Research Article

Formulation and Evaluation of Mouth Dissolving Tablet of Zolpidem Tartrate

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ABSTRACT

Conventional solid dosage form suffers from problem like difficulty in swallowing with age, onset of action and physiological factor of patient like gastric emptying time. To overcome this mouth dissolving tablet is a newer approach to drug delivery. Zolpidem is preferentially used for the short term treatment of insomnia. The aim of present study is to formulate and evaluate mouth dissolving tablets of Zolpidem tartrate to improve bioavailability and circumvent the first pass effect. The tablet of Zolpidem was prepared by directing compression method using croscarmellose sodium, sodium starch glycolate as super disintegrant and mannitol, microcrystalline cellulose, dicalcium phosphate as diluents. The effects of different super disintegrants and diluents on disintegration and dissolution time were optimized and on the basis of these parameters, formula was finalized. FTIR study showed compatibility between drug and excipients. The pre-compression study indicated the excellent flow properties of bulk powder which is within an acceptable range of pharmacopoeia specifications. The post compression evaluation parameters results match the expected criteria. From the entire formulations, best *in-vitro* drug release profile was obtained with the system containing sodium starch glycolate (35mg), mannitol (20mg) and microcrystalline cellulose (60mg). These tablets have a hardness less than 4 kg/cm^2, disintegration time of 24 seconds and 97.71% drug release within 30 minutes.

Keywords: Zolpidem tartrate, direct compression method, mouth dissolving tablet, post compression study.

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INTRODUCTION

Solid dosage form is the most preferred dosage form of drug delivery due to the convenience of the patient. In the market many solid dosage forms are available such as effervescent tablets, chewing gum tablets, mucoadhesive tablets. Mouth dissolving tablets are the new approach included in solid dosage form containing drug uniformly dispersed in powder matrix. These tablets dissolve in saliva within a few seconds to release a drug which can be absorbed through pre and post gastrointestinal epithelium layer, thereby improve drug bioavailability.

Mouth dissolving tablets can prepare by various techniques such as direct compression, wet granulation, moulding, spray drying, freeze drying and sublimation [1]. Out of them, the direct compression method is the most preferred method because it does not require water or heat during the formulation procedure and is the ideal method for moisture and heat-labile medications [2]. The basic approach in development of mouth dissolving tablets is the use of superdisintegrant like croscarmellose, sodium starch glycolate and crospovidone which helps the instantaneous disintegration of the tablet after administrating on the tongue, thereby releasing the drug quickly in the saliva [3].

Zolpidem tartrate is a non-benzodiazepine drug belonging to schedule X; used as sedative-hypnotics. It is a white crystalline powder which is sparingly soluble in water, alcohol and easily soluble in buffer solution,

sulfuric acid, and hydrochloric acid solution. It gives agonistic effect on $GABA_A$ receptors and used in the treatment of insomnia. 5mg and 10 mg is dose strength for oral administration [4, 5, 6]. To obtain quick onset of action of Zolpidem, mouth dissolving tablet is the approach taken into consideration.

In the present study, the aim is to formulate and evaluate a mouth dissolving tablet of Zolpidem tartrate by direct compression method and study the effect of different super disintegrant and diluents on disintegration and dissolution time.

MATERIALS AND METHOD

Materials

Zolpidem tartrate was received as gift sample. Cross carmellose sodium (CCS), sodium starch glycolate (SSG), microcrystalline cellulose (MCC PH 101), and dicalcium phosphate (DCP) were received from Medley Pharmaceutical, Mumbai. Aspartame, talc, magnesium stearate, menthol, mannitol was purchased from Research lab Fine Chem. Industries, Mumbai.

Formulation method

Mouth dissolving tablets of Zolpidem tartrate were prepared by direct compression method according to the formula given in the **(Table 1)**. Nine different formulations were prepared. All the ingredients were sieved separately through sieve no. 40 except magnesium stearate which was sieved through sieve no. 60 and collected. The weighed amount of drug and other ingredients were mixed first and magnesium stearate was finally added and mixed thoroughly. The tablets were compressed using 8 mm punch [7].

