RESEARCH PAPER

Formulation and Evaluation of Biphasic Drug Delivery System of Zolpidem Tartrate using MUPS

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Abstract - Insomnia is a common sleep disorder involving difficulty in falling or staying asleep, or not feeling rested after sleep. It affects a large portion of adults and can result from medical, psychological, or lifestyle factors. If untreated, it increases the risk of conditions such as depression, anxiety, heart disease, and reduced daily performance. When non-drug methods are ineffective, medications like benzodiazepines and non-benzodiazepine "Z-drugs" such as zolpidem are prescribed. Zolpidem tartrate acts quickly to induce sleep but has a short duration of action, often leading to incomplete sleep maintenance. To address this, Biphasic Drug Delivery System using Multiple Unit Pellet Systems (MUPS) have been developed, offering both rapid sleep induction and prolonged effect while minimizing side effects and the risk of dependence.

Keywords: Multiple Unit Pellet Systems (MUPS), Zolpidem tartrate, Biphasic Drug Delivery System, Formulation, Evaluation.

How to cite this article: Rana U, Jadon G, Kishor A, Choudhury PK. Formulation and Evaluation of Biphasic Drug Delivery System of Zolpidem Tartrate using MUPS. Int J Drug Deliv Technol. 2026;16(10s): 671-682; DOI: 10.25258/ijddt.16.10s.81

INTRODUCTION

There is a rising prevalence of stress-related disorders and sleep disturbances in contemporary society. Consequently, an increased number of sedative and hypnotic agents have been developed to manage these conditions. Among the commonly used commercially available agents are VALIUM, XANAX, AMBLEN, SONATA, and LUKESTA. These products typically deliver the active pharmaceutical ingredient promptly after administration, yielding an immediate pharmacological effect, but they often fail to sustain a lasting effect capable of supporting the recommended eight hours of uninterrupted sleep [1] [2].

Although controlled-release dosage forms that dispense therapeutic quantities of the active ingredient over periods of 8 to 24 hours are well established in the pharmaceutical field, few systems exist that rapidly achieve therapeutic levels of a sedative or hypnotic agent immediately after administration while maintaining those levels for approximately eight hours, thereby enabling a full eight hours of restful sleep. [3]

One example of a controlled-release approach aiming to combine rapid initial therapeutic exposure with sustained levels for about eight hours is a biphasic tablet (Stilnoct) of zolpidem tartrate, wherein one layer affords an immediate-release dose and the other layer provides a slow or controlled release of zolpidem tartrate. [4] [5]

However, bilayer tablet formulation presents multiple manufacturing challenges, given that bilayer tablets are effectively two monolayer tablets compressed together:

1. Delamination: The tablet may split into two halves if interlayer adhesion is inadequate, due to poor bonding between granules of the two layers or insufficient hardness of the initial layer. [6]
2. Cross-contamination: Intermingling of granulations from the first and second layers can lead to cross-contamination, undermining the purpose of the bilayer tablet. Effective dust collection substantially mitigates this risk. [7]
3. Production yields: Dust control measures to prevent cross-contamination incur material and process losses, resulting in lower yields for bilayer tablets relative to single-layer tablets.
4. Cost: Bilayer tableting incurs higher costs compared with single-layer tableting for several reasons:
   a. The tablet press itself is more expensive.

b. The press generally operates at a slower rate in bilayer mode.

c. The development of two compatible granulations necessitates additional time for formulation development, analysis, and validation.

If these factors are not adequately controlled or optimized, they can adversely affect bilayer compression and the resulting quality attributes of the tablets, including sufficient mechanical strength to maintain integrity and precise individual layer weight. Consequently, obtaining insight into the root causes is essential to enable the design of a robust product and process.

To address the limitations associated with bilayer tablets, the formulation of MUPS (Multiple-Unit Pellet System) tablets comprising extended pellets with pores filled with immediate-release granules is proposed for Biphasic Release, rather than bilayer tablets. [8] [9] MUPS offers additional advantages:

Advantages of Compaction of Multi-Unit Pellet System (MUPS) Compared with Conventional Modified-Release

1. Pharmacokinetic Advantages
   a. Rapid yet uniform transit of micro-pellets contained within MUPS from the stomach to the small intestine due to their small size, which reduces the risk of localized irritation, enhances drug absorption uniformity, and increases bioavailability. [10]
   b. Consistent emptying of micro-pellets from the stomach into the small intestine facilitates rapid dissolution of the enteric coating. For controlled-release formulations, this leads to more uniform drug release and minimizes the risk of dose dumping and inter-subject variability. [11]
2. Pharmacodynamic Advantages
   a. The rapid and uniform gastric emptying and subsequent uniform dissolution of the pellets—attributable to their small size and increased surface area—promote consistent drug absorption and consequently a stable pharmacological effect.
   b. There is a further reduction in inter- and intra-subject variability in drug absorption and clinical response, since the higher pellet count per MUPS dosage form lowers the likelihood of dose dumping (in the stomach) and incomplete drug release. [12]
3. Patient-friendly dosage form

