International Journal of Multidisciplinary Research and Growth Evaluation.

Design, Prepare and *in vitro* Evaluation of Zolpidem Mouth Dissolving Tablets

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Article Info

ISSN (Online): 2582-7138
Volume: 07
Issue: 06
Received: 08-09-2026
Accepted: 06-10-2026
Published: 04-11-2026
Page No: 275-281

Abstract
The present study was undertaken to design, prepare, and evaluate Zolpidem Mouth Dissolving Tablets (MDTs) with the objective of achieving rapid disintegration, faster drug release, improved patient compliance, and enhanced therapeutic efficacy in the management of insomnia. The prepared tablets were evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, wetting time, disintegration time, and in vitro drug release. All formulations complied with acceptable pharmacopoeial limits for physical characteristics. Among the formulations, F8, containing 20 mg sodium starch glycolate, demonstrated the best performance with the shortest disintegration time (32 seconds), shortest wetting time (47 seconds), highest drug content (92.36%), and maximum cumulative drug release (99.55% within 30 minutes). Drug release kinetic analysis indicated that the dissolution profile was best described by the Korsmeyer–Peppas model, suggesting a diffusion-controlled drug release mechanism. Accelerated stability studies carried out for three months under ICH-recommended conditions confirmed that the optimized formulation remained stable without significant changes in physical appearance or drug release characteristics. In conclusion, the optimized Zolpidem Mouth Dissolving Tablet formulation prepared by the direct compression technique using sodium starch glycolate as the superdisintegrants exhibited excellent physicochemical properties, rapid disintegration, enhanced dissolution, and satisfactory stability.

Keywords: Zolpidem, Mouth Dissolving Tablets, Orally Disintegrating Tablets, Direct Compression, Superdisintegrants, In Vitro Dissolution, Drug Release Kinetics

Introduction

Oral drug delivery is one of the most widely accepted and preferred routes of administration because of its convenience, patient compliance, ease of administration, and cost-effectiveness.[1] Mouth dissolving tablets are solid dosage forms designed to disintegrate rapidly in the oral cavity, generally within a short period after administration, releasing the drug for dissolution and subsequent absorption. [2] The formulation of MDTs commonly involves the incorporation of superdisintegrants and the use of suitable manufacturing techniques to achieve rapid tablet breakup while maintaining adequate mechanical strength. Insomnia is a common sleep disorder characterized by difficulty initiating sleep, difficulty maintaining sleep, or inadequate restorative sleep, often accompanied by impaired daytime functioning. [3] The development of an effective zolpidem mouth dissolving tablet requires careful selection and optimization of formulation components. Superdisintegrants play a critical role in promoting rapid tablet disintegration through mechanisms such as swelling, wicking, and strain recovery. Direct compression is particularly attractive for the preparation of mouth dissolving tablets because it is a simple, economical, and efficient manufacturing process involving fewer processing steps. In vitro evaluation is an essential component of the development of mouth dissolving tablets. [4] Prepared formulations are generally evaluated for physical characteristics such as weight variation, thickness, hardness, friability, and drug content. [5] The present study was therefore undertaken to design, prepare, and evaluate zolpidem mouth

dissolving tablets with the objective of developing a rapidly disintegrating and rapidly releasing oral dosage form. [61] Different formulation variables, particularly the concentration and type of suitable superdisintegrant and directly compressible excipients, can be optimized to obtain tablets with acceptable mechanical properties, rapid disintegration, uniform drug content, and improved dissolution characteristics. The developed formulation is intended to provide a convenient and patient-compliant alternative to conventional zolpidem tablets for the management of insomnia. [7]

Materials

Eplerenone was procured from Hetero Labs, HYD. Crosscaramellose sodium and Sodium Starch glycolate were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

Methodology

Formulation Development

Table 1: Formulation table

S. No	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Zolpidem	10	10	10	10	10	10	10	10
2	Crosscaramellose sodium	5	10	15	20	-	-	-	-
3	Sodium starch glycolate	-	-	-	-	5	10	15	20
4	Mannitol	70	65	60	55	70	65	60	55
5	Magnesium stearate	3	3	3	3	3	3	3	3
6	Talc	2	2	2	2	2	2	2	2
7	Aspartame	5	5	5	5	5	5	5	5
8	MCC	5	5	5	5	5	5	5	5
9	Total wt	100	100	100	100	100	100	100	100