Table 1: Composition of Mouth Dissolving Tablets of Zolpidem Tartrate

Ingredients	Quantity (mg/tablet)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zolpidem Tartrate	5	5	5	5	5	5	5	5	5
Cross carmelose sodium	25	30	35	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	25	30	35	35	35	35
Mannitol	20	20	20	20	20	20	80	-	-
Microcrystalline cellulose (PH 101)	60	60	60	60	60	60	-	-	80
Dicalcium phosphate	-	-	-	-	-	-	-	80	-
Aspartame	2	2	2	2	2	2	2	2	2
Menthol	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	1	1	1	1	1	1	1	1	1

Pre-compression parameters

Angle of repose

The mixture of powder was allowed to flow through the funnel fixed in definite height (h). The angle of repose was then calculated by measuring the height and radius of the pile of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel [8].

$$\theta = \tan^{-1}(h/r)$$

Where , θ = Angle of repose, h = Height of the pile, r = Radius of the pile

Bulk density

Bulk density (ρ_b) was determined by pouring pre-sieved bulk powder blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula [9].

$$\rho_b = M/V_b$$

Tapped density

The tapped density was determined by placing a graduated cylinder containing a known mass of powder on mechanical tapping apparatus, which was operated for a fixed number of taps (around 500) until

the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was calculated by the formula [10].

$\rho_t = M/V_t$

Where, ρ_t = Tapped density, M = Weight of powder, V_t = Volume of powder

Hausner's ratio

The Hausner's ratio is an index of ease of powder flow. Lower the value (< 1.25) indicates better flow properties. It was determined by using formula [11].

Hausner's ratio=ρ_b/ρ_t

Where, ρ_b = Bulk density, ρ_t = Tapped density

Compressibility index

The compressibility index is a measurement of free property of powder, an indication of the ease with which a material can be induced to flow is given by % compressibility that was calculated as follows [12].

$C = (\rho_t - \rho_b)/\rho_t \times 100$

Where, ρ_t = Tapped density, ρ_b = Bulk density

Drug-Excipients compatibility Study

The drug-excipients compatibility was studied using a FTIR spectrophotometer (Shimadzu IR Affinity -1). 1-2 mg of drug, physical mixture of drug-excipients and powdered tablets were placed on sample holding cavity of the instrument and then respective specturm was recorded. The spectra were scanned over 400 to 4000 cm^{-1} range [13].

Post Compression parameters

Weight variation test

Twenty tablets were selected at random, weighed and the average weight was determined by using a weighing balance. Then individual tablets compared with the average weight. Not more than two of the individual weights deviate from the average weight by more than the 7.5% [14].

Hardness

Six tablets were randomly selected from each batch and hardness of tablets was determined by using the Monsanto Hardness Tester. The mean values and standard deviation for each batch were calculated. The hardness was measured in terms of kg/cm^2 [15].

Friability test

Six tablets from each batch were examined for friability using Roche Fribilator and the equipment was running for 4 min at 25 RPM. The tablets were taken out, de-dusted, reweighed and % friability was calculated [16].

% Friability = (loss in weight/initial weight) x 100

Thickness

Thickness was determined by randomly selecting six tablets from each batch using Vernier caliper. The mean values and standard deviation was calculated [17].

Content uniformity

The tablet was randomly selected from each batch, weighed individually and powdered. The powder equivalent to 5 mg of zolpidem was weighed and dissolved in 100 ml phosphate buffer solutions (pH 6.8), to obtain the stock solution. From this stock solution, suitable dilution was prepared and analyzed using previously validated UV method at 238 nm [18].

Water Absorption ratio

A piece of twice folded tissue paper was placed in a small petri dish containing 5 ml of water. A tablet was placed on the paper and the time required for complete wetting was recorded. The wetted tablet was then weighed. Water absorption ratio (R), was calculated using following formula [19].