Enhanced patient adherence is anticipated with multiple-unit pellet system (MUPS) formulations for the following reasons:

   a. Orally disintegrating MUPS dosage forms with palatable flavors are suitable for pediatric and geriatric patients who have difficulty swallowing tablets or capsules. [13]
   b. Oro dispersible MUPS medications can be administered without water, which is advantageous during travel, as the dosage form can be formulated to disintegrate in the mouth and incorporate flavorings and sweeteners to promote salivation and swallowing.
   c. As tablets, MUPS can be designed as divisible dosage forms without compromising the release characteristics of the coated particles contained therein, in contrast to capsule formulations.
   d. MUPS exhibit a reduced tendency to adhere to the esophagus during swallowing.
   e. The smaller size/volume of MUPS tablets tends to improve patient compliance relative to capsules. [13]
4. Processing Advantages

Because MUPS constitutes a tablet dosage form, it inherits the benefits associated with tablets over capsules. [14] Notable advantages include:

   a. Enhanced physicochemical and microbiological stability of pellets facilitated by their incorporation within an inert matrix.
   b. Faster processing relative to capsules when utilizing existing tablet manufacturing facilities.
   c. Reduced processing costs due to higher throughput and the elimination of capsule expenses, among other factors.
   d. The product exhibits relatively tamper resistance.
   e. Compared with conventional tablets, dust generation during compression is diminished.
   f. Pellets intended for compression into MUPS possess favorable flow

characteristics due to their near-spherical shape, facilitating easier tableting than conventional granules.

g. Such formulations require smaller quantities of lubricants during tablet production.

h. MUPS enable assessment of pellet size, shape, and density changes upon compaction by retrieving pellets from disintegration tubes or highly lubricated tablets. [14] [15]

MATERIALS AND METHODS

Materials:

Zolpidem Tartrate was purchased from centaur pharmaceutical's, Celphere CP – 305 was received as a sample from Ashai- Kasei, Methocel E5, Ethocel® Std. 10, Starch 1500, Opadry® II 33K520086 Yellow was a kind gift from Colorcon Asia Ltd., Metalose LH31 was gift sample from Shin-Etsu Chemical, Avicel® PH 200 was received as a gift sample from FMC Corporation, Magnesium Stearate was procured from Peter greven. All other reagents and solvents employed were of analytical or pharmaceutical grade.

Table 1: Formulation Details for evaluating the impact of Drug release and Enteric Release coating:

Batch No.	**F1**	**F2**	**F3**	**F13**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
Metalose LH21 content w.r.t core tablet wt.	**2.5%**	**2.5%**	**2.5%**	**5.0%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**	**2.5%**
Polyethylene Glycol 400 Content w.r.t polymer	**10 %w/w**	**20 %w/w**	**30 %w/w**	**30 %w/w**	**40 %w/w**	**30 %w/w**	**30 %w/w**	**30 %w/w**	**30 %w/w**	**30 %w/w**
Triethyl citrate (TEC) Content w.r.t polymer	**10 %w/w**	**10 %w/w**	**10 %w/w**	**10 %w/w**	**10 %w/w**	**20 %w/w**	**30 %w/w**	**40 %w/w**	**30 %w/w**	**30 %w/w**
Enteric Coating Weight gain	**20 %w/w**	**20 %w/w**	**20 %w/w**	**20 %w/w**	**20 %w/w**	**20 %w/w**	**20 %w/w**	**20 %w/w**	**10 %w/w**	**30 %w/w**
Drug Layering										
Celpheres CP – 305	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Zolpidem Tartrate (Hemitartrate)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Hypromellose (Methocel E5)	17.50	17.50	17.50	17.50	17.50	17.50	17.50	17.50	17.50	17.50
Low-Substituted Hydroxypropyl Cellulose (Metalose LH21)	6.25	6.25	**6.25**	**12.50**	6.25	6.25	6.25	6.25	6.25	6.25
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**80.00**	**80.00**	**80.00**	**86.25**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**
Extended- Release Coating										
Ethyl Cellulose (Ethocel® Std. 10)	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	5.00	15.00
Polyethylene Glycol 400	**1.00**	**2.00**	**3.00**	**3.00**	**4.00**	3.00	3.00	3.00	**1.50**	**4.50**
Triethyl citrate	1.00	1.00	**1.00**	**1.00**	1.00	**2.00**	**3.00**	**4.00**	1.50	4.50
Anhydrous Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**92.00**	**93.00**	**94.00**	**100.50**	**95.00**	**95.00**	**96.00**	**97.00**	**88.00**	**104.00**
Blending, Lubrication and Compression										

Zolpidem Tartrate (Hemitartrate)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Lactose monohydrate (Granulac® 30)	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Microcrystalline Cellulose (Avicel® PH 200)	93.00	92.00	91.00	84.50	90.00	90.00	89.00	88.00	97.00	81.00
Partially Pregelatinized Maize Starch (Starch 1500)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Magnesium Stearate	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Total	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**
Film Coating										
Opadry® II 33K520086 Yellow	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**

