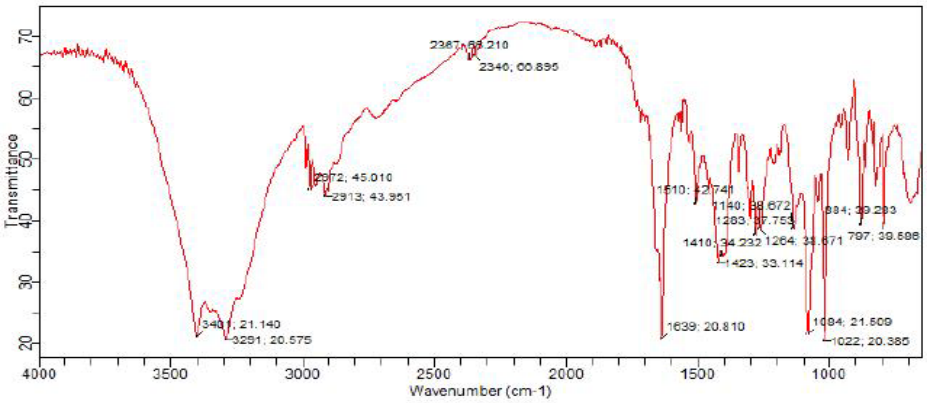

Fig. 3: FTIR spectra of zolpidem tartrate with parteck M 200

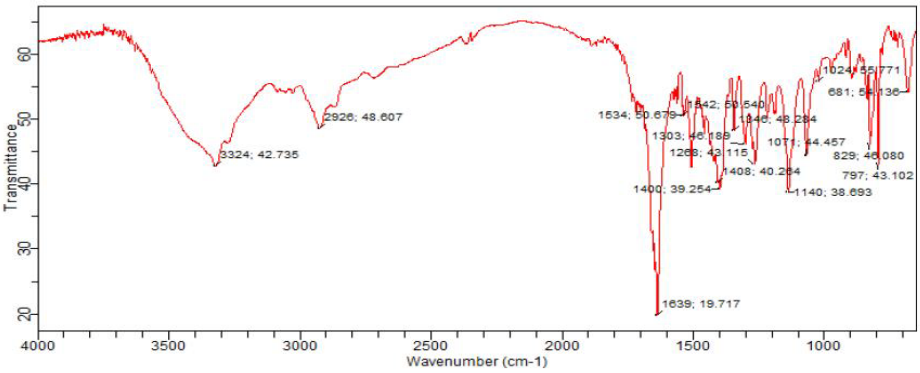

Fig. 4: FTIR spectra of zolpidem tartrate with crospovidone

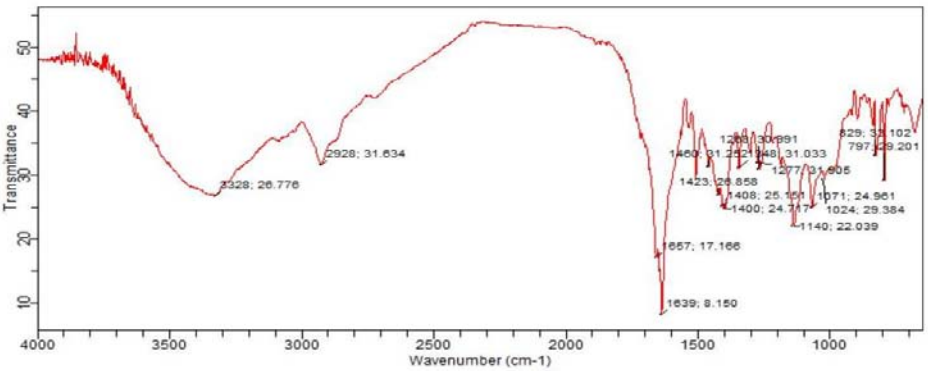

Fig. 5: FTIR spectra of zolpidem tartrate with SSG

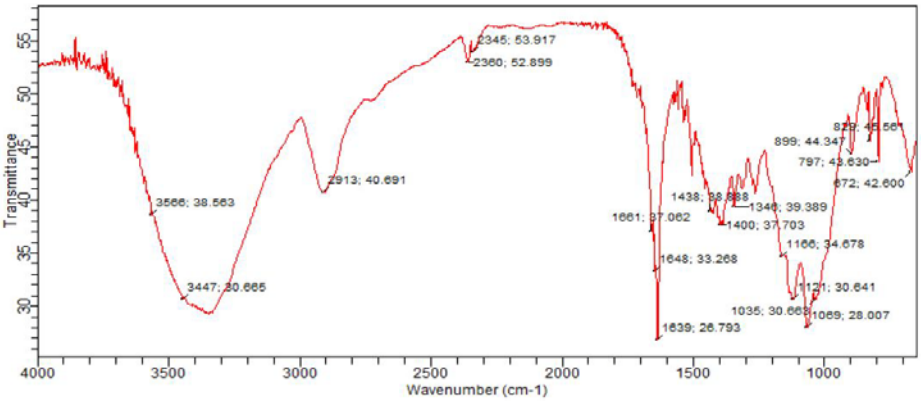

Fig. 6: FTIR spectra of zolpidem tartrate with MCC

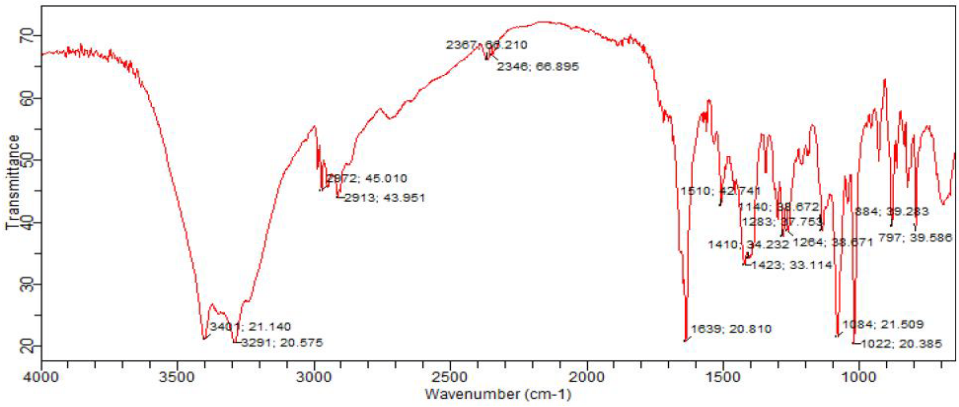

Fig. 7: FTIR spectra of zolpidem tartrate with poloxamer

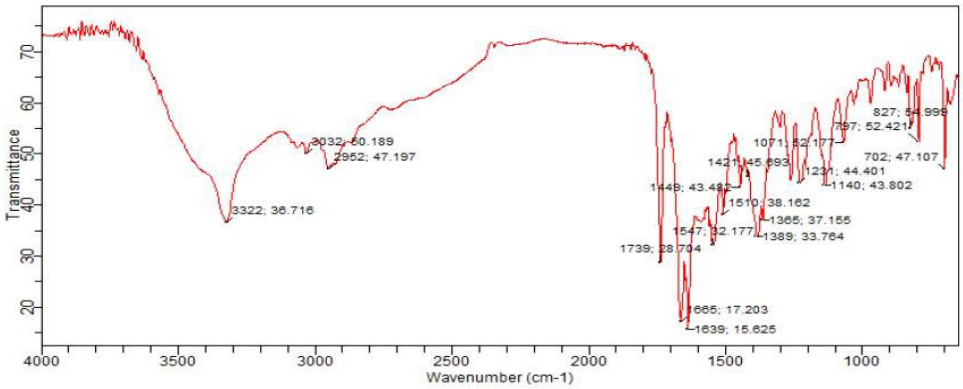

Fig. 8: FTIR spectra of zolpidem tartrate with aspartame

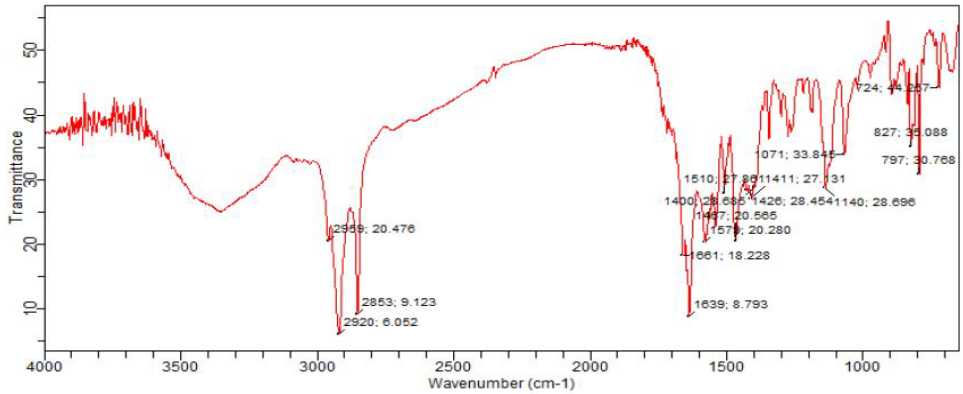

Fig. 9: FTIR spectra of zolpidem tartrate with magnesium stearate

Table 4: Evaluation of pre-compression parameters of formulations F1-F6

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.420±0.03	0.500±0.04	16.00±0.02	1.19±0.01	27.02±0.13
F2	0.431±0.05	0.512±0.06	15.82±0.04	1.18±0.01	25.00±0.11
F3	0.378±0.06	0.445±0.06	15.05±0.03	1.17±0.03	24.25±0.14
F4	0.430±0.08	0.506±0.03	15.01±0.02	1.17±0.05	24.00±0.12
F5	0.391±0.02	0.439±0.04	10.93±0.05	1.12±0.02	20.12±0.13
F6	0.399±0.03	0.456±0.01	11.50±0.04	1.14±0.03	22.13±0.11