Preparation Method

Direct Compression Technique

Zolpidem mouth dissolving tablets were prepared by the direct compression method, which is a simple, economical, and widely used technique for the manufacture of orally disintegrating tablets. Initially, Zolpidem, mannitol, microcrystalline cellulose, aspartame, and the selected superdisintegrant (croscarmellose sodium for formulations F1–F4 or sodium starch glycolate for formulations F5–F8) were passed separately through #60 mesh sieve to remove lumps and obtain a uniform particle size. The sieved ingredients were transferred into a clean, dry mortar or a polybag and blended thoroughly for 10–15 minutes to ensure uniform distribution of the drug and excipients. After obtaining a homogeneous powder blend, talc and magnesium stearate, previously passed through a #80 mesh sieve, were added to the blend. The mixture was gently mixed for an additional 2–3 minutes to avoid over-lubrication, which could adversely affect tablet hardness and disintegration. The final lubricated blend was compressed into tablets using a single-punch tablet compression machine fitted with 8 mm flat-faced round punches. Each tablet was compressed to obtain a final weight of 100 mg, with sufficient compression force to produce tablets having adequate hardness without affecting their rapid disintegration. The compressed tablets were collected and stored in airtight containers at room temperature until further evaluation. [8]

Evaluation of Tablet

Weight Variation

Twenty tablets were selected randomly from each formulation batch and individually weighed using a calibrated digital analytical balance. The average tablet weight was calculated, and the weight of each individual tablet was compared with the average weight. The percentage deviation of each tablet from the average weight was calculated. The tablets were considered to comply with the pharmacopoeial limits if the individual weights were within the specified percentage deviation. [9]

Hardness

The hardness of the prepared tablets was determined using a Monsanto hardness tester (or Pfizer hardness tester). Ten tablets were selected randomly from each formulation batch, and each tablet was placed between the anvils of the hardness tester. Pressure was gradually applied until the tablet fractured. The force required to break the tablet was recorded in kg/cm². The average hardness of ten tablets was calculated and reported. [10]

Friability

The friability test was performed using a Roche friabilator. Twenty tablets were randomly selected, dedusted, and accurately weighed (Initial weight, W_1). The tablets were placed in the friabilator, which was operated at 25 rpm for 4 minutes (100 revolutions). After completion of the test, the tablets were removed, dedusted, and reweighed (Final weight, W_2). The percentage friability was calculated using the following equation. [11]

The percentage friability is calculated using the formula:

$$(F): = W\ int. - W\ fin / W\ int. \times 100$$

Where,
Wint = Initial weight of tablets before friability;
Wfin = Final weight of tablets after friability.

Wetting Time

A piece of double-folded tissue paper was placed in a 90 mm diameter Petri dish containing 6 mL of distilled water. A small quantity of water-soluble dye (eosin) was added to the water to facilitate visualization of wetting. One tablet was carefully placed on the surface of the tissue paper, and a stopwatch was started immediately. The time required for the water to completely wet the upper surface of the tablet was recorded as the wetting time. The test was performed in triplicate for each formulation, and the average value was calculated. [12]

Disintegration Test

The in vitro disintegration time was determined using the USP tablet disintegration test apparatus. One tablet was placed in each of the six tubes of the basket rack assembly. The apparatus was operated using 900 mL of distilled water maintained at 37 ± 0.5°C as the immersion medium. The basket was moved vertically at the specified rate according to the pharmacopoeial procedure. The time required for each tablet to disintegrate completely without leaving any palpable residue, except fragments of the coating (if present), was recorded. The average disintegration time of six tablets was calculated. [12]

***In Vitro* Dissolution Test**

The in vitro dissolution study was carried out using the USP Dissolution Test Apparatus II (Paddle Method). The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. The paddle speed was adjusted to 50 rpm. One tablet was placed in the dissolution vessel, and samples of 5 mL were withdrawn at predetermined time intervals (2, 4, 6, 8, 10, 15, and 20 minutes). After each withdrawal, an equal volume of fresh dissolution medium maintained at the same temperature was added to maintain sink conditions. The withdrawn samples were filtered through Whatman No. 1 filter paper, suitably diluted if required, and analyzed using a UV–Visible spectrophotometer at 295 nm. The cumulative percentage drug release was calculated using the calibration curve of Zolpidem tartrate. [14]

Kinetics OF Drug Release[15]

Drug release kinetics are studied to determine the mechanism by which the drug is released from the dosage form. The dissolution data are fitted into various mathematical models, and the model showing the highest correlation coefficient (R^2) is considered to best describe the release mechanism.