Table 2: Formulation Details for evaluating the impact of Disintegrant, Lubricant and Ratio of Lactose monohydrate (Granulac® 30) and Microcrystalline Cellulose (Avicel® PH 200)

Batch No.	**F10**	**F6**	**F11**	**F12**	**F17**	**F18**	**F14**	**F15**	**F16**
Ingredients	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**	**mg/tab**
Partially Pregelatinized Maize Starch (Starch 1500) Content	**0 % w/w**	**2.5 % w/w**	**5.0 % w/w**	**10 % w/w**	**2.5 % w/w**	**2.5 % w/w**	**2.5 % w/w**	**2.5 % w/w**	**2.5 % w/w**
Magnesium Stearate Content	**1.0 % w/w**	**1.0 % w/w**	**1.0 % w/w**	**1.0 % w/w**	**0.5 % w/w**	**3.0 % w/w**	**1.0 % w/w**	**1.0 % w/w**	**1.0 % w/w**
Ratio of Lactose monohydrate and Microcrystalline Cellulose	**36: 64**	**36: 64**	**36: 64**	**36: 64**	**36: 64**	**36: 64**	**64:36**	**0: 100**	**100: 0**
Drug Layering									
Celpheres CP – 305	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
Zolpidem Tartrate (Hemitartrate)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Hypromellose (Methocel E5)	17.50	17.50	17.50	17.50	17.50	17.50	17.50	17.50	17.50
Low-Substituted Hydroxypropyl Cellulose (Metalose LH21)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**	**80.00**
Extended-Release Coating									
Ethyl Cellulose (Ethocel® Std. 10)	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Polyethylene Glycol 400	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00

Triethyl citrate	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Anhydrous Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**96.00**	**96.00**	**96.00**	**96.00**	**96.00**	**96.00**	**96.00**	**96.00**	**96.00**
Blending, Lubrication and Compression									
Zolpidem Tartrate (Hemitartrate)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Lactose monohydrate (Granulac® 30)	50.00	50.00	50.00	50.00	50.00	50.00	**89.00**	**0.00**	**139.00**
Microcrystalline Cellulose (Avicel® PH 200)	95.25	89.00	82.75	64.00	90.25	84.00	**50.00**	**139.00**	**0.00**
Partially Pregelatinized Maize Starch (Starch 1500)	**-**	**6.25**	**12.50**	**25.00**	6.25	6.25	6.25	6.25	6.25
Magnesium Stearate	2.50	2.50	**2.50**	2.50	**1.25**	**7.50**	2.50	2.50	2.50
Total	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**	**250.00**
Film Coating									
Opadry® II 33K520086 Yellow	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**	**257.50**

Preparation of Extended-Release Pellets

Drug Solution Preparation (5% w/w)

Hypromellose (Methocel® E5) was dispersed in purified water under continuous stirring using an overhead stirrer until a clear solution was obtained. Zolpidem tartrate (hemitartrate) and low-substituted hydroxypropyl cellulose (Metalose® LH31) were then added and stirred further to obtain a homogeneous drug dispersion.

Drug Layering

Celpheres® CP-305 pellets were loaded into a GPCG 1.1 fluidized bed processor fitted with a bottom-spray Wurster column and preheated to 40 °C. Drug layering was performed using the prepared drug dispersion while maintaining the bed temperature at 40 °C ± 5 °C. The coated pellets were cured for 15 min until the loss on drying (LOD) was ≤ 2.0%.

Extended-Release Coating Solution Preparation (5% w/w)

Polyethylene glycol 400 was dissolved in purified water, while ethyl cellulose (Ethocel® Std. 10) was dissolved in anhydrous ethanol under continuous stirring. Triethyl citrate and the aqueous PEG solution were added to the ethyl cellulose solution and mixed until a clear, uniform coating solution was obtained.

Extended-Release Coating

Drug-layered pellets were coated in the GPCG 1.1 using the prepared ethyl cellulose coating solution at a bed temperature of 28 °C ± 5 °C. After coating, pellets were cured at 40 °C ± 5 °C for 15 min until the LOD was ≤ 2.0%.

Blending and Compression

Extended-release coated pellets were blended with zolpidem tartrate, lactose monohydrate, microcrystalline cellulose, and partially pregelatinized maize starch, followed by lubrication with magnesium stearate. The blend was evaluated for flow properties and compressed into tablets using 8.0 mm round punches to an average weight of 250 mg and hardness of approximately 70 N.

Film Coating

Opadry® II coating material was dispersed in purified water to obtain a homogeneous coating dispersion. Compressed tablets were film-coated in an automatic coating pan at 40 °C ± 5 °C and subsequently cured at 50 °C ± 5 °C for 15 min.

Evaluation

Coated pellets were evaluated for appearance, particle size distribution, flow properties, and assay. Core tablets were evaluated for physical parameters including hardness, thickness, weight variation, and friability. Film-coated tablets were evaluated for description, assay, organic impurities, water content, disintegration time, and in-vitro dissolution

using USP Apparatus II (basket) at 100 rpm in 500 mL of 0.01 N HCl.

