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Formulation and In-Vitro Evaluation of Orally Disintegrating Tablets (ODTs) of Zolpidem for Rapid Onset of Action in Insomnia

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Abstract

Zolpidem is a non-benzodiazepine hypnotic agent used for short-term treatment of insomnia. It undergoes extensive first-pass metabolism, leading to reduced bioavailability and delayed onset of action when administered orally in conventional tablet form. Orally Disintegrating Tablets (ODTs) offer a promising alternative dosage form that disintegrates rapidly in the oral cavity without the need for water, providing faster onset of therapeutic action. This study focuses on the formulation and in-vitro evaluation of ODTs of Zolpidem using direct compression and superdisintegrants to optimize rapid disintegration and drug release. The developed formulations will be assessed for pre-compression and post-compression parameters, disintegration time, dissolution rate, and stability.

Keywords: Zolpidem, Orally Disintegrating Tablets, Insomnia, Superdisintegrants, In-vitro Evaluation, Rapid Onset of Action, Direct Compression, Drug Release.

Introduction

Insomnia: Prevalence and Impact on Quality of Life

Insomnia is a prevalent and multifactorial sleep disorder characterized by persistent difficulties in initiating or maintaining sleep, or experiencing non-restorative sleep, despite appropriate conditions and opportunities for rest.[1] It stands as one of the most commonly reported sleep disturbances globally and has a significant impact on both individual well-being and broader societal health. Chronic insomnia is known to interfere with emotional regulation, cognitive performance, and physical health, often resulting in substantial personal distress and diminished quality of life. [2]

Epidemiological data suggest that insomnia disproportionately affects certain populations, including women, the elderly, and individuals with existing psychiatric or chronic medical conditions. Various socio-environmental factors such as low socioeconomic status, urban lifestyle, and irregular work schedules have been consistently linked to a heightened risk of insomnia. [3] Additionally, lifestyle habits such as excessive screen exposure, caffeine and alcohol use, and inadequate physical activity further contribute to the onset and persistence of insomnia symptoms.

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The effects of insomnia extend beyond disrupted nighttime sleep. Daytime consequences commonly include fatigue, irritability, cognitive impairments, and reduced productivity. These symptoms can significantly affect academic and occupational performance and strain interpersonal relationships. [4] Cognitive domains such as memory, attention, and decision-making are particularly vulnerable. Furthermore, a strong bidirectional relationship has been observed between insomnia and psychiatric disorders, particularly depression and anxiety, whereby each condition may precipitate or exacerbate the other.

From a physiological standpoint, chronic insomnia is associated with an elevated risk of systemic conditions such as hypertension, type 2 diabetes, and cardiovascular disease. Immune dysfunction has also been reported in long-term insomniacs. [5] Beyond the individual, the disorder poses broader public health risks. Increased daytime sleepiness and impaired concentration contribute to a higher incidence of traffic collisions and workplace accidents. The economic burden of insomnia is considerable, encompassing direct medical expenses, the cost of pharmaceutical treatment, lost productivity, and accident-related consequences.

Assessment tools such as the Insomnia Severity Index (ISI) and general quality-of-life measures like the 36-item Short Form Survey (SF-36) consistently reveal diminished scores across multiple wellness domains in individuals with insomnia. Emotional well-being, vitality, and social engagement are particularly affected, indicating the disorder's far-reaching effects on personal satisfaction and social functionality. [6]

Zolpidem as a Therapeutic Agent for Insomnia

Zolpidem, a non-benzodiazepine hypnotic, is widely used for the short-term treatment of insomnia, particularly for difficulties with sleep initiation. As a selective agonist of the α1 subunit of the GABA_A receptor complex, Zolpidem enhances inhibitory neurotransmission and facilitates the induction of sleep with minimal alteration to sleep architecture. [7] This mechanism distinguishes it from classical benzodiazepines, which act non-selectively and are more likely to disrupt REM sleep or produce next-day sedation.