$R = 100 \times (W_a - W_b)/W_b$

Where, W_b = Weight of tablet before water absorption, W_a = Weight of tablet after water absorption

***In-vitro* Disintegration test**

The disintegration time was measured using disintegration test apparatus. 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 [20].

***In-vitro* Dissolution time**

Dissolution study was carried using USP II dissolution apparatus. Six tablets were taken from each batch and the dissolution was carried out in a buffer solution (pH 6.8) at 50 rpm, 37± 2°C. 5ml sample was withdrawn from each vessel at the interval of 2 minutes initially, followed by 5 minutes

till it reaches to 30 minutes. Proper dilutions were made and analyzed at 238 nm using UV spectrophotometer [21].

RESULT AND DISCUSSION

Pre formulation study

The results of pre-compression parameters were in the acceptable range as per the specification [22, 23]. The values of Angle of repose, Bulk density, Tapped density, Hausner's ratio and compressibility are shown in the **(Table 2)**, which indicates that the flow property of powder was excellent.

Table 2: Pre Compression Parameters Results of Zolpidem Mouth Dissolving Tablet

Formulation	Bulk density	Tapped density	Hausner's ratio	Compressibility index	Angle of repose (θ)
F1	0.46±0.04	0.52±0.02	1.13±0.01	11.53±0.09	26±0.12
F2	0.49±0.02	0.53±0.02	1.08±0.03	7.54±0.03	31±0.06
F3	0.43±0.05	0.45±0.04	1.04±0.02	4.44±0.07	29±0.7
F4	0.5±0.06	0.57±0.01	1.14±0.02	12.28±0.06	25±0.12
F5	0.41±0.03	0.45±0.02	1.09±0.05	8.88±1.2	33±0.49
F6	0.48±0.05	0.55±0.03	1.14±0.01	4.44±0.07	29±0.98
F7	0.42±0.03	0.45±0.01	1.07±0.03	6.66±0.04	34±0.31
F8	0.39±0.02	0.43±0.02	1.10±0.02	9.30±0.05	27±0.15
F9	0.43±0.01	0.47±0.03	1.09±0.01	8.51±0.09	30±1.2

Values are mean ± S.D.

Compatibility Study

Compatibility study between drug and excipients were carried out using a FTIR spectrophotometer to check any possible drug interaction between them. The spectra of prepared mouth dissolving tablet and the physical mixture were compared with the spectra of pure drug **(Fig. 1)**. The peaks of pure drug remained unaffected suggesting drug compatibility with excipients used in the formulation.