Stability Study

Stability studies of the optimized formulation were conducted as per ICH guidelines for Zone IVB at 30 ± 2 °C/75 ± 5% RH and 40 ± 2 °C/75 ± 5% RH for six months. Samples were evaluated for physical appearance, assay, impurities, water content, and dissolution behavior.

RESULT AND DISCUSSION:

Evaluation of Pellets:

Table 3: Physical and chemical evaluation of pellets

Batch No.	Sieve analysis #20	Sieve analysis #24	Sieve analysis #30	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of repose	Assay (%)
F1	0.00	2.35	97.56	0.61	0.82	35	97.8
F2	0.00	2.98	97.00	0.61	0.82	34	99.1
F3	0.00	3.23	96.56	0.62	0.83	37	96.9
F4	0.00	2.89	96.99	0.62	0.83	35	99.3
F5	0.00	1.26	98.60	0.61	0.81	32	99.2
F6	0.00	2.09	97.59	0.63	0.81	32	99.8
F7	0.00	2.67	96.98	0.61	0.81	38	96.9
F8	0.00	0.69	99.01	0.62	0.83	36	97.6
F9	0.00	7.88	91.50	0.61	0.82	34	98.4
F10	0.00	2.22	97.64	0.62	0.83	32	99.1
F11	0.00	2.78	97.10	0.63	0.82	34	99.4
F12	0.00	2.99	96.85	0.62	0.83	38	98.7
F13	0.00	2.78	96.76	0.64	0.82	34	98.8
F14	0.00	2.98	96.44	0.61	0.81	39	98.1
F15	0.00	2.11	97.23	0.55	0.78	50	98.6
F16	0.00	2.23	97.16	0.65	0.81	36	100.2
F17	0.00	3.56	96.10	0.62	0.82	34	96.7
F18	0.00	3.69	95.86	0.62	0.81	36	102.2

All pellet batches (F1–F9) showed uniform off-white appearance and acceptable size distribution with most pellets retained on sieve #30. Bulk and tapped densities were comparable, indicating uniform packing. Angle of repose values (32°–38°) confirmed good to fair flow properties. Assay results were within acceptable limits (96.9–99.8%), demonstrating uniform drug content. Overall, changes in plasticizer level (TEC), Pore former level (PEG 400) and coating weight gain did not adversely affect pellet quality, and all formulations were suitable for further tablet compression.

Evaluation of Core tablets:

Table 4: Physical evaluation of core tablets

Batch No.	Avg. Wt. (mg)	Individual wt. (mg)	Thickness	Friability	Hardness
F1	250.0	243.2 – 255.4	4.38 - 4.43	0.12	56 -79 N
F2	251.3	242.3 – 258.5	4.41 - 4.45	0.11	58 -82 N
F3	252.0	244.8 – 259.9	4.40 - 4.47	0.11	61 -80 N
F4	251.1	245.6 – 258.4	4.38 - 4.46	0.12	59 -79 N
F5	250.8	241.9 – 256.5	4.40 - 4.46	0.10	58 -83 N
F6	250.2	244.1 – 256.6	4.37 - 4.45	0.11	62 -80 N
F7	251.4	245.2 – 257.5	4.39 - 4.46	0.18	57 -79 N
F8	250.5	246.1 – 257.1	4.40 - 4.45	0.13	61 -82 N
F9	251.6	242.8 – 255.5	4.36 - 4.45	0.12	55 -81 N
F10	250.8	240.2 – 258.5	4.41 - 4.48	0.11	57 -82 N
F11	251.2	241.5 – 259.6	4.37 - 4.44	0.18	60 -81 N
F12	250.1	242.4 – 257.1	4.35 - 4.45	0.21	58 -79 N

Batch No.	Avg. Wt. (mg)	Individual wt. (mg)	Thickness	Friability	Hardness
F13	251.2	241.0 – 259.2	4.34 - 4.44	0.11	61 -77 N
F14	251.7	242.3 – 258.2	4.35 - 4.48	0.12	60 - 74 N
F15	250.1	243.8 – 257.5	4.38 - 4.46	0.12	62 – 82 N
F16	251.2	240.2 – 259.2	4.41 - 4.48	0.13	55 – 61 N
F17	250.5	239.6 – 256.4	4.36 - 4.43	0.09	60 – 84 N
F18	250.1	240.8 – 255.8	4.36 - 4.49	0.63	45 – 55 N

All batches (F1–F9) produced white, round, biconvex tablets with uniform appearance and no visible defects. Average tablet weights were close to the target weight, and individual weight variation was within acceptable limits. Tablet thickness showed minimal variation, indicating consistent compression. Friability values were low (0.10–0.18%), confirming good mechanical strength. Hardness ranged from 55 to 83 N, demonstrating adequate tablet integrity while maintaining compressibility. Overall, all formulations exhibited satisfactory physical characteristics suitable for further evaluation.

