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Original Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF ZOPICLONE BY USING NATURAL AND SYNTHETIC POLYMERS

Dasari Srinu[1], Chandrasekhara Rao Baru[2], Sushma Desai[3]*

[1]*Associate Professor, Department of Pharmacology, Chilkur Balaji College of Pharmacy, Aziznagar, Hyderabad, Telangana, India-500075*
[2]*Professor & Principal, Departmnt of Pharmaceutics, Chilkur Balaji College of Pharmacy, Aziznagar, Hyderabad, Telangana, India-500075*
[3]**Research Scholar, Department of Pharmaceutics, Gitam University, Rudraram, Patencheru, Sangareddy, Hyderabad, Telangana, India-502329*

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ABSTRACT

The objective of the present study was to formulate and evaluate extended-release (ER) matrix tablets of Zopiclone using a combination of natural polymers (Tragacanth and Locust Bean Gum) and synthetic polymers (Carbopol 941P and PVP K30) to provide sustained hypnotic therapy and improve patient compliance for short-term treatment of severe insomnia. Zopiclone is a non-benzodiazepine hypnotic agent with a short biological half-life (~5 hours) and high dosing frequency, making it an ideal candidate for extended-release matrix formulations.Nine formulations (Z1 to Z9) were developed by the direct compression method. The pre-compression properties of the powder blends exhibited good to excellent flowability and compressibility, with an angle of repose. Post-compression evaluation parameters such as tablet weight variation (117.77 to 125.95 mg), thickness (1.72 to 1.88 mm), hardness (2.31 to 2.51 kg/cm^2), friability (0.28% to 0.55%), and drug content (97.28% to 101.19%) were all found to be within official pharmacopoeia specifications.In vitro dissolution studies revealed that formulation Z5 containing 15 mg of Tragacanth achieved an optimal extended drug release of 99.41% over 12 hours. FTIR compatibility studies confirmed no chemical interaction between Zopiclone and the excipients used. Thus, the study demonstrates that natural and synthetic polymer-based matrix tablets provide an effective approach for once-daily oral extended release of Zopiclone.

Keywords: *Zopiclone, Extended release, Matrix tablets, Tragacanth, Locust Bean Gum, Carbopol 941P, Direct compression, Release kinetics..*

INTRODUCTION

Novel drug delivery systems (NDDS) play a vital role in enhancing the therapeutic effectiveness of incorporated drugs by providing extended, controlled delivery and targeting the drug to desired physiological sites Extended-release (ER) formulations optimize the therapeutic efficacy and safety profile of a drug while improving patient convenience and compliance by reducing dosing frequency [1]. Matrix tablets are among the most commercially viable extended-action dosage forms because they involve minimal processing variables, utilize conventional manufacturing equipment, and accommodate a wide range of drug doses [1].

Zopiclone is a non-benzodiazepine hypnotic agent belonging to the cyclopyrrolone class, prescribed for the short-term treatment of severe insomnia [2]. It acts as a full agonist at the GABA-A receptor complex, enhancing GABA-mediated inhibitory neurotransmission [3]. Due to its short elimination half-life (~5 hours) and potential for transient blood level peaks and troughs when administered in conventional immediate-release forms, extended-release matrix systems offer significant advantages [4]. These benefits include maintaining steady-state plasma concentrations, minimizing peak-related adverse effects (e.g., morning drowsiness, metallic taste), and preventing trough-related loss of efficacy [5]. Zopiclone with a short biological half-life (~5 hours) and high dosing frequency, hypothesized making it an ideal candidate for extended-release matrix formulations.

Corresponding author:
Sushma Desai
Research Scholar, Department of Pharmaceutics, Gitam School of Pharmacy, Rudraram, Patencheru, Hyderabad, India-502329
Email: d.sushmapharma@gmail.com
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2. MATERIALS

Zopiclone received as kind gift from Intas Pharmaceuticals, India.Carbopol 941P purchased from SwapnroopDrugs and Pharmaceuticals, Maharastra, India.Tragacanth purchased from Jyoti chemicals, Uttar Pradesh, India.Locust Bean Gum purchased from Lucid Colloids Limited, Maharastra, India. PVP K30 purchased from Krishna Solvechem Limited, Maharastra, India.