*mean±SD, n = 3.

Evaluation of pre-compression parameters

Pre-compression parameters of all formulations were in acceptable range as per the specification [17, 18]. And the results like, Bulk density ranges from 0.358±0.06 gm/cc to 0.431±0.05 gm/cc, Tapped density ranges from 0.410±0.01 gm/cc to 0.512±0.06 gm/cc,

Compressibility or Carr's index ranges from 10.93±0.05 % to 16±0.02 %, Hausner's ratio ranges from 1.09±0.06 to 1.19±0.01 and angle of repose ranges from 20.12±0.13 ° to 27.02±0.13 °. Hence, it concludes that all the prepared formulations fall under excellent flow property except F1 and F12 which falls under good flow property, and it is given in the table no 12 and 13 for the F1-F6 and F7-F12 respectively.

Table 5: Evaluation of pre-compression parameters of formulations F7-F12

Formulations	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F7	0.395±0.04	0.450±0.02	12.22±0.05	1.13±0.03	22.52±0.12
F8	0.358±0.06	0.410±0.01	12.68±0.04	1.14±0.06	22.60±0.15
F9	0.410±0.03	0.466±0.06	12.01±0.02	1.13±0.03	22.97±0.12
F10	0.405±0.07	0.459±0.02	11.76±0.04	1.13±0.05	25.37±0.15
F11	0.398±0.05	0.450±0.04	11.55±0.02	1.13±0.03	23.12±0.11