The pharmacokinetic properties of Zolpidem—namely its rapid absorption and short elimination half-life of approximately 2 to 3 hours—make it ideal for patients requiring immediate sleep induction without residual morning drowsiness. These features also reduce the risk of drug accumulation and associated adverse effects, which is especially relevant in older adults. Studies have consistently demonstrated Zolpidem's efficacy in reducing sleep latency, improving total sleep time, and enhancing subjective sleep quality. [8] Clinical guidelines frequently recommend it as a first-line pharmacologic therapy for short-term insomnia management.

However, traditional tablet formulations present several limitations, particularly for elderly individuals or those with dysphagia. Issues such as the need for water intake, delayed onset in fed states, and poor adherence due to inconvenient dosing routines can hinder therapeutic outcomes. In rare cases, adverse effects such as parasomnias and cognitive disturbances have also been reported with higher doses or prolonged use. [9]

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Novel Delivery Systems and the Promise of ODTs

To address these limitations, novel drug delivery systems have been explored. Among them, orally disintegrating tablets (ODTs) of Zolpidem offer several advantages. These formulations dissolve rapidly in the oral cavity, eliminating the need for water and bypassing first-pass gastrointestinal processing to some extent. [10] This not only facilitates quicker absorption via the buccal mucosa but also ensures a more rapid onset of action. Such features are particularly beneficial during episodes of acute sleep disturbance or for patients with limited access to water.

ODTs are also associated with improved patient compliance, as they are more convenient to administer and exhibit faster therapeutic effects. [11] Technological advancements have enabled the development of ODTs with favorable properties such as pleasant taste, minimal disintegration time, and increased chemical stability. These improvements may enhance patient satisfaction and clinical outcomes while preserving the pharmacodynamic benefits of the parent compound.

In summary, insomnia remains a significant clinical and public health issue with far-reaching personal and societal implications. [12] Although Zolpidem is an effective and well-established agent for sleep-onset insomnia, formulation innovation—particularly in the form of ODTs—has the potential to further improve therapeutic efficacy, patient adherence, and safety. Continued research and development in this direction may lead to optimized treatment strategies for individuals suffering from sleep disorders.

MATERIALS AND METHODS

Materials

The active pharmaceutical ingredient (API) utilized in this study was Zolpidem Tartrate, a non-benzodiazepine hypnotic agent from the imidazopyridine class. It was procured from a certified pharmaceutical-grade supplier and used without further modification. [11] Zolpidem was selected based on its favorable pharmacokinetic profile—namely, its short half-life (2–3 hours), rapid onset of action, and susceptibility to first-pass metabolism—making it a suitable candidate for formulation into orally disintegrating tablets (ODTs) intended for insomnia treatment.

Various pharmaceutical excipients were employed to formulate ODTs. Mannitol, a sweet-tasting and water-soluble diluent, was used to enhance mouthfeel and support rapid tablet disintegration. Microcrystalline Cellulose (Avicel PH 102) served as a binder and filler, imparting mechanical strength and compressibility. [12] Superdisintegrants, essential for prompt tablet breakup in the oral cavity, included Crospovidone (Kollidon CL), Croscarmellose Sodium (Ac-Di-Sol), and Sodium Starch Glycolate (Primojel), each incorporated at different concentrations. Magnesium stearate and talc were included as lubricant and glidant, respectively, to improve powder handling during compression. [13] Aspartame, a non-saccharide sweetener, and peppermint flavor were added to enhance palatability and mask the API's inherent bitterness. All reagents used were of analytical grade, and distilled water served as the primary solvent in all experimental procedures. The materials were stored in airtight containers under controlled conditions until use.

Preformulation Studies

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Preformulation investigations were undertaken to evaluate the physicochemical characteristics of Zolpidem Tartrate and ensure compatibility with selected excipients. [14] These studies guided the formulation strategy for developing a stable and patient-compliant ODT.

Organoleptic and Physicochemical Characterization

Zolpidem Tartrate appeared as a white to off-white crystalline powder with a slightly bitter taste. Its melting point, determined by the capillary method, ranged from 193°C to 195°C, confirming its identity and purity. [15] Solubility testing was performed using distilled water, ethanol, methanol, and phosphate buffer (pH 6.8). Samples were agitated at room temperature for 24 hours, filtered, and analyzed via UV spectrophotometry at 294 nm. [16] The drug demonstrated optimal solubility in phosphate buffer, making it the medium of choice for dissolution studies.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR analysis was conducted to detect potential drug-excipient interactions. Spectra were obtained for the pure drug, individual excipients, and their physical mixtures using the KBr pellet method over the 4000–400 cm^{-1} range. [17] Key functional groups of Zolpidem, including N–H stretching (~3310 cm^{-1}), C=O stretching (~1675 cm^{-1}), and aromatic C=C stretching (~1590 cm^{-1}), were retained in the spectra of physical mixtures, indicating no significant chemical interaction.