Sodium Bicarbonate purchased from Tata Chemicals Pvt. Ltd, Ghaziabad, Gujarat. Microcrystalline Cellulose (MCC PH-102) purchased from Maple Biotec Pvt. Ltd. Aerosil & Magnesium Stearate purchased from Triveni Interchem Pvt.Ltd.

3. METHODOLOGY

3.1 Analytical Method Development

3.1.1 Buffer Preparation

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed thoroughly.

Preparation of 0.2M Sodium Hydroxide Solution: Accurately weighed 8.0 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed thoroughly.

Preparation of pH 6.8 Phosphate Buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen orthophosphate and 112.5 mL of 0.2M NaOH were transferred into a 1000 mL volumetric flask. The volume was made up to 1000 mL with distilled water.

3.1.2 Determination of Absorption Maxima (λmax)

100 mg of Zopiclone pure drug was dissolved in 100 mL of 0.1N HCl (Stock Solution-1, 1000 µg/mL). From this, 10 mL was taken and diluted to 100 mL using 0.1N HCl (Stock Solution-2, 100 µg/mL). From Stock Solution-2, 10 mL was taken and diluted to 100 mL with 0.1N HCl to obtain a concentration of 10 µg/mL. The solution was scanned using a double-beam UV/Vis Spectrophotometer in the spectrum range of 200–400 nm against 0.1N HCl as blank, giving an absorption peak (λmax) at 304 nm.

3.1.3 Preparation of Calibration Curve

100 mg of Zopiclone pure drug was dissolved in 15 mL of Methanol and the volume was made up to 100 mL with 0.1N HCl (Stock Solution-1). From this, 10 mL was diluted to 100 mL using 0.1N HCl to get Stock Solution-2 (100 µg/mL). Aliquots of 1.0, 2.0, 3.0, 4.0, and 5.0 mL were transferred into 10 mL volumetric flasks and made up to volume with 0.1N HCl to yield concentrations of 10, 20, 30, 40, and 50 µg/mL of Zopiclone. The absorbance was measured at 304 nm using a UV-Spectrophotometer taking 0.1N HCl as blank. Calibration curves were plotted (Concentration vs Absorbance) and linear regression was evaluated. The same procedure was repeated using pH 6.8 phosphate buffer.

3.2 Formulation Development of Extended Release Tablets

All extended release tablet formulations (Z1 to Z9) were prepared by direct compression method using varying concentrations of synthetic (Carbopol-941P) and natural polymers (Tragacanth, Locust Bean Gum). Master compositions are shown in Table 1. Zopiclone and excipients were passed through Sieve No. 60. Ingredients were mixed thoroughly by trituration for 15 minutes. The powder mixture was lubricated with Aerosil, Magnesium Stearate, and Talc.Directly compressed into 120 mg tablets using a rotary tablet press.

Table 1: Formulation Composition of Zopiclone Extended Release Matrix Tablets (Z1 - Z9)

Ingredients (mg)	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
Zopiclone	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Carbopol-941P	7.5	15	22.5	-	-	-	-	-	-
Tragacanth	-	-	-	7.5	15	22.5	-	-	-
Locust Bean Gum	-	-	-	-	-	-	7.5	15	22.5
PVP K30	7	7	7	7	7	7	7	7	7
Sodium Bicarbonate	5	5	5	5	5	5	5	5	5
Aerosil	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3
MCC (Avicel PH102)	87	79.5	72	87	79.5	72	87	79.5	72
Total Weight (mg)	120	120	120	120	120	120	120	120	120

3.3 Evaluation Parameters

3.3.1 Pre-Compression & Post-Compression Protocols

Standard procedures were followed for micromeritic testing (Bulk Density, Tapped Density, Carr's Index, Hausner Ratio, Angle of Repose) and tablet quality evaluation (Weight Variation, Hardness, Friability, Thickness, Drug Content, In-vitro Dissolution in USP Paddle apparatus at 50 rpm, 37°C).