F12	0.384±0.08	0.432±0.04	11.11±0.05	1.09±0.06	26.78±0.16

*mean±SD, n = 3.

Evaluation of post-compression parameters

The results for Thickness (2.5-3.5 mm), Hardness (3.2-3.4 kg/cm^2), Friability (Not more than 1 %), Average weight (Range is 90-110 mg), Weight variation (±5 % from the average weight) and content uniformity (90-110 %). All these parameters of formulation F1-F4 are given in table 6, F5-F8 is given in table 7 and F9-F12 is given in table 8. This shows all formulations are within the prescribed ranges as specified by the pharmacopeia [19]. Hence, all prepared formulations pass the post-compression studies.

Table 6: Post-compression parameters of formulations F1–F4

Tests	Specification	F1	F2	F3	F4
Thickness* (mm)	2.5-3.5 mm	2.9±0.01	2.7±0.01	2.9±0.02	3.0±0.01
Hardness* (kg/cm^2) (%)	3.2-3.4 kg/cm	3.4±0.10	3.3±0.05	3.3±0.02	3.2±0.01
Friability*	Not more than (1 %)	0.10	0.09	0.12	0.11
Average weight* (mg)	Range is 90-110 mg	100±0.5	105±0.8	98±0.2	110±0.5
Weight variation*	±5 % from the average weight	2.5 %	2.1 %	2.6 %	2.10 %
Assay* Zolpidem Tartrate	90-110 %	94.20±0.52	98.60±0.64	99.30±0.46	97.78±0.50

*mean±SD, n = 3.