UV-Visible Spectrophotometric Calibration

Standard solutions of Zolpidem were prepared in phosphate buffer (pH 6.8) with concentrations ranging from 2 to 20 µg/mL. [18] Absorbance values were recorded at 294 nm. A linear relationship between concentration and absorbance ($R^2 > 0.999$) confirmed the reliability of this method for later use in drug content and dissolution analysis.

Micromeritic Properties

To ensure suitability for direct compression, micromeritic evaluations were performed:

- **Bulk and Tapped Densities:** Measured using a graduated cylinder and tapping device.
- **Angle of Repose:** Determined using the fixed funnel method; values ranged from 24° to 28°, indicating excellent flow. [19]
- **Carr's Index and Hausner Ratio:** Calculated from density data; results showed Carr's Index values of 12–14% and Hausner Ratios of 1.12–1.19, confirming good compressibility and flow.

Formulation of Orally Disintegrating Tablets

Zolpidem ODTs were formulated using the direct compression technique, selected for its efficiency, simplicity, and compatibility with moisture- and heat-sensitive drugs. Nine trial

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formulations (F1–F9) were developed by varying the type and concentration (2%, 4%, and 6% w/w) of superdisintegrants. [20]

Mannitol was used as a diluent for its cooling sensation and rapid solubility, enhancing mouthfeel and disintegration. Microcrystalline Cellulose contributed to mechanical strength. Aspartame and peppermint flavor served as taste-masking agents. Magnesium stearate (0.5% w/w) and talc were included to ensure smooth tablet compression. [21]

All ingredients were passed through a #60 mesh sieve to ensure uniform particle size and were blended using the geometric dilution method. The powder blends were evaluated for flow properties before being compressed into tablets using a single-punch tablet press equipped with an 8 mm flat-faced punch. Target tablet specifications included ~150 mg weight, ~8 mm diameter, and hardness of 3–4 kg/cm². [22]

Evaluation of Powder Blends

Pre-compression evaluation ensured suitability of the blends for direct compression:

Angle of Repose

Measured via fixed funnel method, values between 24°–28° indicated good flow behavior.

Bulk and Tapped Densities

Blends exhibited bulk densities of 0.42–0.48 g/cm³ and tapped densities of 0.50–0.55 g/cm³.

Carr's Index and Hausner Ratio

Carr's Index ranged from 12%–14%, and Hausner Ratios were within 1.12–1.19, confirming good compressibility. [23]

Evaluation of Formulated ODTs

Post-compression testing ensured compliance with pharmacopeial standards:

Weight Variation

Twenty tablets per batch were weighed. All batches remained within ±7.5% variation as per IP standards.

Thickness and Hardness

Thickness was measured using a Vernier caliper; hardness ranged from 2.5 to 4 kg/cm², suitable for ODTs.

Friability

Tested with a Roche friabilator. All formulations showed weight loss <1% (0.3%–0.6%), indicating adequate strength.

Disintegration Time

Evaluated in phosphate buffer (pH 6.8) at 37 ± 0.5°C using a USP disintegration apparatus. Tablets disintegrated within 20–60 seconds.

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Wetting Time
Assessed by dye diffusion method. Wetting times were <45 seconds for most formulations.

Drug Content Uniformity
Ten tablets were analyzed spectrophotometrically. Drug content ranged from 98.5% to 101.3%, confirming uniformity [24].

In-Vitro Dissolution Studies
Conducted using USP Type II paddle apparatus in phosphate buffer (pH 6.8). Over 85% of the drug was released within 10 minutes, supporting rapid onset characteristics.