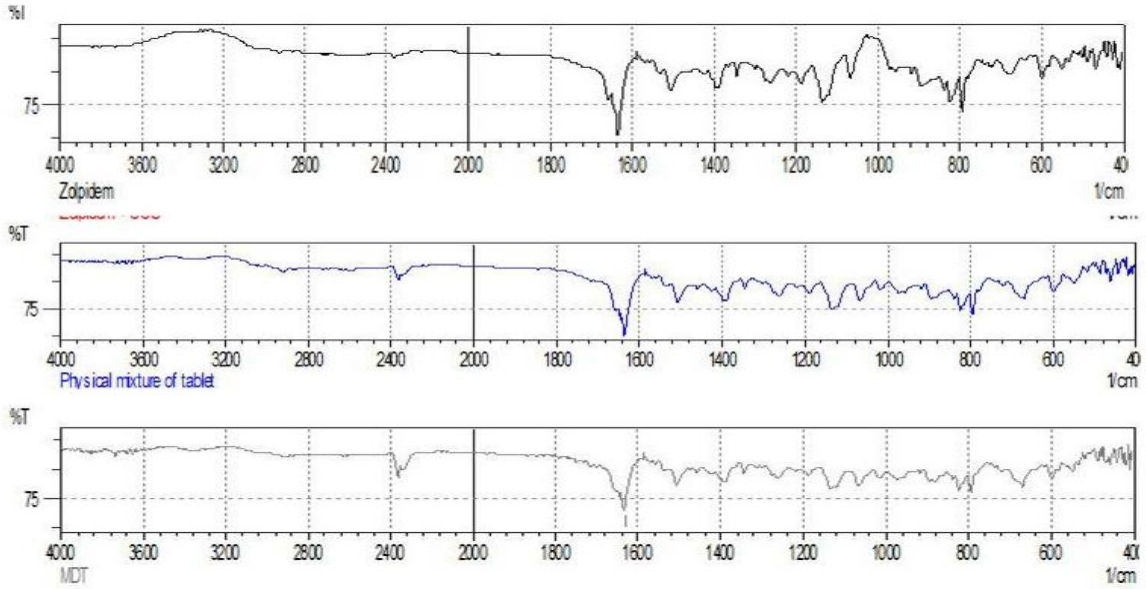

Figure 1: Ftir Spectrum of Mouth Dissolving Tablet and Zolpidem With Excipients

Post compression evaluation study

The values of Weight Variation, friability, hardness, thickness, water absorption ratio and content uniformity are shown in the **(Table 3)**. The results of post-compression parameters were in the acceptable range as per pharmacopoeia specified [24].

Table 3: Evaluation of Post Compression Parameters of Zolpidem Mouth Dissolving Tablets

Formulation	Weight variation (mg)	Hardness (kg/cm²)	Friability test (%)	Thickness (mm)	Content uniformity (%)	Water Absorption ratio (%)
F1	115.52±0.96	3.66±0.10	0.60±0.19	2.17±0.08	99.43±0.44	9.18±0.93
F2	120.97±0.65	3.68±0.09	0.79±0.28	2.26±0.01	99.06±1.11	9.96±0.99
F3	125.52±0.87	3.74±0.14	0.88±0.11	2.21±0.02	100.02±0.39	8.34±0.42
F4	115.76±0.73	3.69±0.08	0.66±0.11	2.16±0.01	99.80±0.46	10.46±0.64
F5	121.87±0.81	3.68±0.11	0.89±0.50	2.15±0.01	99.58±0.33	10.24±0.33
F6	125.80±0.88	3.64±0.07	0.56±0.09	2.22±0.01	99.88±0.22	9.73±0.33
F7	125.17±0.88	2.71±0.11	1.08±0.09	2.23±0.02	99.36±0.25	9.62±0.36
F8	125.52±0.93	3.77±0.13	0.91±0.08	2.27±0.02	99.21±0.44	9.57±0.54
F9	126.07±0.69	3.71±0.12	0.85±0.45	2.21±0.02	100.76±0.96	9.39±0.66

Values are mean ± S.D.

Disintegration study

All the formulations showed variable results of disintegration time depending on the type and quantity of super disintegrants used. Formulation A1 - A3 containing CCS as super disintegrants showed the disintegration time in the range of 34-40 seconds, while the formulation A4 - A6 containing SSG as super disintegrants had disintegration time between 24-31seconds which was quite lower then formulations containing CCS. Also it was observed that as a concentration of super disintegrants increases, disintegration time decreases respectively. Hence, from this **(Table 4)**, it was concluded that formulation A6 was the best among all.

Table 4: Evaluation of Disintegration Time of Zolpidem Mouth Dissolving Tablets

Formulation	Time (sec)
F1	40.15±1.43
F2	38.69±1.20
F3	34.03±1.49
F4	31.64±1.38
F5	27.26±1.21
F6	24.39±1.05
F7	16.25±1.15
F8	31.98±1.28
F9	37.41±1.36

Values are mean ± S.D.

***In-vitro* dissolution study**

Dissolution study was performed using a phosphate buffer solution (pH 6.8) as a dissolution medium in specified condition. The drug release from formulation A1, A2 and A3 were found 87.82%, 90.72% and 93.32% respectively within 30 minutes **(Fig. 2)**, while the formulation A4, A5 and A6 containing sodium starch glycolate showed the drug release of 92.31%, 94.83% and 97.17% respectively within 30 minutes **(Fig. 3)** Suggesting that dissolution rate of formulation is dependent on the type and the concentration of super-disintegrants.