Procedure

The cumulative percentage drug release data obtained from the dissolution study were fitted into different kinetic models, including:

- *Zero-Order Model*
- *First-Order Model*
- *Higuchi Diffusion Model*
- *Korsmeyer–Peppas Model*

Stability Studies

Stability studies are carried out to evaluate the ability of the formulated Zolpidem Mouth Dissolving Tablets (MDTs) to retain their physical, chemical, and pharmaceutical properties during storage. These studies help determine the shelf life of the formulation and ensure that the tablets remain safe, effective, and of acceptable quality throughout their intended storage period. Stability testing is performed according to the International Council for Harmonization (ICH) Guideline Q1A(R2). [16]

Results and Discussion

Evaluation Parameters

Table 2: Evaluation Parameters for Zolpidem mouth dissolving tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation(mg)	100	99	101	100	100	99	100	100
Thickness (mm)	2.5	2.9	3.1	2.7	2.6	2.3	2.7	3.1
Hardness (kg/cm^2)	3.2	3.3	3.5	3.6	3.1	3.5	3.8	3.9
Friability (%)	0.42	0.38	0.43	0.39	0.42	0.45	0.48	0.41
Disintegration time(Sec)	44	53	57	48	41	39	35	32
Drug content (%)	78.94	81.29	83.20	79.86	82.36	84.58	89.69	92.36
Wetting time	59	58	52	51	55	62	51	47

Discussion

The weight variation of all formulations ranged from 99 to 101 mg, which complied with the Indian Pharmacopoeial limits for tablets weighing 100 mg (±7.5%). The uniformity in tablet weight indicates accurate die filling and uniform distribution of the powder blend during the direct compression process. No significant variation in tablet weight was observed among the formulations.

The thickness of the tablets varied between 2.3- and 3.1-mm. Formulation F6 exhibited the lowest thickness (2.3 mm), whereas F3 and F8 showed the highest thickness (3.1 mm). The slight variation in tablet thickness may be attributed to differences in powder packing and compression characteristics. However, all formulations exhibited uniform dimensions, indicating consistent compression during tablet manufacture.

The hardness of the tablets ranged from 3.1 to 3.9 kg/cm². Formulation F5 exhibited the lowest hardness (3.1 kg/cm²), while F8 showed the highest hardness (3.9 kg/cm²). The hardness values were within the acceptable range for mouth dissolving tablets (approximately 2–4 kg/cm²), indicating sufficient mechanical strength to withstand handling and transportation without adversely affecting tablet disintegration.

The friability values of all formulations ranged between 0.38% and 0.48%, which were well below the pharmacopoeial limit of 1%. Formulation F2 exhibited the lowest friability (0.38%), whereas F7 showed the highest friability (0.48%). These results indicate that all tablets possessed adequate mechanical resistance and were unlikely to undergo significant abrasion or breakage during packaging and handling.

The disintegration time of the formulations varied from 32 to 57 seconds. Formulation F8 exhibited the shortest disintegration time (32 seconds), followed by F7 (35 seconds) and F6 (39 seconds), while F3 showed the longest disintegration time (57 seconds). The decrease in disintegration time observed in formulations containing higher concentrations of sodium starch glycolate (F5–F8) suggests that this superdisintegrant promoted faster tablet breakup than the corresponding croscarmellose sodium formulations. Rapid disintegration is a desirable

characteristic of mouth dissolving tablets because it facilitates quicker drug release and onset of action.

The drug content of the formulations ranged from 78.94% to 92.36%. Formulation F8 exhibited the highest drug content (92.36%), followed by F7 (89.69%), whereas F1 showed the lowest value (78.94%). Although the formulations demonstrated increasing drug content with changes in formulation composition, the values for F1–F7 are below the pharmacopoeial acceptance limit (typically 90–110%). Only F8 falls within the generally acceptable range. These findings suggest that optimization of the manufacturing process or blend uniformity would be required if these data represent actual experimental results.