Table 7: Post-compression parameters of formulations F5–F8

Tests	Specification	F5	F6	F7	F8
Thickness* (mm)	2.5-3.5 mm	2.5±0.01	2.6±0.01	3.2±0.02	2.9±0.01
Hardness* (kg/cm^2) (%)	3.2-3.4 kg/cm	3.3±0.10	3.2±0.05	3.4±0.02	3.3±0.01
Friability*	Not more than (1 %)	0.18	0.10	0.05	0.08
Average weight* (mg)	Range is 90-110 mg	99±0.5	105±0.8	98±0.2	110±0.5
Weight variation*	±5 % from the average weight	2.6%	2.7%	2.5%	2.1%
Assay* Zolpidem Tartrate	90-110 %	102.80±0.25	104.09±0.5	93.37±0.71	96.08±0.62

*mean±SD (n=3)

Table 8: Post-compression parameters of formulations F9–F12

Tests	Specification	F9	F10	F11	F12
Thickness* (mm)	2.5-3.5 mm	2.8±0.02	2.5±0.01	3.3±0.02	2.6±0.01
Hardness* (kg/cm^2) (%)	3.2-3.4 kg/cm	3.4±0.10	3.2±0.05	3.3±0.12	3.4±0.11
Friability*	Not more than (1 %)	0.15	0.14	0.12	0.10
Average weight* (mg)	Range is 90-110 mg	95±0.5	90±0.5	90±0.2	98±0.5
Weight variation*	±5 % from the average weight	2.2 %	2.1 %	2.6 %	2.7 %
Assay* Zolpidem Tartrate	90-110 %	92.00±0.72	98.72±0.52	97.23±0.53	99.00±0.56

*mean±SD, n = 3.

Table 9: Evaluations for wetting time, water absorption ratio and disintegration time of Formulations F1-F6

Formulations	Wetting time (s)	Water absorption ratio (%) AM±SD	Disintegration time (s)
F1	25.00±2.00	32.03±0.75	29±1.15
F2	22.67±1.53	34.69±1.33	25±1.12
F3	18.00±1.00	40.11±1.17	20±1.23
F4	16.33±0.58	39.94±1.12	18±1.23
F5	8.22±0.58	48.00±1.46	14±1.16
F6	11.12±0.58	45.50±1.08	16±1.41

*mean±SD, n = 3.

Evaluations from wetting time, water absorption ratio and disintegration time

The evaluation of prepared all formulations for wetting time ranges from 8.22±0.58 s to 28.00±1.00 s, water absorption ratio ranges from 32.03±0.75 % to 48.00±1.46 % and disintegration time ranges from 14±1.16 s to 31±1.15 s and the results of the formulations from F1-F6 are given table 9 and the formulations F7-F12 are given in

table 10. The values of wetting time, water absorption ratio and disintegration time were in the acceptable range as per the pharmacopeia [19]. Results of all formulations are variable and depend on the type and quantity of mannitol and super disintegrating agents used. Formulation F1-F6 contains Crospovidone while the formulations F7-F12 contain SSG as a super disintegrating agent. Also, it was observed that as the concentration of both super disintegrating agent increases, wetting time and disintegration time decreases and water absorption ratio increases but contradictorily effect seen in F6 formulation as compared to F5. Hence, from the table 9 and 10, it was concluded that formulation F5 was the best among all.

Table 10: Evaluations for wetting time, water absorption ratio and disintegration time of Formulations F7-F12

Formulations	Wetting time (s)	Water absorption ratio (%) AM±SD	Disintegration time (s)
F7	28.00±1.00	35.03±0.85	31±1.15
F8	26.67±2.53	36.69±1.33	30±1.12
F9	24.00±1.00	37.11±1.16	28±1.23
F10	19.33±0.58	39.94±1.13	24±1.23
F11	17.22±0.58	41.00±1.46	20±1.16
F12	13.12±0.58	44.50±1.11	17±1.41

*mean±SD, n = 3.

Iv-vitro dissolution study

In-vitro dissolution studies to the prepared Zolpidem Tartrate sublingual tablets are given in table 11 of F1-F6 and in table 12 of F7-F12 formulations. The graphical representations of formulation F1-F3, F4-F6, F7-F9 and F10-F12 are given in fig. 10, 11, 12 and 13 respectively; this concludes that at 30th min the *in-vitro* release of all formulations ranges from 48.45±0.26 % to 103.10±0.42.

Among all prepared formulation, F5 showed immediate and highest drug release due to the type and concentration of both mannitol and super disintegrating agents used.