Evaluation of Coated tablets:

All parameters used in Characterization of Coated Tablet showed results within the acceptable limits. The results are summarized in the table below:

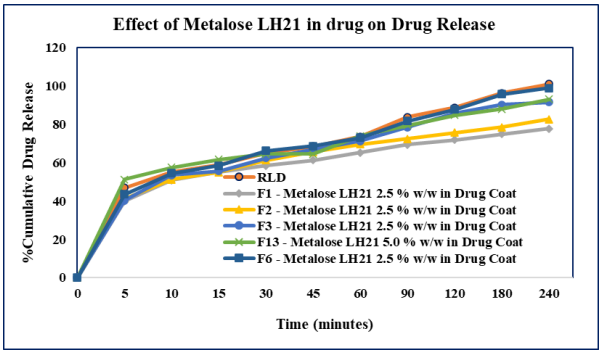
Table 5: Physical evaluation of Coated tablets

Batch No.	Avg. Wt. (mg)	Thickness (mm)	Hardness (N)
F1	258.0	4.41 - 4.59	79 -99 N
F2	259.3	4.43 - 4.54	74 -92 N
F3	260.1	4.44 - 4.57	73 -92 N
F4	259.1	4.41 - 4.57	69 -99 N
F5	258.8	4.44 - 4.55	71 -93 N
F6	258.2	4.42 - 4.58	69 -95 N
F7	259.4	4.45 - 4.54	71 - 89 N
F8	258.5	4.46 - 4.55	67 – 82 N
F9	259.7	4.43 - 4.54	72 -89 N
F10	258.8	4.45 - 4.53	78 -87 N
F11	259.2	4.42 - 4.56	72 -90 N
F12	258.1	4.44 - 4.54	71 -89 N
F13	259.2	4.43 - 4.58	69 -90 N
F14	259.8	4.48 - 4.59	68 - 88 N
F15	258.1	4.44 - 4.53	69 – 89 N
F16	259.2	4.47 - 4.60	72 – 68 N
F17	257.9	4.47 - 4.60	71 – 88 N
F18	258.6	4.47 - 4.60	62 – 72 N

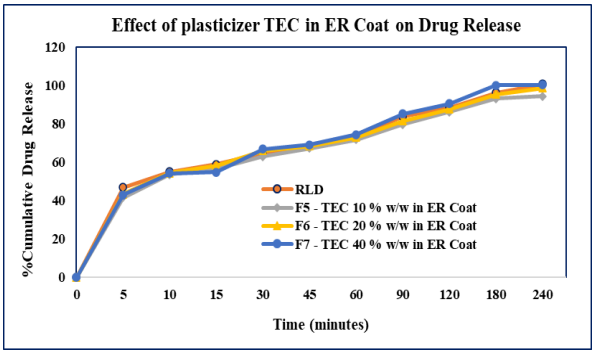
Table 6: % cumulative drug release of coated tablets

Batch No.	RLD	F1	F2	F3	F13	F4	F5	F6	F7	F8	F9	F10	F11	F12	F14	F15	F16	F17	F18
Time (min)		**% Cumulative Drug Release**																	
5	46.9	39.8	41.2	40.2	51.2	41.9	41.5	43.5	43.1	43.1	39.8	27.0	47.1	51.1	48.4	46.2	53.5	48.8	34.5
10	55.0	50.8	51.2	53.4	57.4	52.2	53.7	54.5	54.3	54.3	49.8	36.1	56.0	57.2	58.5	53.1	58.6	60.7	49.9
15	58.9	54.9	54.9	55.5	61.5	55.2	56.7	58.3	54.9	54.9	52.9	45.6	62.5	61.5	61.3	57.4	60.3	63.9	55.5
30	64.8	58.3	61.3	62.4	64.4	62.6	62.9	66.1	66.9	67.9	55.3	55.9	66.7	67.2	65.3	63.9	66.3	75.1	57.5
45	68.4	61.2	65.6	66.6	64.5	68.5	67.2	68.5	69.2	73.2	58.7	63.1	70.0	69.9	69.9	68.5	70.9	83.6	59.2
60	73.4	65.2	69.5	71.2	73.8	72.1	71.7	72.9	74.4	84.4	61.2	70.9	74.2	76.5	74.1	71.8	74.1	90.2	63.5
90	83.7	69.3	72.3	78.4	79.3	78.5	79.8	81.6	85.3	95.5	64.3	77.8	81.4	84.3	84.9	79.8	85.9	97.9	74.3

120	88.5	71.8	75.6	85.7	84.7	83.5	86.3	87.7	90.5	100.3	68.6	82.7	89.9	92.4	87.7	85.7	89.5	102.1	79.2
180	96.2	74.8	78.3	90.1	87.9	89.8	93.1	95.5	100.2	100.5	70.8	86.5	96.6	94.7	97.1	90.5	97.6	102.1	83.4
240	100.8	77.6	82.6	91.5	92.9	91.7	94.5	98.7	100.3	100.5	73.3	91.9	99.2	98.7	99.1	94.9	100.2	101.9	88.1



(a)