The wetting time ranged from 47 to 62 seconds. Formulation F8 exhibited the shortest wetting time (47 seconds), followed by F4 and F7 (51 seconds each), whereas F6 showed the longest wetting time (62 seconds). The reduction in wetting time observed in formulation F8 indicates more rapid penetration of the dissolution medium into the tablet, which correlates well with its shorter disintegration time. Faster wetting enhances the performance of mouth dissolving tablets by promoting rapid tablet dispersion in the oral cavity.

In-Vitro Dissolution Profiles for Tablets

Table 3: Drug release studies of all formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	27.48	28.10	29.82	27.43	30.12	30.15	31.25	33.69
10	38.42	37.48	37.46	35.26	41.25	42.23	43.25	47.18
15	53.69	55.39	54.25	55.28	59.83	61.28	63.59	65.88
20	73.28	74.32	75.12	78.12	79.82	78.55	77.48	79.83
25	84.20	83.20	81.22	85.55	87.89	86.58	85.35	89.52
30	93.26	94.58	95.86	97.82	95.25	96.20	97.83	99.55

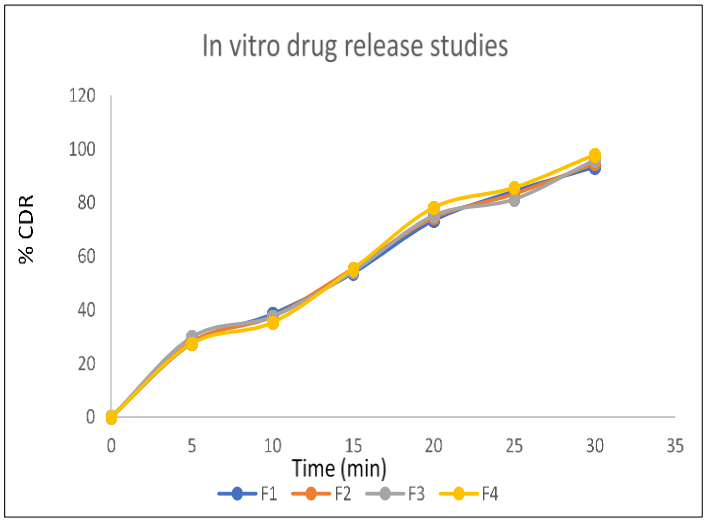


Fig 1: Dissolution Profile of F1 to F4 formulation

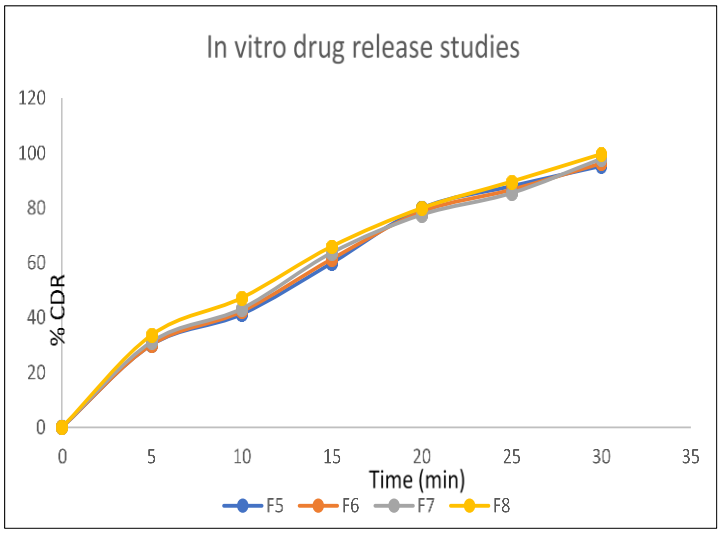


Fig 2: Dissolution Profile of F1 to F4 formulation

Discussion

Overall, among all the formulations evaluated, F8 exhibited the best dissolution characteristics with 99.55% cumulative drug release within 30 minutes, indicating its suitability as the optimized formulation for Zolpidem Mouth Dissolving Tablets.