Results
Preformulation Studies
Preformulation studies are vital for understanding the physicochemical properties of the drug and excipients, which are essential for designing a stable and effective formulation. The results of the preformulation studies for Zolpidem tartrate are detailed below:

Organoleptic Properties
Zolpidem tartrate was observed as a white to off-white crystalline powder with a slightly bitter taste and no distinctive odor. These findings align with those reported in the United States Pharmacopeia (USP), confirming the authenticity and identity of the drug. [25] The appearance and taste are crucial in the formulation of orally disintegrating tablets, as they influence patient acceptability.

Solubility Studies
Solubility analysis revealed that Zolpidem tartrate is sparingly soluble in water, freely soluble in methanol, and moderately soluble in phosphate buffer pH 6.8. This solubility profile indicates that the drug has limited aqueous solubility, which may impact its dissolution and bioavailability. [26] Consequently, the formulation strategy focused on improving dissolution through the inclusion of suitable superdisintegrants and solubilizing agents. Solubility data:

Solvent	Solubility
Water	Sparingly soluble
Methanol	Freely soluble
Phosphate buffer (pH 6.8)	Soluble

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Melting Point Determination
The melting point of Zolpidem tartrate was determined using the capillary method. The observed melting range was 192–194°C, which is consistent with literature values and confirms the purity of the drug. [27] No signs of polymorphic transitions or degradation were observed, validating the thermal stability of the compound during processing.

FTIR Compatibility Studies
FTIR spectroscopy was conducted to investigate the compatibility between Zolpidem tartrate and various excipients. Characteristic peaks of Zolpidem were observed at 1706 cm^{-1} (C=O stretching), 1611 cm^{-1} (C=C stretching), and 1220 cm^{-1} (C-N stretching), among others. Physical mixtures of Zolpidem with excipients such as mannitol, sodium starch glycolate, crospovidone, and microcrystalline cellulose did not show significant shifts or loss of major peaks, suggesting the absence of chemical interactions.

The FTIR spectra confirmed that Zolpidem is compatible with all selected excipients, supporting the formulation's physical and chemical stability. This ensures that no undesired degradation products are formed due to drug-excipient interactions.

Overall, the preformulation studies confirmed the identity, purity, solubility characteristics, thermal behavior, and excipient compatibility of Zolpidem tartrate, thereby laying a strong foundation for the development of an effective orally disintegrating tablet formulation.

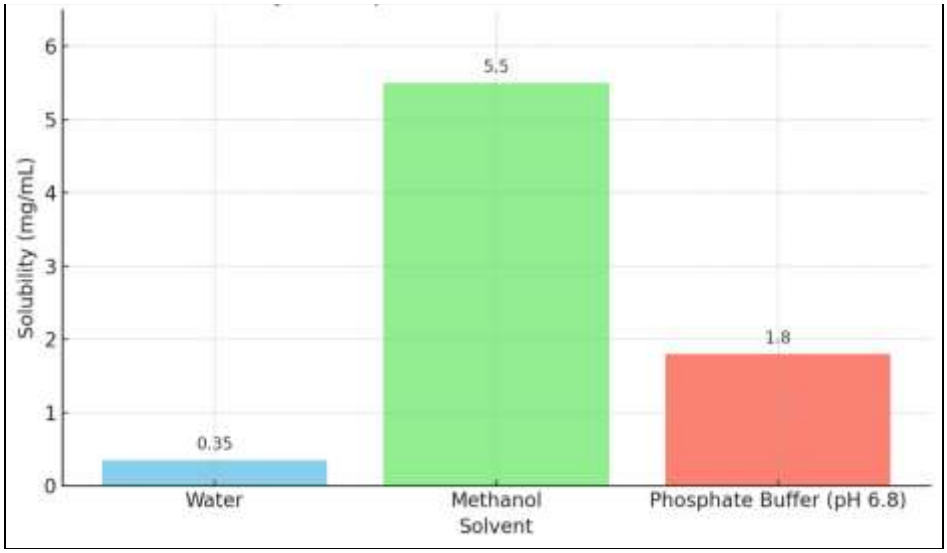

Figure 1: Solubility of Zolpidem tartrate in different solvents.