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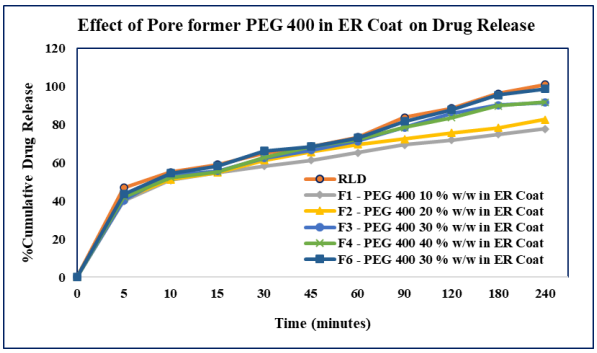
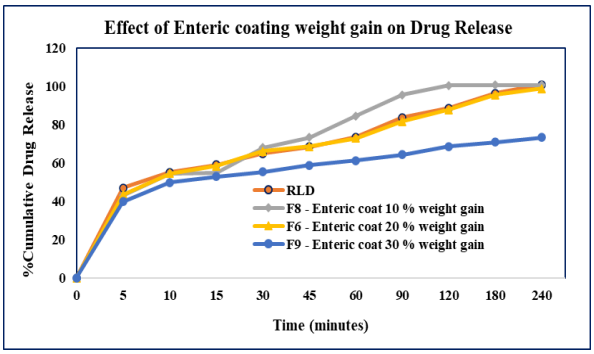
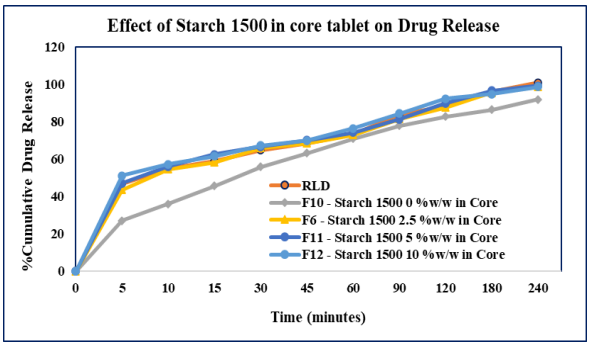


(c)

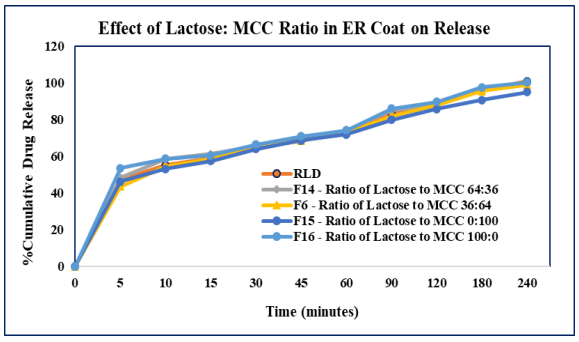


(d)

Figure 1: (a) Effect of disintegrant Metalose LH21 in drug coat on Drug Release (b) Effect of plasticizer TEC in ER Coat on Drug Release (c) Effect of Pore former PEG 400 in ER Coat on Drug Release (d) Effect of Enteric coating weight gain on Drug Release



(a)



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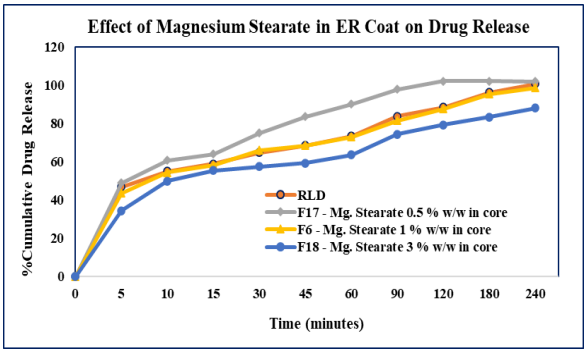

(c)

Figure 2: (a) Effect of Disintegrant Starch 1500 in core tablet on Drug Release (b) Effect of Diluent Lactose: MCC Ratio in ER Coat on Release (c) Effect of

Magnesium Stearate in ER Coat on Drug Release

Effect of Polyethylene Glycol 400 in Extended-Release Coating

Variation in PEG 400 concentration (10–40% w/w with respect to polymer) significantly influenced the permeability of the ethyl cellulose–based extended-release (ER) coating. Formulations containing lower PEG levels (F1, F2) exhibited retarded drug release throughout the dissolution period, indicating inadequate pore formation within the coating matrix. Conversely, higher PEG levels (F3 and F4) resulted in accelerated release at later time points (≥120 min), deviating from the reference listed drug (RLD) profile due to excessive plasticization and increased diffusional pathways. None of the PEG-only modified formulations achieved a consistent match with the RLD across the entire release duration.

Effect of Metalose LH21 Concentration in Drug Layer

The impact of Metalose LH21 concentration in the drug layer was evaluated at 2.5% and 5.0% w/w. Increasing the polymer content to 5.0% (F13) enhanced initial drug release owing to increased swelling and improved water uptake; however, this also resulted in marginally higher cumulative release beyond 120 min compared to the RLD. Formulations containing 2.5% Metalose LH21 provided improved control over release kinetics, indicating that higher polymer levels may compromise sustained release performance when not adequately counterbalanced by ER coating parameters.