Table 11: *Iv-vitro* release studies of formulations F1 to F6

Time (min)	% Drug release					
	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
2	7.63±0.09	41.63±0.31	41.26±0.49	44.92±0.33	94.29±0.21	84.05±0.52
4	11.68±0.57	67.46±0.26	68.56±0.25	71.14±0.66	95.18±0.45	95.18±0.45
6	16.50±0.44	75.88±0.57	75.52±0.36	75.92±0.21	99.73±0.52	95.99±0.60
8	22.81±0.02	78.49±0.16	77.03±0.62	77.43±0.54	100.76±0.22	97.60±0.26
10	26.23±0.64	81.48±0.45	77.82±0.11	78.22±0.50	100.78±0.41	99.23±0.35
15	34.42±0.49	83.76±0.66	78.97±0.35	79.75±0.45	101.00±0.50	100.96±0.46
20	42.65±1.14	86.04±0.59	81.60±0.42	81.64±0.40	101.80±0.31	101.10±0.32
25	47.27±0.56	87.60±0.21	83.14±0.13	83.55±0.35	102.00±0.12	102.00±0.37
30	51.92±0.34	91.36±0.35	83.95±0.19	87.65±0.02	102.00±0.21	103.10±0.42

*mean±SD, n = 3.

Table 12: *Iv-vitro* release studies of formulations F7 to F12

Time (min)	% Drug release					
	F7	F8	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00	0.00
2	3.96±0.35	22.61±0.51	62.11±0.29	7.62±0.43	71.25±0.50	73.81±0.30
4	7.64±0.52	38.83±0.39	72.69±0.30	27.41±0.25	72.01±0.36	82.63±0.28
6	11.34±0.42	42.70±0.42	77.12±0.36	53.53±0.61	74.61±0.54	89.67±0.16
8	18.71±0.50	48.42±0.36	78.64±0.33	62.23±0.35	80.14±0.31	92.73±0.25
10	22.47±0.61	48.69±0.15	80.17±0.42	62.94±0.23	82.04±0.52	94.33±0.60
15	33.57±0.10	54.80±0.41	83.16±0.24	79.01±0.56	82.48±0.21	95.21±0.25
20	37.41±0.11	56.93±0.36	85.08±0.50	85.66±0.33	83.66±0.11	97.19±0.31
25	41.27±0.35	65.29±0.38	85.54±0.61	90.52±0.38	84.11±0.40	100.00±0.26
30	48.45±0.36	66.37±0.44	86.73±0.19	99.79±0.50	84.93±0.41	101.00±0.43

*mean±SD, n = 3.

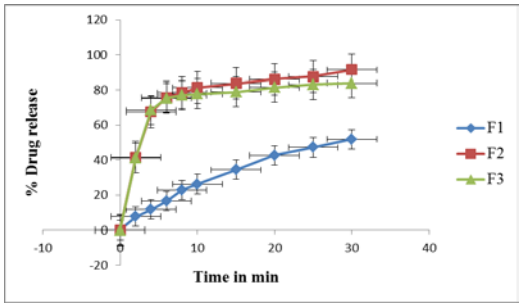

Fig. 10: *In-vitro* release of formulations F1 to F3

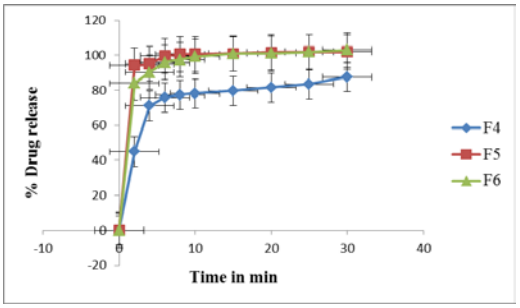

Fig. 11: *In-vitro* release of formulations F4 to F6

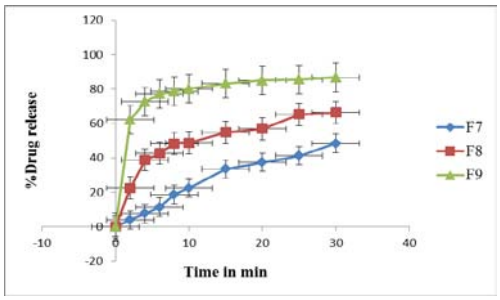

Fig. 12: *In-vitro* release of formulations F7 to F9

Stability study

The accelerated stability study of selected formulation F5 and formulation F6 results were given in table 13 and table 14 respectively, and it concludes that all the parameters were within the acceptable ranges, and even there is no alteration in the physical appearance of formulation F5 and F6.

