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

Dr. Rama Krishna * 1, Dr. B Rajkamal, Banothu Susmitha, Begari Madhuri, Behari Manasa, Bukya Arun

[1]*Department of Pharmaceutics, Avanthi Institute of Pharmaceutical Science, Gunthapally, Abdullapurmet, Near Ramoji Film City, Ranga Reddy, Telangana-501512.*

*Corresponding Author: **Dr. Rama Krishna***
Email: principalgn@gmail.com

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Abstract: 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.

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 compliance[1]. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations[2]. The design of oral extended release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug[3]. Matrix tablets are considered to be the commercially feasible extended action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. These remains an

interest in developing novel formulations that allow for extended the drug release using readily available, inexpensive excipient by matrix-based formulation[4-5]A tablet is a dosage form used in pharmaceuticals. It is made up of a powdered mixture of active ingredients and excipients that is pressed or compressed into a solid dosage. To facilitate efficient tableting, excipients can include diluents, binders or granulating agents, glidants (flow aids), and lubricants: disintegrate to encourage tablet break-up in the digestive tract; sweeteners or flavours to improve taste; and pigments to make the tablets visually appealing[6]. A polymer coating is frequently used to make tablets smoother and easier to swallow, to manage the active ingredient's release rate, to make them more resistant to the environment (increasing their shelf life), or to improve their look. Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/ subcutaneous injections of suspensions of insoluble drug complexes, e.g., procaine penicillin, protamine zinc insulin, insulin zinc suspensions or injections of the drug in oil,[7].Advances in technology have resulted in novel oral modified- release dosage forms. Many terms are used to describe modified-release products including extended-release, prolonged-release, controlled-release, controlled-delivery, slow release and sustained-release. Delayed-release Products are modified-release, but they are not extended-release by definition. They entail the release of a discrete amount(s) of medicament after it has been administered. e.g., Enteric-coated products, have a lag time in which little or no absorption takes place[8].While there are a variety of modified-release pharmaceuticals available as prescription and over-the-counter medications, only a small number have been proved to provide a therapeutic benefit. Rather for being designed for clinical benefit, several of the formulations appear to have been devised to extend patents or give a marketing advantage over conventional-release medications. Various prototype formulation trails were taken and assessed with various quality controls such as dissolving and assay to achieve these goals[9]. 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 compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly[10].

Tablets have been the most preferred oral dosage form for the patients suffering from chronic diseases like bronchial asthma, chronic bronchitis and chronic obstructive pulmonary diseases (COPD) because of low-cost therapy and ease of administration[11,12]. The traditional tablets provide only a single and transient release of the drug. The pharmaceutical effect has only seen for the time duration in which the concentration of the drug remains within the therapeutic range that can be best achieved with ER tablets[13]. The significance of administering single-dose extended-release tablet that has discharged over an extended timeframe instead of multiple doses becomes the area of interest for the formulation designing scientists in the Pharmaceutical industry[14]. The oral prolonged discharge dosage form has been prepared for those medications that are comfortably absorbed from the gastrointestinal tract (GIT), have a short half-life and eliminated quickly from the bloodstream[15]. The terms sustained action, sustained discharge, controlled discharge, timed release, prolonged action, depot, extended action and repository formulations have been used to represent the novel drug delivery system (NDDS) and formulated to get an extended therapeutic effect by continuously discharging drug over a prolonged time period after administration of a single dose[16]. There might be several other reasons also for the attractiveness of these dosage forms viz. provides enhanced bioavailability of medication, lessening in the recurrence of administration to extend the timeframe of effective blood levels, reduces the fluctuation of the peak-trough level and adverse effects and possibly enhances the particular distribution of the medication[17].