Effect of Triethyl Citrate in Extended-Release Coating

Triethyl citrate (TEC) concentration exerted a pronounced effect on drug release modulation. F5 (10% TEC) demonstrated comparatively slower release, reflecting limited film flexibility. In contrast, F7 (40% TEC) showed faster release at later stages due to excessive coating plasticization. **F6, containing 20% TEC**, exhibited a dissolution profile closely aligned with the RLD across all sampling intervals, suggesting an optimal balance between coating flexibility, integrity, and controlled diffusional resistance.

Effect of Enteric Coating Weight Gain

Enteric coating weight gain was a critical determinant of release behavior. Formulation F8 (10% weight gain) showed premature drug release, whereas F9 (30% weight gain) caused excessive retardation, particularly during the early and mid-release phases. **F6 with 20% enteric coating weight gain** demonstrated a controlled and reproducible release profile that was comparable to the RLD, confirming the necessity of an optimized coating level for biphasic release performance.

Effect of Disintegrant (Starch 1500) Level in Core Tablet

The influence of Starch 1500 content (0–10% w/w) on drug release was evident. Absence of disintegrant (F10) resulted in delayed initial release due to limited core hydration. Increasing the disintegrant level improved early release; however, higher concentrations (≥5% w/w, F11 and F12) led to comparatively faster release beyond 120 min. **F6, containing 2.5% Starch 1500**, provided optimal hydration without compromising extended-release characteristics.

Effect of Lactose Monohydrate to Microcrystalline Cellulose Ratio

The ratio of lactose monohydrate to microcrystalline cellulose (MCC) significantly influenced matrix porosity and compaction behavior. MCC-dominant formulations (F15) showed slower drug release due to increased compactness, whereas lactose-rich systems (F16) exhibited accelerated release. **F6 with a lactose:MCC ratio of 36:64** achieved a balanced matrix structure, yielding dissolution behavior closely matching the RLD.

Effect of Magnesium Stearate Level

Lubricant concentration markedly affected both dissolution and mechanical properties. Reduced magnesium stearate content (0.5%, F17) led to faster drug release due to decreased hydrophobicity, whereas elevated levels (3.0%, F18) significantly retarded release and adversely impacted tablet hardness and friability. **F6 containing 1.0% magnesium stearate** ensured controlled release with acceptable manufacturability.

Evaluation of Physical Parameters

All formulations exhibited acceptable average weight, thickness, and friability, with the exception of F18, which demonstrated elevated friability (0.63%) and reduced hardness (45–55 N). Variations in plasticizer, lubricant, and excipient composition influenced compaction characteristics and tablet strength. **F6 showed optimal hardness (62–80 N)**, ensuring mechanical integrity while maintaining the target dissolution profile.

Stability Evaluation:

Table 7: Stability Study Results of Zolpidem Tartrate Extended-Release Tablets 12.5 mg, B. No.

F6 in PVC Blister pack: 40°C±2 °C/75% ±5% RH

Tests	Specification	Time (Months)			
		Initial	1M	3M	6M
Description	Yellow colored, round shaped, biconvex bilayer tablets, film coated tablets with bevelled edges plain on both sides. The tablets should be free from physical defects.	Yellow colored, round shaped, biconvex bilayer tablets, film coated tablets with bevelled edges plain on both sides. The tablets are free from physical defects.			
Dissolution Dissolution (By UV) USP TEST 2 Media: 500 mL, 0.01 N HCl Apparatus: USP Type – I (Basket) RPM: 100 Time Points: 30, 90 and 240 mins Temperature: 37°C	At the end of 30 min: Between 55% and 75%	Min: 64.3 Max: 69.6 Avg: 66.1	Min: 68.3 Max: 73.4 Avg: 69.9	Min: 60.4 Max: 66.8 Avg: 63.0	Min: 56.9 Max: 60.0 Avg: 58.7
	At the end of 90 min: Between 70% and 90%	Min: 79.6 Max :84.6 Avg: 81.6	Min: 84.5 Max: 89.6 Avg: 86.5	Min: 83.1 Max: 86.5 Avg: 85.0	Min: 83.0 Max: 85.8 Avg: 84.4
	At the end of 240 min: Not less than 85% of the labelled amount of Zolpidem Tartrate is Dissolved	Min: 96.1 Max :104.6 Avg: 98.7	Min: 99.4 Max: 105 Avg: 101.6	Min: 94.1 Max: 96.8 Avg: 95.2	Min: 93.1 Max: 96.1 Avg: 94.4
Average weight (mg)	258 ±5.0 % w/w	261.92	255.69	258.46	259.02
Assay (By HPLC)	Zolpidem Tartrate ER tablets contain NLT 90 % and NMT 110% of the labeled amount of zolpidem tartrate	99.25%	99.25%	98.95%	100.05%
Water content (By KF) (%w/w)	NMT 10.0 % w/w	4.25%	5.79%	6.17%	5.73%
ND - Not detected, Min- Minimum, Max- Maximum, NMT- Not more than					

Table 8: Stability Study Results of Zolpidem Tartrate Extended-Release Tablets 12.5 mg, Batch. F6 in PVC Blister pack: 30°C/75% RH