4. RESULTS AND DISCUSSION

4.1 Analytical Calibration Studies

The UV scanning of Zopiclone showed λmax at 304 nm in 0.1N HCl and pH 6.8 phosphatebuffer. Standard curves constructed in 0.1N HCl (Table 8.1, Fig. 8.1) and pH 6.8 phosphate buffer Table 2, Figure. 2 showed linearity with R^2 = 0.9998 and 0.9999, respectively.

Table 2: Standard Calibration Data of Zopiclone at 304 nm

Concentration (µg/mL)	Absorbance in 0.1N HCl	Absorbance in pH 6.8 Buffer
0	0.000	0.000
10	0.107	0.101
20	0.216	0.214
30	0.317	0.321
40	0.417	0.426
50	0.522	0.532

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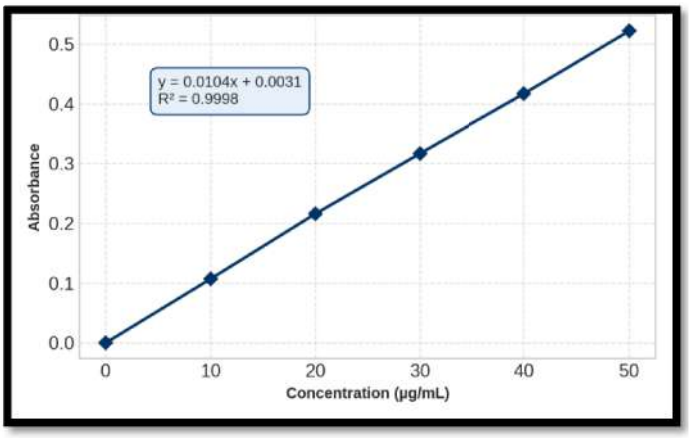


Fig 1: Calibration Curve of Zopiclone in 0.1 N HCl at 304 nm

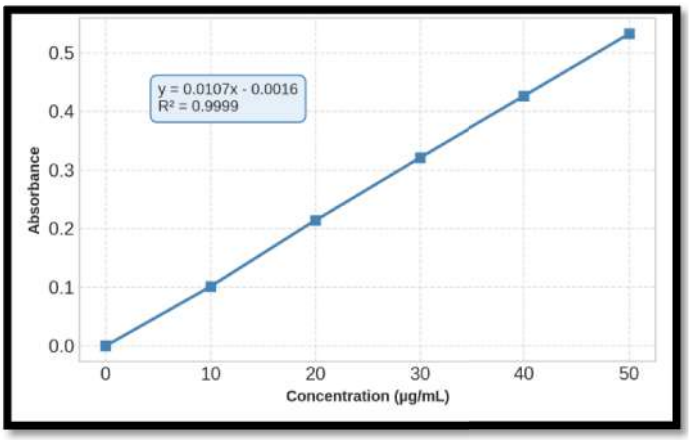


Fig 2: Calibration Curve of Zopiclone in Phosphate Buffer pH 6.8 at 304 nm

4.2 Pre-Compression Parameters

Pre-compression evaluation Table 3 demonstrated excellent powder flow properties across formulations Z1–Z9.

