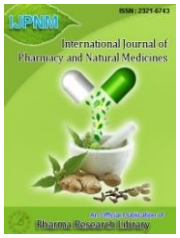

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Formulation and Evaluation of Extended Release Matrix Tablets of Zopiclone by using Natural and Synthetic Polymers

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A B S T R A C T

The objective of this study was to develop and evaluate extended-release matrix tablets of Zopiclone, a hypnotic agent, utilizing both natural and synthetic polymers to achieve a controlled drug release profile. Zopiclone, known for its efficacy in treating insomnia, requires a formulation that provides sustained release to improve therapeutic outcomes and patient compliance. Matrix tablets were formulated using various combinations of natural polymers (Tragacanth and Lactose Bean gumm) and synthetic polymers Carbopol-941P, PVP K30. The tablets were prepared by the direct compression method and evaluated for various parameters, including tablet hardness, friability, drug content, and in vitro drug release. The extended-release characteristics were assessed using dissolution testing, where the impact of different polymer combinations on the drug release rate was analyzed. The results indicated that the use of synthetic polymers, particularly Carbopol-941P, provided a more controlled and consistent release profile compared to natural polymers alone. A combination of natural and synthetic polymers achieved an optimal balance, ensuring a sustained release of Zopiclone over an extended period. The optimized formulations demonstrated desirable release kinetics with a controlled drug release extending up to 12 hours, aligning with the therapeutic needs for extended release. These findings suggest that a judicious selection and combination of natural and synthetic polymers can effectively tailor the release profile of Zopiclone, enhancing its clinical efficacy and patient adherence.

Keywords: Zopiclone, Carbopol-941P, Tragacanth and Lactose Bean gumm

A R T I C L E I N F O

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C o n t e n t s

1. Introduction

The vital role of novel drug delivery system that improve the therapeutic effectiveness of integrated drugs by providing extended, controlled delivery and or targeting the drug to desired site. Extended-release formulations make the drug available over extended time period after oral administration. The extended-release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance1

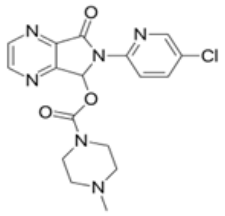

Fig.1: Zopiclone

IUPAC Name: 6-(5-chloropyridin-2-yl)-7-oxo-5H,6H,7H-pyrrolo[3,4-b]pyrazin-5-yl4-methylpiperazine-1carboxylate
Molecular Formula : $C_{17}H_{17}C_lN_6O_3$
Molecular Weight : 388.808 gm/mole.
Official Pharmacopoeia : BP
Physicochemical properties:
Description(Physical State): Solid
Solubility: Soluble in water
Dosage : Tablet
Melting point : 178 °C
pKa(strongest acidic): 13.04
Log P : 0.8
Pharmacokinetic properties:
Bioavailability : 75-80 %
Half-life : 5 hrs
Absorption : Rapidly absorbed following oral administration.
Protein binding : Approximately 45%
Metabolism : Hepatic through CYP3A4 and CYP2E1
Time of peak action : 1.5-2 hr
Excretion : Urine (80%)

Table.1: Drug Information

S.N	Drug name	Label Claim	Brand name	Company
1	Zopiclone	7.5 mg	Zonap	Unichem

2. Materials and Methods

Analytical method development:

Buffer Preparation:

0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 1000ml of distilled water and mixed.

pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium

Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Determination of absorption maxima:

100mg of Zopiclone pure drug was dissolved in 100ml of 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the ranges of 200 – 400 nm.

Preparation calibration curve:

100mg of Zopiclone pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 1.0, 2.0,3.0, 4.0 and 5.0 ml of solution and make up to 10ml with 0.1N Hcl to obtain 10,20,30,40 and 50 µg/ml of Zopiclone per ml of solution. The absorbance of the above dilutions was measured at 304nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Formulation development of Extended release Tablets:

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table 7.1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Zopiclone

Procedure:

- Zopiclone and all other ingredients were individually passed through sieve no ≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Evaluation Parameters

Pre- Compression parameters

Bulk density (D_B)

Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

$$\textbf{Bulk density } (D_B) = W / V_0$$

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume.

Tapped Density (D_T)

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula

Tapped density = mass of the powder/ tapped volume

$$\textbf{Tapped density } (D_T) = W/V_f$$

Hausner's ratio

Hausner's ratio[47] is an indirect index of ease of powder flow and was calculated by the formula,

$$\textbf{Hausner's ratio} = D_T/D_B$$

Where, D_T is the tapped density

D_B is the bulk density

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

$$\textbf{\% Compressibility index} = V_o - V/V_o \times 100$$

Angle of repose

Angle of repose was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane. The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14

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

Where, θ is the angle of repose

h is the height in cm

r is the radius in cm

Post Compression parameters

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Table.2: IP standards of uniformity of weight

S. No.	Average wt of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss(F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

***In vitro* drug release studies**

Apparatus --USP-II, Paddle Method

Dissolution Medium -- 0.1 N HCl, p H 6.8 Phosphate buffer

RPM --50

Sampling intervals (hrs)--0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 11,12

Temperature--37°c ± 0.5°c

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued up to 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at wavelength of drug using UV-spectrophotometer.