Kinetic Modelling of Drug Release

All the 8 formulation of prepared MDTs were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's
4. Classical Diffusion Equation)
5. Log of cumulative % release Vs log time (Pappas Exponential Equation)

Zero Order Kinetics

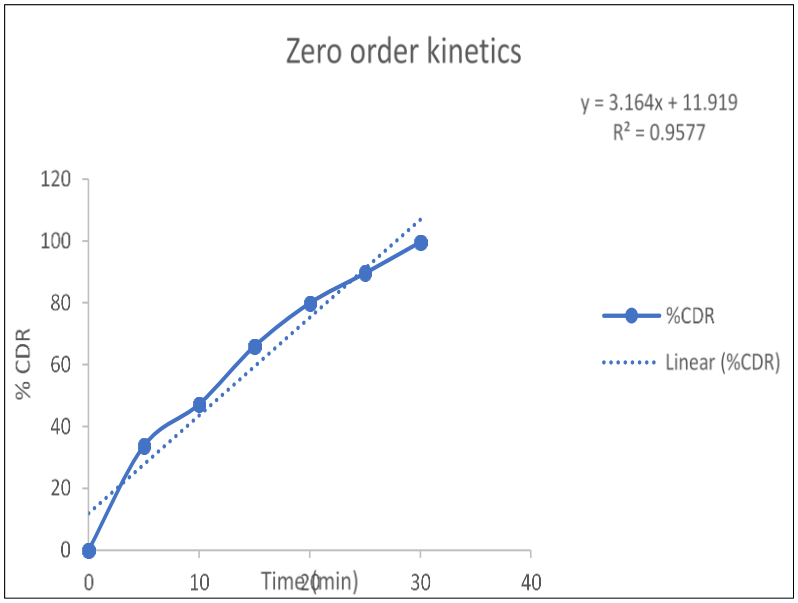


Fig 3: Zero order kinetics of optimized formulation

First Order Kinetics

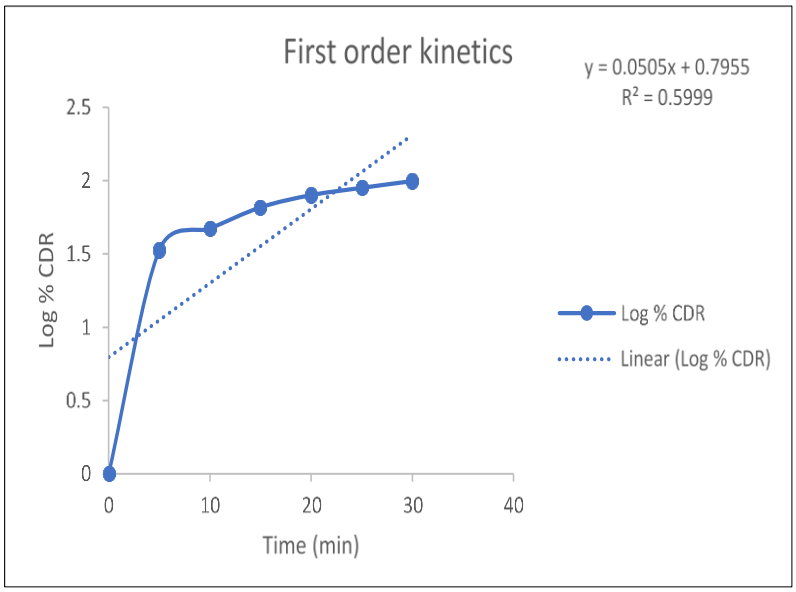


Fig 4: First order kinetics of optimized formulation

Higuchi Model

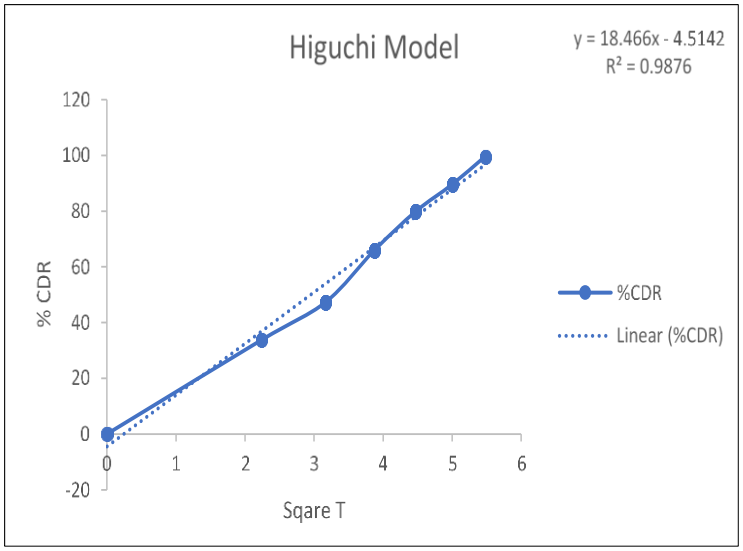


Fig 5: Higuchi model of optimized formulation

Korsmeyer Peppas

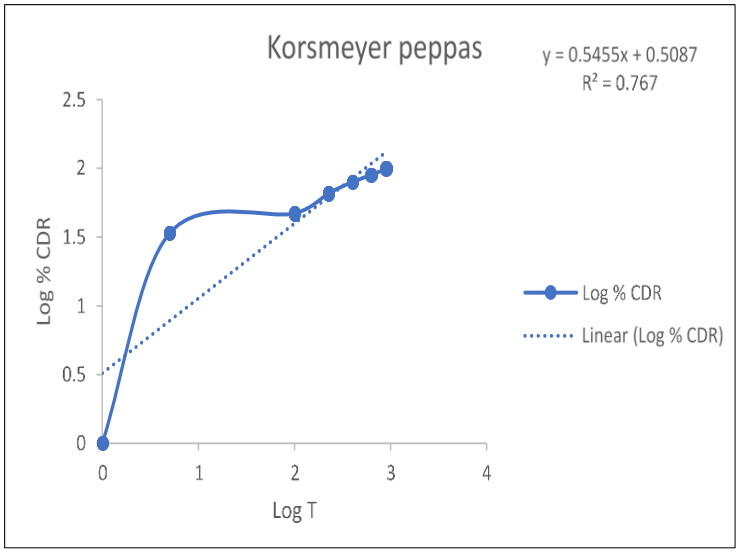


Fig 6: Korsmeyer peppas of optimized formulation

The kinetic values obtained for formulation F8 were shown. The values of in vitro release were attempted to fit into various mathematical models. The table indicates that r^2 values are higher for Korsmeyer peppas model compared for all the tablets. Hence drug release from all the fast dissolving followed diffusion rate-controlled mechanism.

Discussion

Among the models evaluated, the Korsmeyer–Peppas model exhibited the highest R^2 value, indicating the best fit for the dissolution data. This suggests that the release of Zolpidem from the mouth dissolving tablets was predominantly governed by a diffusion-controlled mechanism. The Higuchi model also demonstrated good linearity, supporting the contribution of diffusion during drug release. In contrast, the Zero-order and First-order models showed comparatively lower correlation coefficients, indicating that they did not adequately describe the release behaviour.

Stability Study

There was no significant change in physical and chemical properties of the mouth dissolving tablets of formulation F-8 after 3 months. Parameters quantified at various time intervals were shown.

Table 4: Stability studies of all formulations

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	25^0C/60%RH	99.55	98.53	97.48	96.72	Not less than 85%
