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Vikas Kumar Chaudhari
Research Scholar, Department of Pharmacy, Himalayan University, Arunachal Pradesh, India

Dr. Vishal Bhargava
Professor, Department of Pharmacy, Himalayan University, Arunachal Pradesh, India

Correspondence
Vikas Kumar Chaudhari
Research Scholar, Department of Pharmacy, Himalayan University, Arunachal Pradesh, India

Study on the evaluation and formulation of zolpidem tartrate

Vikas Kumar Chaudhari and Dr. Vishal Bhargava

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Abstract
Traditional solid dose forms have a number of drawbacks, including difficulties in swallowing as patients get older, a delayed commencement of action, and issues with physiological factors such as the length of time it takes for the stomach to empty. A tablet that dissolves in the mouth is a relatively recent development in the field of drug delivery. The use of zolpidem in the treatment of insomnia for a relatively short period of time is preferred. The purpose of this study is to improve the bioavailability of zolpidem tartrate and get around the effect of the first transit through the body by formulating and evaluating mouth-dissolving tablets of the drug. The tablet containing Zolpidem was made by employing the directed compression method, with croscarmellose sodium and sodium starch glycolate serving as the super disintegrants, and mannitol, microcrystalline cellulose, and dicalcium phosphate serving as the diluents. The effects of several super disintegrants and diluents on disintegration and dissolving time were optimized, and the formula was completed on the basis of these characteristics. The FTIR investigation revealed that the medication and the excipients were compatible with one another. According to the results of the pre-compression investigation, the bulk powder possesses outstanding flow qualities and falls within a range of pharmacopoeia standards that is considered acceptable. The findings of the post-compression evaluation of the parameters match the criterion that was anticipated. From all of the different formulations, the one that had the highest amounts of sodium starch glycolate (35 mg), mannitol (20 mg), and microcrystalline cellulose yielded the greatest results for the *In vitro* drug release profile (60 mg). These tablets have a hardness that is lower than 4 kg/cm^2, a disintegration period that is only 24 seconds long, and they release 97.71 percent of their pharmacological content within 30 minutes.

Keywords: Zolpidem tartrate, direct compression

Introduction
In terms of patient preference, solid dosage forms are the most common type of drug administration. There are many different types of solid dosage forms on the market. To combat this, a novel technique has been developed: orally disintegrating tablets, which consist of a powder matrix holding the medicine in a uniform distribution. These tablets boost drug bioavailability since the medicine is released in the saliva and can be absorbed by the pre- and post-gastrointestinal epithelial layer. Dissolving tablets for the mouth can be made using a number of different methods, including: direct compression, wet granulation, moulding, spray drying, freeze drying, and sublimation. With no need for either water or heat, direct compression stands out as the best option for handling drugs that are sensitive to both. In order to make tablets that dissolve quickly in the mouth, scientists typically employ a superdisintegrant such as croscarmellose, sodium starch glycolate, or crospovidone. Schedule X substance zolpidem tartrate is a sedative-hypnotic that is not a benzodiazepine. The powder is crystalline and white; it dissolves just slightly in water and alcohol but dissolves completely in buffer solution, sulfuric acid, and hydrochloric acid solution. Useful for combating sleeplessness, it has an agonistic impact on GABAA receptors. Oral dosage strengths of 5 mg and 10 mg are available. The idea of a fast-acting Zolpidem pill that dissolves in the mouth is being considered. The purpose of this research was to formulate and assess a mouth dissolving tablet of Zolpidem tartrate using the direct compression method, and to investigate how varying concentrations of super disintegrant and diluents affected the tablet's disintegration and dissolve rates.

Materials and Methods
A sample of zolpidem tartrate was generously provided to us. Medley Pharmaceutical of Mumbai provided cross carmellose sodium (CCS), sodium starch glycolate (SSG),

microcrystalline cellulose (MCC PH 101), and dicalcium phosphate (DCP). It was from Research lab Fine Chem. Industries in Mumbai that we acquired the aspartame, talc, magnesium stearate, menthol, and mannitol.