Extended-release formulations[18-21] are the slow release drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 to 12 hours), drugs are metabolized before absorption either in the lumen (or) the tissues of the intestine, can show decreased bioavailability from the extended releasing system. These oral formulations are low-risk dose dumping, flexibility, of blending to attain difference release pattern as well as reproducible and short gastric residence time. Transfer of drug from one compartment to other if follows zero-order kinetic process then such drugs are a poor candidate for oral ER delivery system, it should be of first-order kinetics.[22]

Solid dosage forms are popular because of ease of administration, self-medication, pain avoidance as compared with parenteral, and low cost.[23]One of the most common approaches used for prolonging and controlling the rate of drug release is to incorporate a drug in hydrophilic colloid matrix such as hydroxyl propyl methyl cellulose (HPMC K15M) and PEO available anti -human immunodeficiency virus(HIV) drugs can be classified into the following three categories: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. Most of these drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and

undesirable side effects. Efforts have been made to design drug delivery systems for anti HIV agents to: (a) reduce the dosing frequency, (b) increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, (c) improve the central nervous system (CNS) penetration and inhibit the CNS efflux, and (d) deliver them to the target cells selectively with minimal side.[24]Stavudine (D4T, thymidine) is the Food and Drug Administration approved drug for clinical use for the treatment of HIV infection, acquired immune deficiency syndrome (AIDS) and AIDS related conditions, either alone or in combination with other antiviral agents. The most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[25].

Oral route of drug administration is oldest and safest mode of drug administration. It does not possess the sterility problem and minimal risk of damage at the site of administration. It provides accurate dosing without assistantship of administration. In conventional oral drug delivery system, there is little or no control over release of drug, and effective concentration at the target site can be achieved by administration of grossly excessive dosage form[26]. This kind of dosing pattern result in constantly changing, unpredictable and often sub or supra therapeutic plasma concentration, leading to marked side effects in some cases. Moreover, the rate and extent of absorption from conventional formulation may vary greatly, depending on factor such as physiochemical properties of drug, presence of excipients, various physiological factors such as presence or absence of food, pH of gastrointestinal tract, G.I. motility etc. Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier, which is usually a water-insoluble polymer. In general, two types or subclasses of diffusion systems are recognized: reservoir devices and matrix devices[27]. Since a controlled-release system is designed to alleviate repetitive dosing, it is naturally contained greater amount of drug that a corresponding conventional dosage form. For lose drugs requiring large conventional doses, the volume of sustained dose may be so large so to be impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled-release system, e.g., drugs with shorter half-life. For oral route, the volume of the product is limited by patient acceptance[28].

METHODOLOGY

7.1. Analytical method development:

Buffer Preparation:

Preparation of 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.

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

Preparation of 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.

a) Determination of absorption maxima:

100 mg 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.

b) Preparation calibration curve:

100 mg 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.

7.2 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:

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

Table 7.1: 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

7.3 Evaluation Parameters

7.3.1 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

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

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

Hausner's ratio

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

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

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

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

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

Flow property

Table 7.2: 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

7.3.2 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 7.3: IP standards of uniformity of weight

S. No.	Average weight 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

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 and 12

Temperature – 37°c $\pm$ 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 $\pm$ 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.

7.4 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

$$\text{Log } (100\text{-}F) = kt$$

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.

7.4. 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.

RESULTS AND DISCUSSION

8.1 Analytical Method

8.1.1 Standard graph of Zopiclone in 0.1N HCl:

The scanning of the 10µg/ml solution of Zopiclone in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 304nm. The standard concentrations of Zopiclone (2-10µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer-Lamberts law.