The formulation A7 contains SSG as super-disintegrants and mannitol as diluent. It showed the immediate drug release with initial burst effect due to the high water solubility of mannitol, but problems associated with it was high friability and less hardness. To overcome these problems of hardness and friability in formulation A8-

DCP and A9-MCC was used as diluent, which showed only 85.77% and 75.16% of drug release within 30 minutes **(Fig. 4)**. This low drug release might be due to inorganic nature of DCP and water insolubility of MCC. From this it can conclude that mannitol is best diluent among all but due to hardness and friability problem associated with it, combinations of other diluent should be used. The amount of drug release at various time intervals is shown in **(Table 5)**.

CONCLUSION

From the present study, it can be concluded that Mouth dissolving tablet of Zolpidem tartrate was successfully formulated by direct compression method to improve the drug release profile. The formulation A6 happens to be best among all, as it gave maximum release of drug with faster disintegration time. The combination of diluents like mannitol and MCC were preferred as it gives acceptable hardness and friability to the tablets. Formulation A6 qualifies all the acceptance criteria of mouth dissolving tablet and would be considered as a better alternative to conventional tablets available in the market.

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Table 5: Evaluation of Dissolution Time of Zolpidem Mouth Dissolving Tablets

Time (Minutes)	Cumulative % Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	34.15	37.74	39.27	38.92	40.16	43.31	55.47	31.58	27.48
5	46.05	48.6	51.64	50.55	53.67	56.86	67.72	41.64	37.06
10	55.35	59.16	61.61	61.14	64.51	68.5	77.23	50.65	46.93
15	65.57	69.71	72.42	71.26	74.86	78.92	84.18	59.34	54.83
20	76.41	78.46	81.87	80.45	83.43	87.55	90.44	68.16	62.1
25	81.29	85.19	88.74	87.58	90.56	93.03	96.15	77.28	69.76
30	87.82	90.72	93.32	92.31	94.83	97.17	96.15	85.77	75.16