Application of release rate kinetics to dissolution data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time 't', and 'K_o' is the zero-order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used

for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a bruker FTIR facility.

3. Results and Discussion

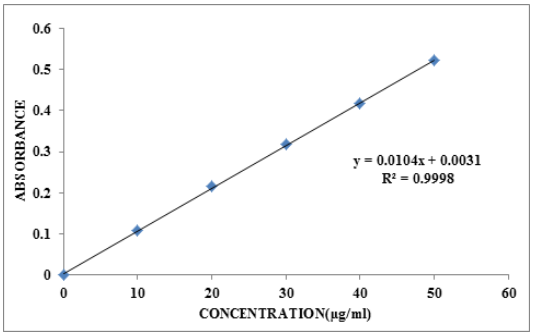

Fig.2: Calibration curve of Zopiclone in 0.1N HCl at 304 nm

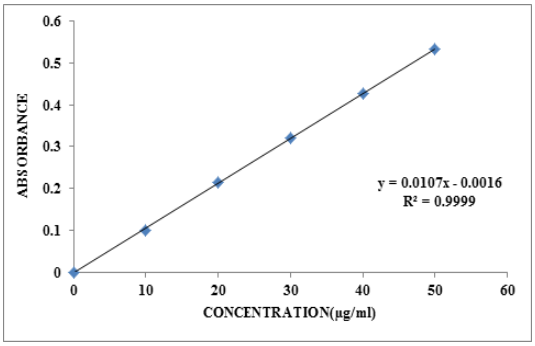

Fig.3: Calibration of Zopiclone in Phosphate buffer pH 6.8

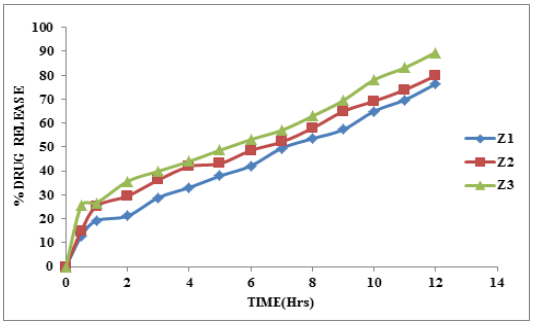

Fig.4: Dissolution study of Zopiclone Extended tablets (Z1 to Z3)

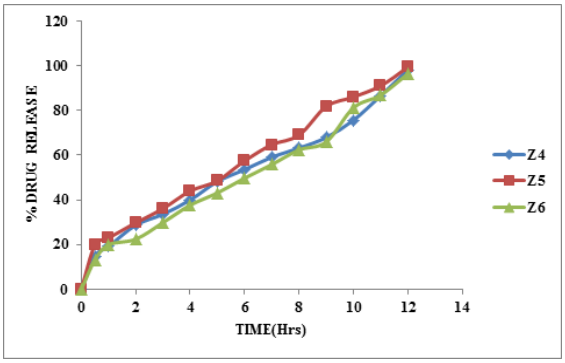

Fig.5: Dissolution study of Zopiclone tablets (Z4 to Z6)

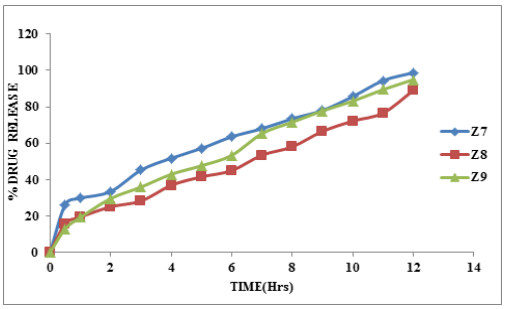

Fig.6: Dissolution study of Zopiclone tablets (Z7 to Z9)