F-8	30^0C/75% RH	99.55	98.22	97.53	96.20	Not less than 85%
F-8	40^0C/75% RH	99.55	98.16	97.19	96.38	Not less than 85%

Discussion

Overall, the stability study confirmed that the optimized Zolpidem Mouth Dissolving Tablet formulation maintained its quality, drug release characteristics, and performance during storage for 3 months, demonstrating satisfactory stability and indicating that the formulation is suitable for storage under recommended environmental conditions.

Conclusion

Among the eight formulations, F8, containing 20 mg of sodium starch glycolate, was identified as the optimized formulation based on its superior performance. It exhibited the shortest disintegration time (32 seconds), shortest wetting time (47 seconds), and the highest cumulative drug release (99.55% within 30 minutes). The dissolution study confirmed rapid drug release, while kinetic analysis indicated that the release followed the Korsmeyer–Peppas model, suggesting a diffusion-controlled release mechanism. Furthermore, the optimized formulation remained stable during 3 months of accelerated stability testing, demonstrating its suitability for storage. Overall, the study indicates that Zolpidem Mouth Dissolving Tablets prepared using sodium starch glycolate as the superdisintegrant provide rapid tablet disintegration, enhanced dissolution, and the potential for a faster onset of therapeutic action. These characteristics make the optimized formulation a promising alternative to conventional tablets, particularly for patients who have difficulty swallowing and require immediate relief from insomnia.

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How to Cite This Article

Saritha A, Sriya A. Design, prepare and in vitro evaluation of zolpidem mouth dissolving tablets. International Journal of Multidisciplinary Futuristic Development. 2026;7(6):275-281.

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