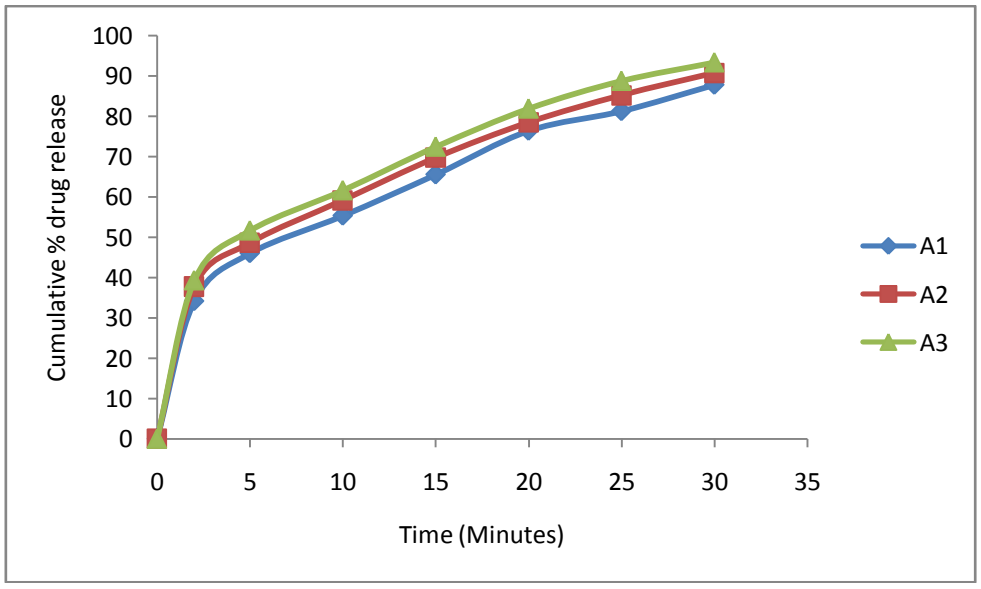

Figure 2: *In-Vitro* Drug Release Profile of Formulation A1, A2, A3

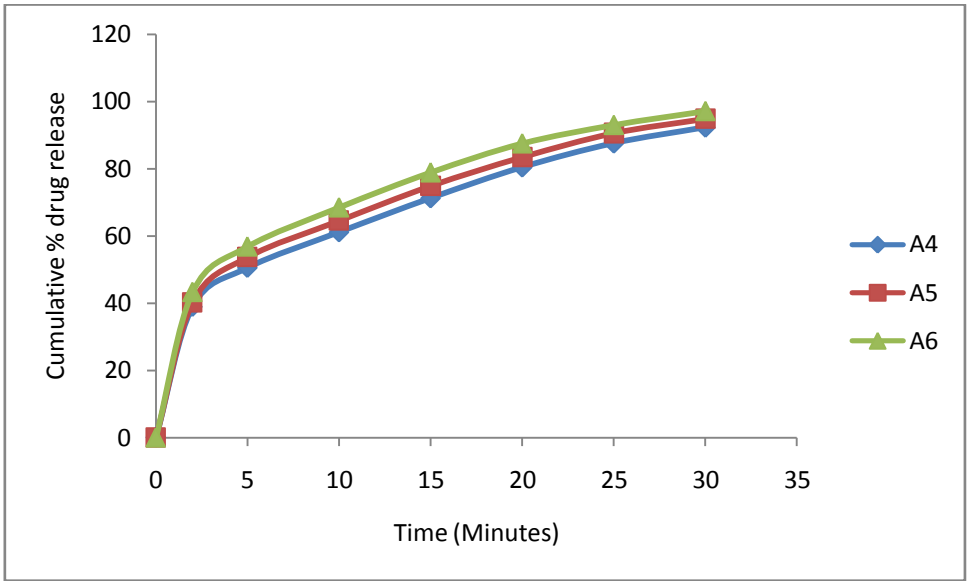

Figure 3: *In-Vitro* Drug Release Profile of Formulation A4, A5, A6

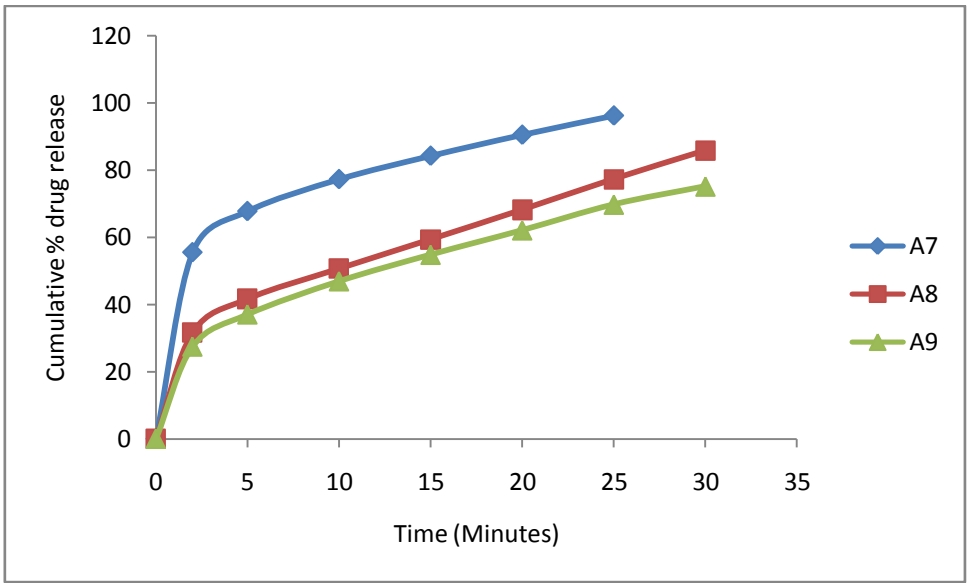

Figure 4: *In-Vitro* Drug Release Profile of Formulation A7, A8, A9

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