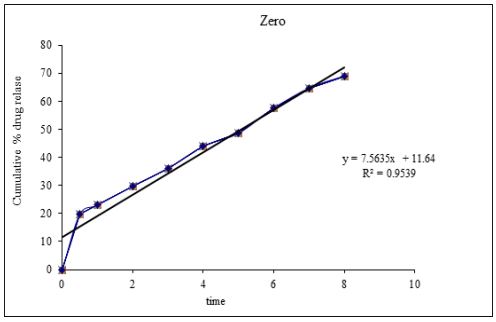

Fig.7: Graph of zero order kinetics

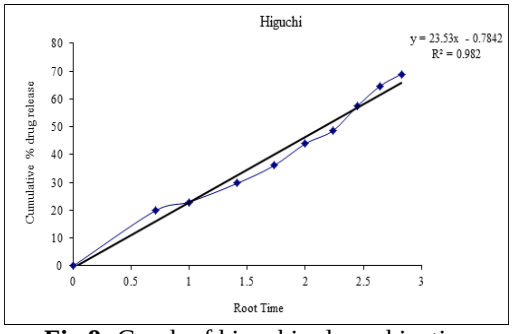

Fig.8: Graph of higuchi release kinetics

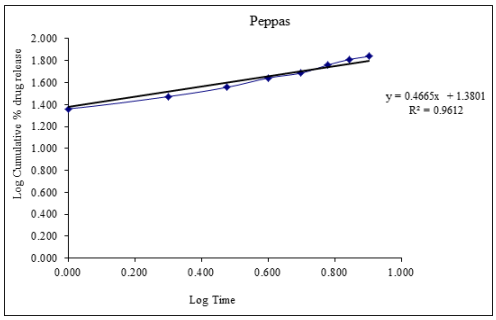

Fig.9: Graph of peppas release kinetics

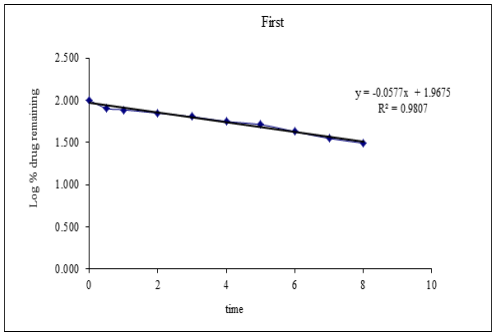

Fig.10: Graph of first order release kinetics

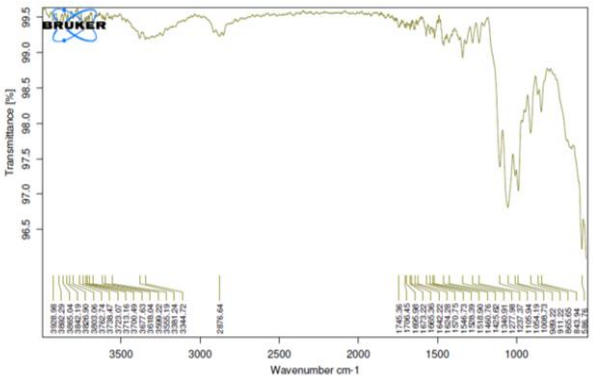

Fig.11: FTIR graph of pure drug of Zopiclone

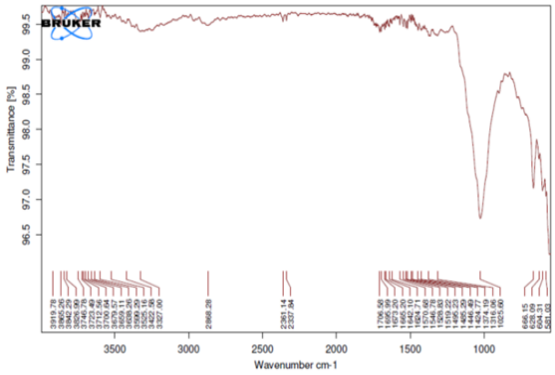

Fig.12: FTIR Spectrum of optimized formulation

Table 3: Formulation of Extended release tablets

Ingredients (MG)	Formulation codes								
	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	-	-	-
Lactose 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
Mg stearate	3	3	3	3	3	3	3	3	3
MCC	87	79.5	72	87	79.5	72	87	79.5	72
Total weight	120	120	120	120	120	120	120	120	120

Table.4: The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

Table.5: Standard curve of Zopiclone in 0.1N HCl

Concentration (µg/ mL)	Absorbance
0	0
10	0.107
20	0.216
30	0.317
40	0.417
50	0.522

Table.6: Standard curve of Zopiclone in Phosphate buffer pH 6.8

Concentration (µg / ml)	Absorbance
0	0
10	0.101
20	0.214
30	0.321
40	0.426
50	0.532

Table.7: Pre-compression parameters of powder blend

Formulation Code	Pre-compression parameters of powder blend				
	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	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

Table.8: Post compression parameters of tablets

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

Table.9: Dissolution Data of Zopiclone Tablets

TIME (H)	Cumulative percent drug released								
	Z1	Z2	Z3	Z4	Z5	Z6	Z7	Z8	Z9
0	0	0	0	0	0	0	0	0	0
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	57.86	62.89	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

4. Conclusion

The study effectively demonstrated the formulation and evaluation of extended-release matrix tablets of Zopiclone utilizing both natural and synthetic polymers. The incorporation of various polymers significantly influenced the release profile of Zopiclone, showcasing the potential to tailor drug release rates to meet therapeutic needs. Natural polymers, such as Tragacanth and Lactose Bean gum, provided satisfactory control over drug release, though with some variability in release kinetics. Synthetic polymers, like Carbopol-941P and PVP K30, offered more consistent and predictable release.The formulation with a combination of natural and synthetic polymers achieved an optimal balance, exhibiting sustained release characteristics that align well with the desired pharmacokinetic profile for extended-release applications. These findings underscore the efficacy of utilizing a blend of polymer types to fine-tune drug release and enhance patient compliance through improved dosing intervals.

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