Method of Formulation

Formulation for direct compression method used to produce orally disintegrating tablets of Zolpidem tartrate (Table 1). There were nine distinct iterations of the formula made. Each ingredient was then sieved through No. 40 before being collected, with the exception of magnesium stearate, which was sieved through No. 60. First, the medicine and its other ingredients were combined together after being accurately measured, and then magnesium stearate was added and properly blended. We used an 8 mm punch to compact the tablets.

Table 1: Composition of mount dissolving tablets of zolpidem tartrate

Ingredients	Quantity (mg/tablet)								
	Fl	**F2**	**F3**	**F4**	**FS**	**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	80
Dicalcium phosphate									
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.

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

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 (Vb) and weight of powder (M). Was determined. The bulk density was calculated using the formula.

$\rho_b = M/V_b$

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

$\rho_t = M/V_t$

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.

Hausner's ratio=ρ_b/ρ_t

Where, ρb = Bulk density, ρt = 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.

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

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 cm1 range.

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% . **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.

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.

% 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.

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.

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.

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

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.

Results and Discussion

The results of pre-composition parameters were in the acceptable range as per the specification. The values of Angle of repose, Bulk Density, Tapped Density, Hausner's Ratio and Compressibility are shown in 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 (0)
Fl	0.46±0.04	0.52±0.02	1.13±0.01	11.530.09	26±0.12
F2	0.49±0.02	0.53±0.02	1.08±0.03	7.540.03	31±0.06
F3	0.430.05	0.45±0.04	1.04±0.02	4.440.07	29±0.7
F4	0.50.06	0.57±0.01	1.14±0.02	12.28±0.06	25±0.12
FS	0.410.03	0.450.02	1.09±0.05	8.88±1.2	33±0.49
AS	0.480.05	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

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 drug remained unaffected suggesting drug compatibility with excipients used in the formulation.