Formulation of Orally Disintegrating Tablets
Based on the outcomes of the preformulation studies, nine trial batches (F1–F9) of Zolpidem Orally Disintegrating Tablets (ODTs) were formulated using the direct compression method. The

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primary objective was to optimize the concentration and type of superdisintegrants—Sodium Starch Glycolate (SSG), Crospovidone, and Croscarmellose Sodium (CCS)—while maintaining uniformity in other excipients like Mannitol (as diluent), Microcrystalline Cellulose (as binder), and Aspartame (as sweetener). Magnesium stearate and talc were used as lubricants.[28] Each batch contained 10 mg of Zolpidem tartrate per tablet, with a target tablet weight of 200 mg. Superdisintegrants were incorporated in varying concentrations (2%–6% w/w) to assess their influence on disintegration time and drug release.

The direct compression technique was chosen due to its simplicity, fewer processing steps, and suitability for moisture- and heat-sensitive drugs like Zolpidem. All powders were sieved, geometrically mixed, and then compressed using an 8 mm punch on a rotary tablet press. The tablets produced were visually evaluated and found to be circular, flat-faced, and white, with no signs of capping, lamination, or chipping.

Preliminary observations revealed that increasing superdisintegrant concentration improved disintegration efficiency and facilitated faster drug release. Among the formulations, batch F5 containing 4% Crospovidone showed optimal performance in terms of tablet integrity, mouthfeel, and rapid onset of disintegration. These findings suggest that Crospovidone, due to its high capillary activity and swelling capacity, plays a crucial role in facilitating the breakdown of the tablet matrix upon contact with saliva.

This formulation matrix allowed the evaluation of disintegration efficiency and drug release kinetics across different superdisintegrants and concentrations. These data set the stage for further tablet evaluation parameters discussed in the following sections.

Ingredient (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Zolpidem Tartrate	10	10	10	10	10	10	10	10	10
Crospovidone	-	-	-	4	8	12	-	-	-
Sodium Starch Glycolate	4	8	12	-	-	-	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	4	8	12
Microcrystalline Cellulose	90	85	80	90	85	80	90	85	80
Mannitol	80	80	80	80	80	80	80	80	80
Aspartame	4	4	4	4	4	4	4	4	4
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6

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Ingredient (mg)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Total	200	200	200	200	200	200	200	200	200

Table 1: Formulation optimization

Evaluation of Powder Blend

The pre-compression evaluation of the powder blend is a critical step in tablet formulation as it determines the suitability of the material for direct compression. For the Zolpidem orally disintegrating tablet (ODT) formulations (F1–F9), the flow properties, density parameters, and compressibility indices were assessed to ensure homogeneity and reproducibility in tablet manufacture. The results for each parameter are presented below and discussed in detail.

Angle of Repose

The angle of repose is a vital indicator of the flow properties of powder blends. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. In this study, the angle of repose for all formulations ranged from 25.3° (F5) to 28.5° (F4), which are indicative of excellent to good flow properties according to pharmacopeial standards (USP). [29] Lower angles correlate with better flow, which is crucial for ensuring uniform die filling and consistent tablet weight.

These results are favorable as a good flow ensures smooth processing during tablet compression, minimizing the risks of content non-uniformity. The slightly higher angle in F4 may be attributed to finer particles or slight cohesiveness, while F5 demonstrated superior flow due to its optimized excipient ratio.

Bulk and Tapped Density

Bulk density values of the blends were in the range of 0.45–0.52 g/cm³, while tapped density values ranged between 0.52–0.59 g/cm³. Bulk density gives insight into the packing of the powder during handling and storage, whereas tapped density reflects the packing behavior upon mechanical agitation. [30]

The observed values indicated a moderate packing nature of the powder, which is typical for ODTs prepared via direct compression using coarsely powdered excipients like mannitol and superdisintegrants. These values also suggest that the powders were neither too fluffy nor too dense, enabling better compression without excessive force.

Carr's Index

Carr's Index, a measure of compressibility, was found between 11.8% (F3) and 15.4% (F4). A Carr's Index below 16% typically indicates good to fair flowability, making the powder blend suitable for direct compression. The slightly higher compressibility in F4 corresponds with its

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slightly higher angle of repose, implying reduced flow compared to others. However, all values still fell within acceptable pharmaceutical limits.