Table 3: Pre-Compression Parameters of Powder Blends (Z1 - Z9)

Formulation Code	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
Z1	24.52 ± 0.23	0.40 ± 0.16	0.47 ± 0.14	14.35 ± 0.26	1.17 ± 0.03
Z2	23.60 ± 0.42	0.42 ± 0.12	0.48 ± 0.08	11.95 ± 0.17	1.14 ± 0.06
Z3	24.72 ± 0.19	0.44 ± 0.07	0.51 ± 0.11	13.21 ± 0.07	1.15 ± 0.01
Z4	24.40 ± 0.27	0.47 ± 0.14	0.54 ± 0.12	12.48 ± 0.18	1.14 ± 0.02
Z5	25.92 ± 0.51	0.48 ± 0.08	0.56 ± 0.16	13.82 ± 0.22	1.16 ± 0.05
Z6	25.84 ± 0.47	0.46 ± 0.13	0.53 ± 0.06	12.71 ± 0.14	1.15 ± 0.03
Z7	25.44 ± 0.29	0.47 ± 0.11	0.55 ± 0.13	14.08 ± 0.08	1.16 ± 0.07
Z8	25.89 ± 0.37	0.48 ± 0.10	0.55 ± 0.07	12.25 ± 0.16	1.14 ± 0.02
Z9	25.97 ± 0.43	0.48 ± 0.12	0.56 ± 0.04	13.82 ± 0.19	1.16 ± 0.04

4.3 Post-Compression Parameters

Physical evaluation of Zopiclone matrix tablets confirmed strict compliance with IP specifications Table 4.

Table4: Post-Compression Evaluation Parameters (Z1 - Z9)

Formulation Code	Weight Variation (mg)	Hardness (kg/cm²)	Friability (% loss)	Thickness (mm)	Drug Content (%)
Z1	119.23 ± 0.5	2.47	0.28	1.78	99.22
Z2	118.48 ± 0.4	2.36	0.34	1.88	98.37
Z3	121.36 ± 0.6	2.44	0.55	1.72	99.43
Z4	120.47 ± 0.3	2.39	0.49	1.81	97.28
Z5	120.51 ± 0.4	2.45	0.41	1.72	101.19
Z6	125.95 ± 0.7	2.51	0.29	1.77	98.52
Z7	119.28 ± 0.5	2.49	0.36	1.85	99.73
Z8	117.77 ± 0.4	2.37	0.44	1.76	97.39
Z9	121.53 ± 0.6	2.31	0.39	1.84	98.44

4.4 In-Vitro Dissolution Profiles

Dissolution profiles over 12 hours for all formulations are listed in Table 8.5 and graphically depicted in Figures 3, 4, and 5. Formulation Z5 exhibited an ideal release profile (99.41% at 12 h).

Table 5: In-Vitro Cumulative Percentage Drug Release Profiles (Z1 - Z9)

Time (h)	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	12.83	14.95	25.51	14.79	19.85	13.15	26.15	15.58	12.85
1	19.25	25.31	26.69	19.14	22.98	19.93	29.73	19.34	19.13
2	21.18	29.53	35.63	28.70	29.73	22.41	33.41	24.99	29.51
3	28.86	36.25	39.89	33.57	36.12	29.85	45.17	28.15	35.82
4	33.05	41.89	43.99	39.96	43.97	37.65	51.69	36.79	42.89
5	37.94	43.11	48.69	48.25	48.56	43.12	57.12	41.47	47.56
6	42.12	48.59	53.12	53.57	57.53	49.75	63.51	44.95	53.32
7	49.51	52.13	57.01	59.12	64.71	55.87	67.98	53.42	65.28
8	53.52	62.89	57.86	63.24	69.02	62.41	73.46	58.03	71.56
9	57.29	64.92	69.47	67.95	81.84	65.97	78.04	66.52	77.78
10	64.97	69.19	78.09	75.71	86.09	81.27	85.67	72.17	83.14
11	69.75	73.93	83.18	86.65	91.11	86.94	94.42	76.59	89.51
12	76.38	79.89	89.55	98.23	99.41	96.53	98.83	89.02	94.97