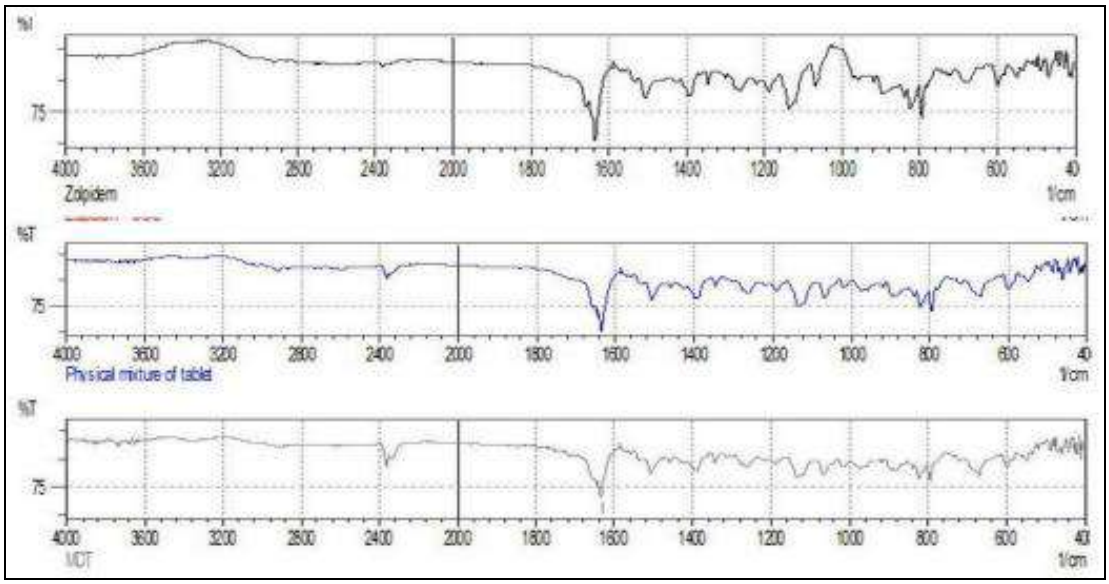

Fig 1: FTIR Spectrum of Mouth Dissolving Tablet and Zolpidem with Excipients

Post Compression Evaluation Study

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

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

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Friability test (%)	Thickness (mm)	Content uniformity	Water Absorption ratio (%)
I	115.520.96	3.66±0.10	0.60±0.19	2.17±0.08	99.43±0.44	9.18±0.93
F2	120.970.65	3.68±0.09	0.79±0.28	2.26±0.01	99.06±1.11	9.96±0.99
F3	125.520.87	3.74±0.14	0.88±0.11	2.21±0.02	100.02±0.39	8.34±0.42
F4	115.760.73	3.69±0.08	0.66±0.11	2.16±0.01	99.80±0.46	10.46±0.64
F5	121.870.81	3.68±0.11	0.89±0.50	2.15±0.01	99.58±0.33	10.24±0.33
F6	125.800.88	3.64±0.07	0.56±0.09	2.22±0.01	99.88±0.22	9.73±0.33
F7	125.170.88	2.71±0.11	1.08±0.09	2.23±0.02	99.36±0.25	9.62±0.36
F8	125.520.93	3.77±0.13	0.91±0.08	2.27±0.02	99.21±0.44	9.57±0.54
F9	126.070.69	3.71±0.12	0.85±0.45	2.21±0.02	100.76±0.96	9.39±0.66

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)
Fl	40.15±1.43
F2	38.69±1.20
F3	34.03±1.49
F4	31.64±1.38
FS	27.26±1.21
F6	24.39±1.05
F7	16.25±1.15
F8	31.98±1.28
F9	37.41±1.36