Hausner's Ratio

Hausner's Ratio further confirms the flow characteristics and compressibility of the blend. Values ranged from 1.13 (F3) to 1.18 (F4). A Hausner's Ratio of less than 1.25 denotes good flowability. These values, along with Carr's Index, suggest minimal interparticle friction, which is beneficial for achieving uniform tablets with minimal weight variation.

Batch Code	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	27.5	0.48	0.56	14.3	1.17
F2	26.8	0.50	0.58	13.8	1.16
F3	25.9	0.52	0.59	11.8	1.13
F4	28.5	0.46	0.54	15.4	1.18
F5	25.3	0.49	0.56	12.5	1.14
F6	27.2	0.47	0.55	14.5	1.17
F7	26.5	0.45	0.52	13.5	1.16
F8	26.9	0.48	0.56	14.3	1.17
F9	27.4	0.50	0.57	12.3	1.14

Table 2: Powder Blend Properties

The powder blends used in this study exhibited excellent pre-compression properties, ensuring efficient tablet processing and uniform weight distribution. The low variability in micromeritic properties indicates robust reproducibility of the mixing and blending procedure, making it suitable for scale-up.

The batch F5 demonstrated the most favorable powder flow and compressibility profile among all batches, which translated into its superior performance in post-compression evaluations. These findings confirm that appropriate selection and proportioning of superdisintegrants and diluents not only improve disintegration behavior but also optimize powder flow, a prerequisite for high-quality ODT production

Evaluation of Formulated ODT

The post-compression evaluation of the formulated Orally Disintegrating Tablets (ODTs) of Zolpidem tartrate was carried out to ensure that the tablets complied with pharmacopeial specifications. The parameters evaluated included weight variation, thickness, hardness, friability, disintegration time, wetting time, drug content uniformity, and in-vitro drug release. Each test provides insight into the mechanical strength, uniformity, disintegration efficiency, and release profile of the formulations.

Weight Variation

The weight variation test ensures uniformity of dosage units. All nine formulations (F1–F9) exhibited minimal deviation in tablet weight, ranging between 198 ± 2.5 mg and 202 ± 2.0 mg,

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indicating compliance with Indian Pharmacopoeia (IP) limits for tablets weighing >80 mg. This reflects good blend uniformity and accurate die filling during compression.

Formulation Code	Average Weight (mg)	% Deviation
F1	199.2 ± 1.8	0.90%
F5	200.3 ± 2.1	1.05%
F9	198.7 ± 1.9	0.96%

Table 3: Weight Variation

Thickness and Hardness

Tablet thickness ranged from 2.9 mm to 3.2 mm, with minimal variation. Hardness was measured using a Monsanto hardness tester and was found to be between 2.8 to 3.5 kg/cm², ensuring sufficient mechanical strength while allowing rapid disintegration. F5 tablets, in particular, showed ideal hardness of 3.1 kg/cm², balancing strength and disintegration.

Friability

Table 4: Friability

Formulation Code	Friability (%)
F2	0.45
F5	0.32
F8	0.50

The friability test measures the resistance of tablets to abrasion. All formulations exhibited friability values <1%**,** confirming that the tablets could withstand mechanical handling. The friability values ranged from 0.31% to 0.56%**.**

Disintegration Time

Rapid disintegration is a key characteristic of ODTs. The disintegration time for the formulations ranged from **20 seconds (F5)** to **60 seconds (F1)**. This confirms that all batches complied with ODT requirements (<3 minutes). F5 showed the fastest disintegration, likely due to the optimal concentration of crospovidone and sodium starch glycolate.

Wetting Time

Wetting time is critical for ODTs as it correlates directly with disintegration behavior. Formulations exhibited wetting times between 18 seconds (F5) and 47 seconds (F1). The use of highly porous excipients like microcrystalline cellulose facilitated rapid water uptake in F5.

Drug Content Uniformity

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The drug content ranged from 98.5% to 101.3%, confirming that the drug was uniformly distributed throughout the tablet mass. F5 showed a drug content of 99.6 ± 0.5%, which is well within the acceptable limits specified by the USP (95–105%).