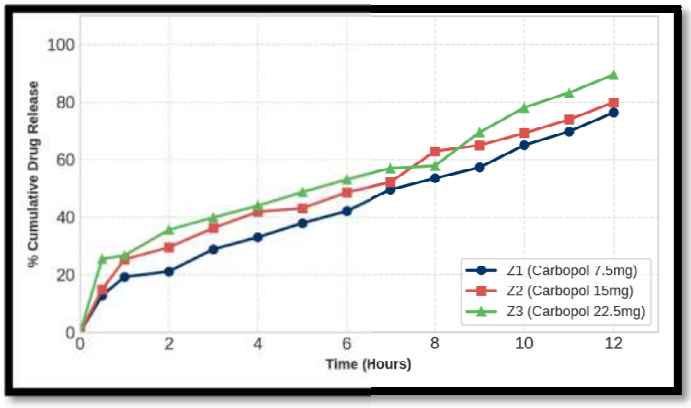


Fig 3: Dissolution Study of Zopiclone Extended Tablets (Z1 to Z3 - Carbopol 941P)

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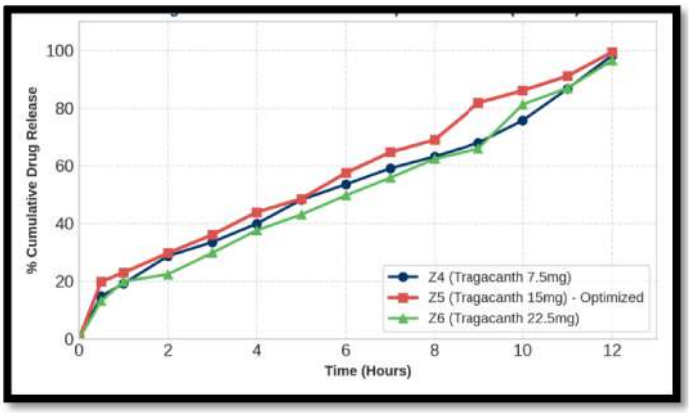


Fig 4: Dissolution Study of Zopiclone Extended Tablets (Z4 to Z6 - Tragacanth)

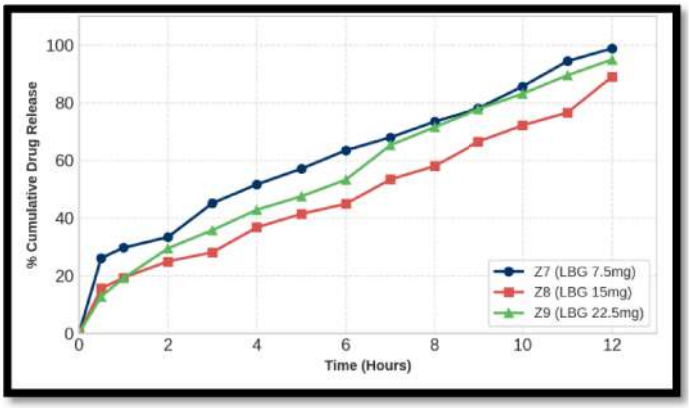


Fig 5: Dissolution Study of Zopiclone Extended Tablets (Z7 to Z9 - Locust Bean Gum)

4.5 Release Kinetic Modeling of Optimized Formulation (Z5)

Kinetic parameter calculations for Z5 are given in Table6. The corresponding mathematical plots are presented in Figure 6 to 9.

Table 6: Release Kinetics Mathematical Data for Optimized Formulation (Z5)

Time (h)	Cum % Release (Q)	Root Time (√t)	Log Cum % Rel	Log Time	Log % Rem	1/Cum % Rel	% Rem
0	0.00	0.000	-	-	2.000	-	100.00
0.5	19.85	0.707	1.298	-0.301	1.904	0.0504	80.15
1	22.98	1.000	1.361	0.000	1.887	0.0435	77.02
2	29.73	1.414	1.473	0.301	1.847	0.0336	70.27
3	36.12	1.732	1.558	0.477	1.805	0.0277	63.88
4	43.97	2.000	1.643	0.602	1.748	0.0227	56.03
5	48.56	2.236	1.686	0.699	1.711	0.0206	51.44
6	57.53	2.449	1.760	0.778	1.628	0.0174	42.47
7	64.71	2.646	1.811	0.845	1.548	0.0155	35.29
8	69.02	2.828	1.839	0.903	1.491	0.0145	30.98
9	81.84	3.000	1.913	0.954	1.259	0.0122	18.16
10	86.09	3.162	1.935	1.000	1.143	0.0116	13.91
11	91.11	3.317	1.960	1.041	0.949	0.0110	8.89
12	99.41	3.464	1.997	1.079	-0.229	0.0101	0.59