***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).

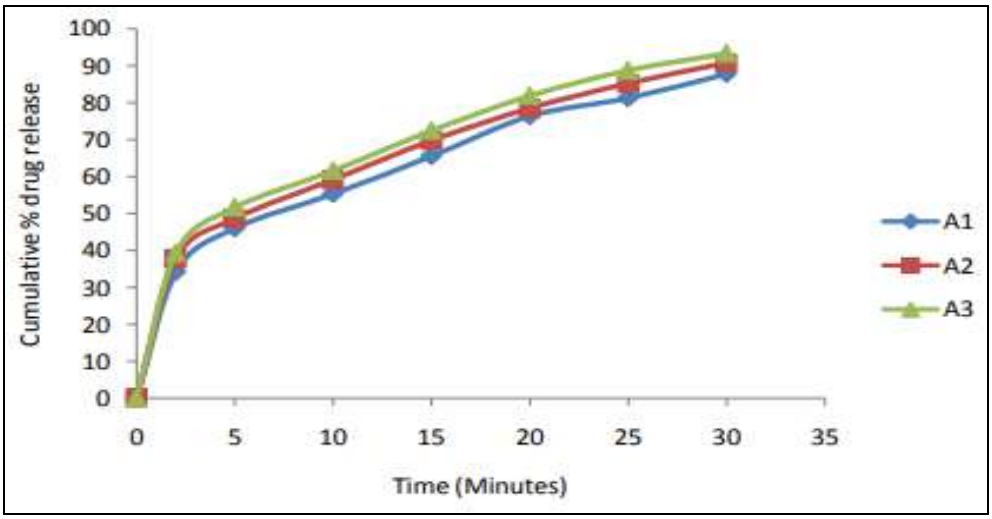

Fig 2: *In vitro* drug Release of Formulation A1, A2 and A3

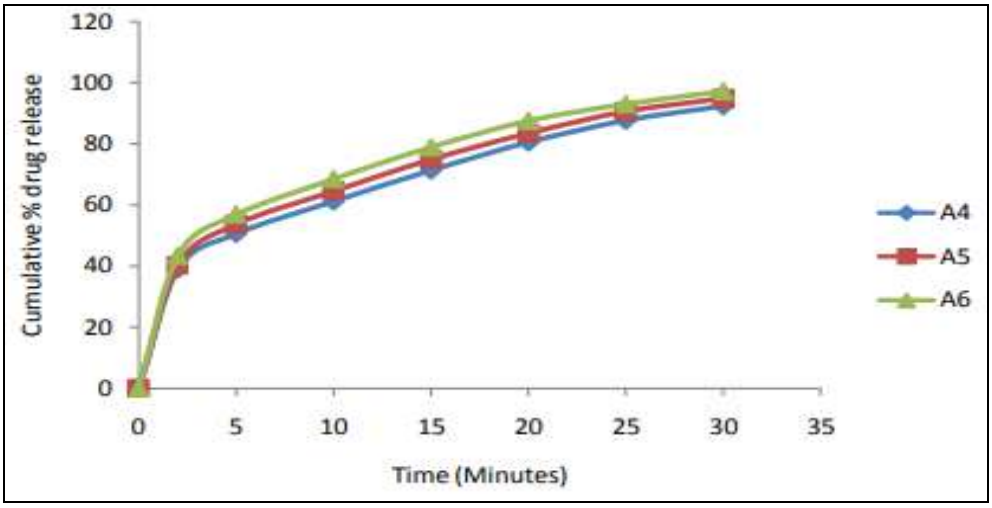

Fig 3: *In vitro* drug Release Profile of Formulation A4, A5 and A6

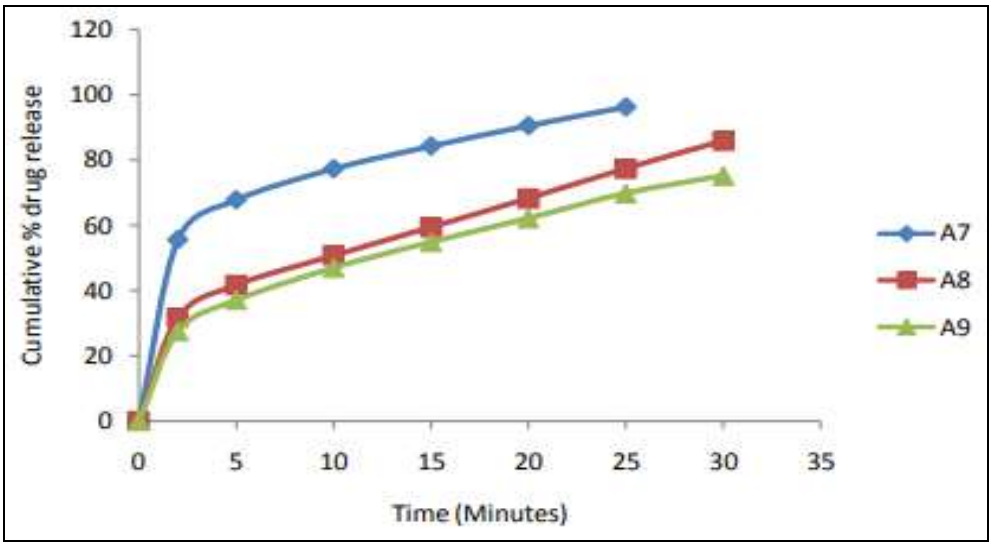

Fig 4: *In vitro* Drug Release Profile of Formulation A7, A8, A9

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

Time (Minutes)	Cumulative % Drug release								
	Fl	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

Conclusion

The results of the current investigation show that a direct compression method was successful in developing a mouth dissolving tablet of Zolpidem tartrate with an enhanced drug release profile. The A6 formulation proved to be the most effective overall because it allowed for the greatest medication release in the shortest amount of time. Due to its capacity to produce tablets with a satisfactory balance of hardness and friability, the combination of mannitol and MCC was favored. Formulation A6 meets all the requirements for a mouth dissolving tablet and might be used as a substitute for standard tablets.

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