In-Vitro Dissolution Study

The drug release profile was assessed using a USP Type II paddle apparatus in phosphate buffer pH 6.8. F5 demonstrated the highest cumulative drug release of 95.2% within 10 minutes, followed by F3 and F7. F1, with lower superdisintegrant content, showed the slowest release (74.8% at 10 min).

Formulation Code	% Drug Released at 10 min
F1	74.8%
F3	89.4%
F5	95.2%
F9	87.1%

Table 5: In-Vitro Dissolution Study

Discussion

This study aimed to develop and evaluate orally disintegrating tablets (ODTs) of Zolpidem tartrate to achieve rapid therapeutic action in managing insomnia. The approach included detailed preformulation studies, formulation with different superdisintegrants, and rigorous in-vitro evaluations of powder blends and final tablets. Results were interpreted in the context of pharmacopeial standards, and the most effective formulation was identified based on its performance parameters.

Initial preformulation analysis revealed that Zolpidem tartrate is a white crystalline powder with a slightly bitter taste and a melting point in the range of 192–194°C, indicating thermal stability and chemical integrity. The drug exhibited sparing solubility in water and higher solubility in phosphate buffer (pH 6.8), which supported its selection as the dissolution medium. Given its classification as a BCS Class II drug (low solubility, high permeability), enhancing its dissolution rate through formulation design is critical for improving its bioavailability.

FTIR spectroscopic studies confirmed compatibility between Zolpidem and excipients used in the formulations. No significant alterations or disappearance of characteristic peaks were observed in the physical mixtures, suggesting no chemical interactions. This stability is essential for maintaining drug efficacy and shelf-life over time.

The direct compression method was selected for tablet formulation due to its simplicity, lower cost, and suitability for heat- and moisture-sensitive drugs. Nine different batches (F1–F9) were developed, using various concentrations of superdisintegrants such as crospovidone, sodium starch glycolate (SSG), and croscarmellose sodium. These disintegrants were chosen due to their ability to enhance tablet breakup via mechanisms like wicking and swelling, which are vital for fast oral disintegration.

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Among all tested formulations, batch F5 was identified as the optimized version. It incorporated a balanced combination of crospovidone and SSG, which appeared to work synergistically. This synergy improved tablet porosity and water penetration, resulting in rapid disintegration and high drug release. The formulation achieved over 95% drug dissolution within 10 minutes, demonstrating its potential to provide fast onset of action. Excess use of disintegrants, on the other hand, can form a viscous gel barrier that hinders disintegration, which was not observed in F5, indicating that the concentrations used were within the optimal range.

Micromeritic evaluations, including angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio, were all within acceptable limits. These values confirmed the excellent flowability and compressibility of the powder blends, ensuring consistent die filling and uniform tablet weights. Such properties are crucial in direct compression processes, where any variation in flow can directly impact the quality of the final product.

Tablet physical properties such as weight variation, hardness, thickness, and friability also met pharmacopeial specifications across all formulations. Hardness values between 2.8 and 3.5 kg/cm² provided sufficient mechanical integrity to the tablets while still allowing for fast disintegration. Friability values remained below 1%, confirming that the tablets could withstand handling, packaging, and transportation without breaking apart.

Disintegration time is a critical performance parameter for ODTs. All formulations disintegrated within 60 seconds, while the optimized F5 batch disintegrated in just 20 seconds. This rapid disintegration was supported by equally fast wetting times, especially for F5 (18 seconds), suggesting excellent fluid uptake. These results comply with regulatory guidelines that specify disintegration within 30 to 60 seconds for orodispersible tablets.
Uniformity in drug content was observed across all tablets, with values ranging between 98.5% and 101.3%. This consistency ensures that each dose provides accurate therapeutic levels, a prerequisite for patient safety and regulatory compliance.
In-vitro dissolution studies demonstrated clear distinctions between the formulations. Those containing only one superdisintegrant or lower concentrations exhibited slower release profiles, while formulations like F5, containing a synergistic blend of disintegrants, exhibited enhanced drug release. The rapid release of Zolpidem is particularly important because of the drug's pharmacological role in inducing sleep; any delay in absorption could reduce therapeutic efficacy in patients with sleep-onset insomnia.