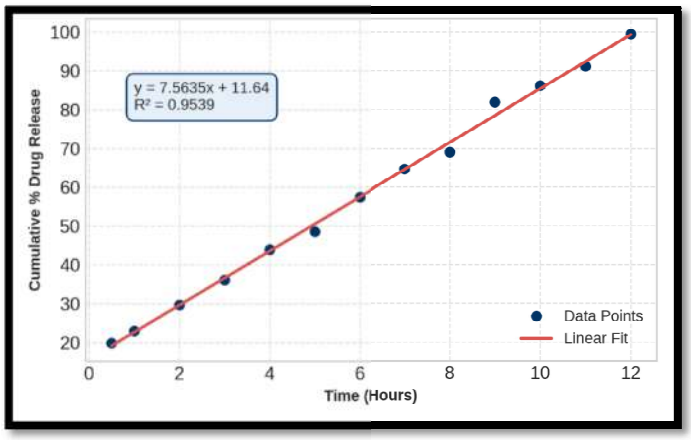


Fig 6: Graph of Zero-Order Release Kinetics for Z5

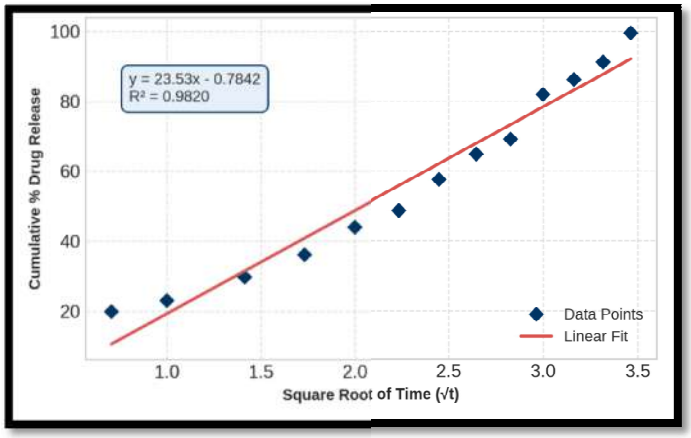


Fig 7: Graph of Higuchi Release Kinetics for Z5

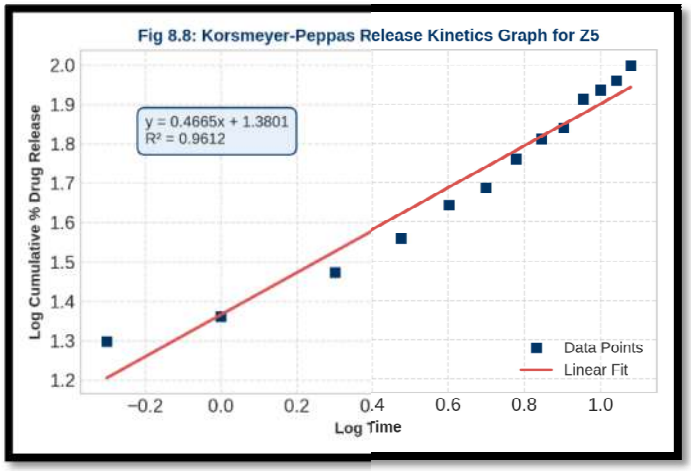


Fig 8: Graph of Korsmeyer-Peppas Release Kinetics for Z5

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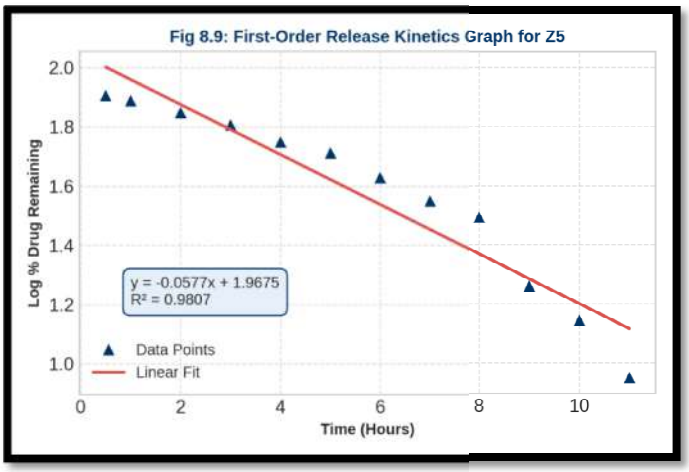


Fig 9: Graph of First-Order Release Kinetics for Z5

The highest correlation coefficient was observed in the Higuchi model (R^2 = 0.9820), confirming diffusion-controlled drug release. The Korsmeyer-Peppas release exponent n = 0.4665 indicates Fickian diffusion transport mechanism.

4.6 Drug-Excipient Compatibility Studies (FTIR)

FTIR spectra of pure Zopiclone drug and optimized formulation blend Z5 are shown in Figures 10 and 11. The absence of significant peak shifts confirms complete drug-excipient compatibility.

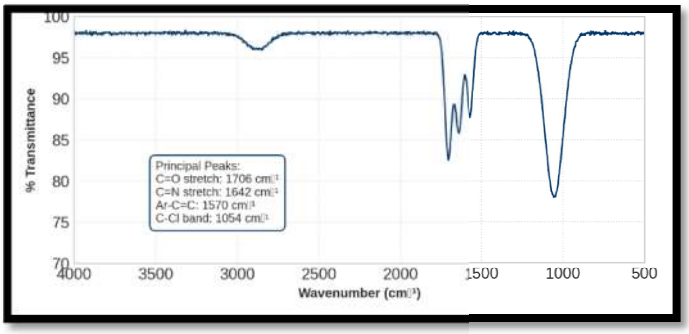