Tests	Specification	Time (Months)			
		Initial	3M	6M	12M
Description	Yellow colored, round shaped, biconvex bilayer tablets, film coated tablets with bevelled edges plain on both sides. The tablets should be free from physical defects.	Yellow colored, round shaped, biconvex bilayer tablets, film coated tablets with bevelled edges plain on both sides. The tablets are free from physical defects.			
Dissolution Dissolution (By UV) USP TEST 2 Media: 500 mL, 0.01 N HCl Apparatus: USP Type – I (Basket) RPM: 100 Time Points: 30, 90 and 240 mins Temperature: 37°C	At the end of 30 min: Between 55% and 75%	Min: 64.3 Max: 69.6 Avg: 66.1	Min: 63.6 Max: 66.9 Avg: 65.6	Min: 59.7 Max: 66.1 Avg: 62.6	Min: 57.3 Max: 59.4 Avg: 58.5
	At the end of 90 min: Between 70% and 90%	Min: 79.6 Max :84.6 Avg: 81.6	Min: 83.3 Max: 87.3 Avg: 85.5	Min: 81.3 Max: 85.5 Avg: 83.4	Min: 81.3 Max: 83.7 Avg: 82.9
	At the end of 240 min: Not less than 85% of the labelled amount of Zolpidem Tartrate is Dissolved	Min: 96.1 Max :104.6 Avg: 98.7	Min: 96.0 Max: 100.0 Avg: 98.5	Min: 97.5 Max: 99.4 Avg: 98.7	Min: 93.4 Max: 95.2 Avg: 94.5
Average weight	258 ±5.0 % w/w	261.92mg	257.98mg	255.12mg	258.28mg

Tests	Specification	Time (Months)			
		Initial	3M	6M	12M
Assay (By HPLC)	Zolpidem Tartrate ER tablets contain NLT 90 % and NMT 110% of the labeled amount of zolpidem tartrate	99.25%	98.70%	99.50%	100.00%
Water content (By KF) (%w/w)	NMT 10.0 % w/w	4.25%	6.01%	5.59%	6.02%
ND - Not detected, Min- Minimum, Max- Maximum, NMT- Not more than					

Stability studies of the optimized formulation F020 (final optimized equivalent of F6 composition) were conducted under accelerated (40 °C ± 2 °C/75% ± 5% RH for 6 months) and long-term (30 °C/75% RH for 12 months) conditions in PVC blister packs, in accordance with ICH Q1A(R2) guidelines.

Physical Appearance and Tablet Integrity

Throughout the stability study period, tablets retained their original yellow color, biconvex shape, film coating integrity, and absence of physical defects under both storage conditions. No evidence of coating cracks, mottling, discoloration, or deformation was observed, confirming the robustness of the optimized coating system.

Dissolution Profile Stability

Dissolution testing conducted at 30, 90, and 240 min demonstrated that the release characteristics of F020 remained within specified limits at all stability time points.

Under accelerated conditions, a marginal reduction in early-stage dissolution (30 min) was observed over time; however, values consistently remained within the acceptance criteria (55–75%). Release at 90 min and 240 min remained well within specification, with ≥94% drug release at 240 min even after 6 months.

Similarly, under long-term conditions, dissolution profiles showed minimal variability up to 12 months. Although a slight decrease in early dissolution was noted at later time points, the overall release pattern remained comparable to the initial profile and aligned with the intended extended-release behavior. These findings indicate no significant impact of temperature or humidity on polymer permeability or coating integrity.

Assay and Chemical Stability

Assay values for zolpidem tartrate remained within 98.7–100.1% of the labeled claim throughout the stability period under both storage conditions, complying with the specified range of 90–110%. This confirms the chemical stability of the active pharmaceutical ingredient within the optimized formulation.

Water Content

Water content showed a controlled and acceptable increase over time, remaining well below the specified limit of NMT 10.0% w/w. The observed moisture uptake did not adversely affect dissolution behavior, assay, or physical integrity, confirming the effectiveness of the PVC blister packaging system in protecting the dosage form from moisture-induced instability.

Conclusion

The present study successfully established a robust extended-release formulation of zolpidem tartrate through systematic optimization of ER coating composition, plasticizer concentration, enteric coating weight gain, and core excipient ratios. Among all formulations evaluated, **F6 was identified as the optimized prototype**, and its finalized composition (**F020**) demonstrated **dissolution behavior closely matching the Reference Listed Drug (RLD)** along with acceptable mechanical properties.

Stability evaluation under both **accelerated and long-term conditions** confirmed that the optimized formulation maintained **physical integrity, dissolution performance, assay, and moisture control** throughout the study duration. Minor variations in early dissolution observed during storage remained within specification and did not compromise the intended extended-release profile.

Overall, the results confirm that **F020 is a physically and chemically stable extended-release formulation**, suitable for scale-up and further in vivo bioequivalence evaluation. The optimized formulation meets regulatory expectations for **modified-release oral dosage**

forms, supporting its potential as a **bioequivalent alternative to the RLD** with adequate shelf-life stability.

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