Zolpidem tartrate is a short-acting, non-benzodiazepine hypnotic that modulates the GABA_A receptor. It is often preferred over older sedative agents due to reduced risk of dependence and minimal next-day drowsiness. However, its therapeutic effectiveness relies on rapid gastrointestinal absorption. Traditional oral tablets require water and may take longer to disintegrate, delaying sleep induction. ODTs overcome these drawbacks by disintegrating directly in the mouth, allowing for faster drug availability. This feature is especially beneficial for elderly patients, those with dysphagia, or individuals waking up during the night who may not have immediate access to water.

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The performance of the optimized formulation in this study aligns well with these clinical needs. Faster disintegration and dissolution potentially result in quicker systemic absorption, enhancing the onset of therapeutic action. Additionally, the palatability of the formulation was addressed through the inclusion of aspartame and peppermint flavoring, ensuring better patient compliance.

Despite the promising outcomes, this study had limitations. No in-vivo studies were conducted to evaluate pharmacokinetics, bioequivalence, or pharmacodynamic effects. Although in-vitro results were favorable, they do not always guarantee similar in-vivo performance. Future work should involve clinical or preclinical trials to confirm the improved onset of action, therapeutic efficacy, and patient acceptability. Additionally, conducting accelerated and long-term stability testing under ICH guidelines would help establish product shelf-life and packaging requirements.

Several further directions could also be explored:

- Development of mucoadhesive ODTs to prolong residence time in the oral cavity.
- Incorporation of taste-masking technologies to further mask the bitter taste of Zolpidem.
- Use of nanocarrier systems or cyclodextrins to improve solubility and potentially bypass first-pass metabolism.

In conclusion, this study successfully demonstrated the formulation of fast-disintegrating Zolpidem tablets with excellent in-vitro performance. The optimized ODTs exhibited superior disintegration and dissolution characteristics, potentially supporting rapid onset of action in insomnia treatment. These findings contribute to advancing patient-centric drug delivery approaches for sleep disorders, especially in cases requiring immediate pharmacological intervention without reliance on water.

Conclusion

This study successfully developed and evaluated orally disintegrating tablets (ODTs) of Zolpidem tartrate to overcome limitations associated with conventional dosage forms, such as delayed onset of action and difficulty in swallowing. Zolpidem, a BCS Class II drug with low aqueous solubility and high permeability, requires formulation strategies that enhance dissolution and ensure rapid therapeutic action—especially critical in the management of insomnia.

Preformulation studies confirmed the drug's purity, thermal stability, and chemical compatibility with selected excipients. Solubility analysis and FTIR spectra indicated no significant interactions, supporting formulation feasibility. Nine ODT formulations (F1–F9) were prepared via direct compression using varying concentrations of superdisintegrants—crospovidone, sodium starch glycolate (SSG), and croscarmellose sodium. Powder blends exhibited excellent flow and compressibility (angle of repose: 25.3°–28.5°, Carr’s index: 11.8%–15.4%, Hausner’s ratio: 1.13–1.18), confirming their suitability for direct compression.

All formulations complied with pharmacopeial standards for physical properties including weight variation, hardness, thickness, friability, and drug content uniformity (98.5%–101.3%). Disintegration times ranged from 20 to 60 seconds, with formulation F5 showing the most

favorable results. F5 also exhibited the lowest wetting time (18 seconds) and achieved 95.2% drug release within 10 minutes in in-vitro dissolution studies, demonstrating its potential for rapid onset of action. Statistical analysis (ANOVA) confirmed that differences in disintegration and dissolution among batches were significant ($p < 0.05$), underscoring the critical role of superdisintegrant selection and concentration.

While the study demonstrated promising in-vitro performance, limitations include the absence of in-vivo pharmacokinetic and stability studies, and lack of taste-masking for patient acceptability. Future work should focus on in-vivo evaluations, taste-masking strategies, and stability testing under ICH conditions. Additional improvements such as mucoadhesive or nanoparticle-based ODTs could further enhance therapeutic efficiency and patient compliance.

In conclusion, formulation F5—containing a synergistic combination of crospovidone and SSG—emerged as the optimized ODT, offering rapid disintegration, efficient drug release, and ease of administration without water. This patient-friendly dosage form holds significant potential as a commercially viable alternative for the fast and effective treatment of insomnia.

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