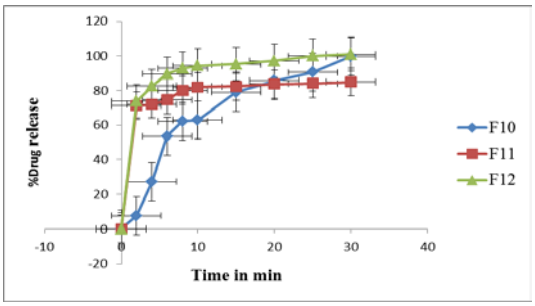

Fig. 13: *In-vitro* release of formulations F10 to F12

Table 13: Stability studies of sublingual tablets of zolpidem tartrate at 40 °C/75% RH of formulation (F5)

Test	Formulation at 40 °C/75 % RH			
	Initial	1 Mo	2 Mo	3 Mo
Hardness*	3.3 kg/cm²	3.3 kg/cm²	3.2 kg/cm²	3.2 kg/cm²
Assay	102.80%	101.15%	100.72%	100.07%
In-vitro disintegration time	14.00 s	14.32 s	15.00 s	15.12 s
Time (min)	% Drug release			
2	94.29±0.21	93.32±0.49	90.16±0.66	88.19±0.16
4	95.18±0.45	94.19±0.71	92.17±0.82	90.57±0.28
6	99.73±0.52	96.54±0.15	94.33±0.54	92.43±0.93
8	100.76±0.22	99.66±0.84	97.81±0.16	93.06±0.85
10	100.78±0.41	100.32±0.89	98.58±0.91	93.34±0.64
15	101.00±0.50	100.75±0.61	99.24±0.93	94.95±0.28
20	101.80±0.31	101.61±0.64	100.36±0.45	96.46±0.48
25	102.00±0.12	101.65±0.14	100.00±0.37	98.67±0.63
30	102.00±0.21	101.85±0.20	100.13±0.52	98.89±0.36

Table 14: Stability studies of sublingual tablets of zolpidem tartrate at 40 °C/75 % RH of Formulation (F6)

Test	Formulation at 40 °C/75 % RH			
	Initial	1 Mo	2 Mo	3 Mo
Hardness*	3.2 kg/cm²	3.1 kg/cm²	3.1 kg/cm²	3.0 kg/cm²
Assay	104.09%	103.15%	102.72%	102.07%
In-vitro disintegration time	16.00 s	16.32 s	18.00 s	18.12 s
Time (min)	% Drug release			
2	84.29±0.52	82.62±0.45	80.16±0.65	77.19±0.20
4	90.37±0.25	84.29±0.27	83.77±0.65	80.13±0.19
6	95.99±0.60	87.68±0.13	85.54±0.25	83.37±0.89
8	97.60±0.26	94.20±0.64	92.23±0.68	88.23±0.95
10	99.23±0.35	96.72±0.36	94.65±0.85	90.45±0.74
15	100.96±0.46	97.80±0.45	98.59±0.36	94.95±0.28
20	101.10±0.32	99.56±0.58	99.24±0.93	94.42±0.90
25	102.00±0.37	100.19±0.14	99.00±0.54	95.76±0.14
30	103.10±0.42	100.95±0.30	99.16±0.45	97.56±0.50

CONCLUSION

Sublingual tablets of Zolpidem Tartrate can be efficiently and successfully formulated by the direct compression method. Under the pre-formulation studies, API (Active Pharmaceutical Ingredient) characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics. The formulations were prepared by using Crospovidone and SSG as the super disintegrant along with the other excipients. The rapid disintegration was observed for Crospovidone containing tablets, comparing the two classes of super disintegrants represented by Crospovidone and SSG. The disintegration efficiency was found to be better for Crospovidone compared to SSG.

From all the formulations, F5 and F6 containing 4% and 5% Crospovidone showed less wetting time and disintegration time also the dissolution study that has been carried out was found to be faster when compared with that of other formulations. Various physicochemical parameters tested for these formulations have shown good results. Therefore, F5 and F6 were selected as the optimized formulations.

It was concluded that this lowered dose of sublingual tablets of Zolpidem Tartrate (5 mg) prepared by direct compression technique has enough efficacy and can be used efficiently as an alternative to other marketed formulations of Zolpidem Tartrate for short-term treatment of insomnia.

CONFLICT OF INTERESTS

Declare none

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