Fig 10: FTIR Spectrum of Pure Drug Zopiclone

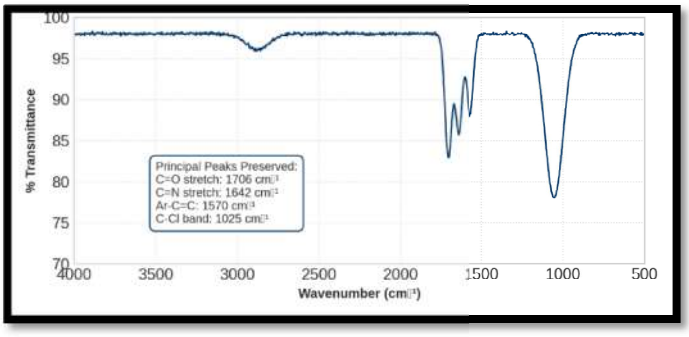


Fig 11: FTIR Spectrum of Optimized Formulation (Z5 Blend)

5. CONCLUSION

The present study successfully developed extended-release matrix tablets of Zopiclone using natural (Tragacanth, Locust Bean Gum) and synthetic polymers (Carbopol 941P) by direct compression. Formulation Z5 containing 15 mg Tragacanth polymer was optimized based on its ideal drug release profile (99.41% over 12 h), excellent tablet physical integrity, zero-order kinetics, and non-Fickian diffusion mechanism. FTIR studies confirmed the stability and compatibility of the drug with all formulation ingredients. This extended-release matrix system offers a promising strategy for once-daily management of insomnia, minimizing blood level fluctuations and enhancing therapeutic efficacy and patient compliance.

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