Table 8.1: 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

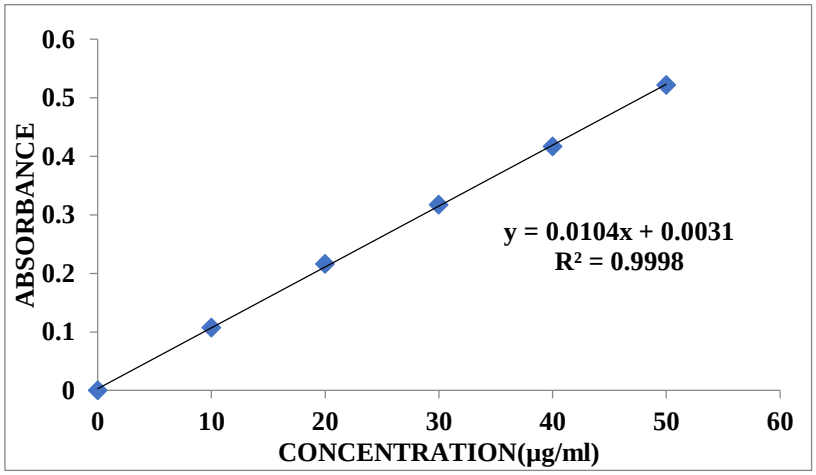

Fig. 8.1: Calibration curve of Zopiclone in 0.1 N HCl at 304 nm

8.1.2 Standard Curve of Zopiclone in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Zopiclone in the ultraviolet range (200-400nm) against 6.8 pH phosphate buffer as blank gave the λ_{max} as 304 nm. The standard concentrations of Zopiclone (2-10µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 8.2: 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

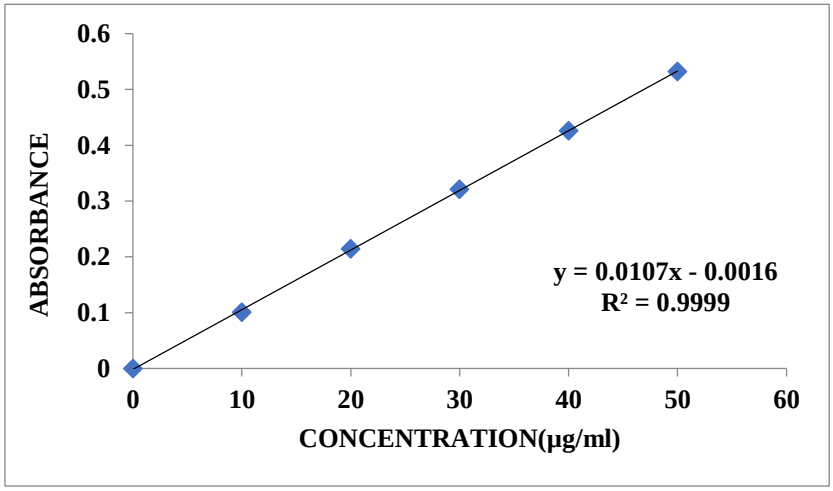

Fig.8.2: Calibration of Zopiclone in Phosphate buffer pH 6.8

8.2 EVALUATION PARAMETERS

8.2.1 Pre-compression parameters

Table 8.3: 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

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 23.60±0.42 to 25.97±0.43; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.40±0.16 - 0.48±0.12 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to

be in the range of 0.47±0.14 - 0.56±0.16 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11.95±0.17 to 14.35±0.26 which showed that the powder has good flow properties. All the formulations were showed the Hausner ratio ranging from 1.14±0.02 to 1.16±0.07 indicating the powder has good flow properties.

8.2.2 Post Compression parameters for tablets

Table 8.4: 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

Weight variation and thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 8.4. The average tablet weight of all the formulations was found to be between118.48 to 121.53**.** The maximum allowed percentage weight variation for tablets weighing >200.02 mg is 1.5% and no formulations are not exceeding this limit. Thus, all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 1.72 to 1.88.

Hardness and friability: All the formulations were evaluated for their hardness, using Monsanto hardness tester and the results are shown in table 8.4. The average hardness for all the formulations was found to be between **(**2.31 to 2.51**)** Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 8.4. The average percentage friability for all the formulations was between 0.28 and 0.55, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 8.4. The drug content values for all the formulations were found to be in the range of **(**97.28 to 101.19**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

In vitro drug release studies

The formulations prepared with different natural polymers and synthetic polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 8.5: 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

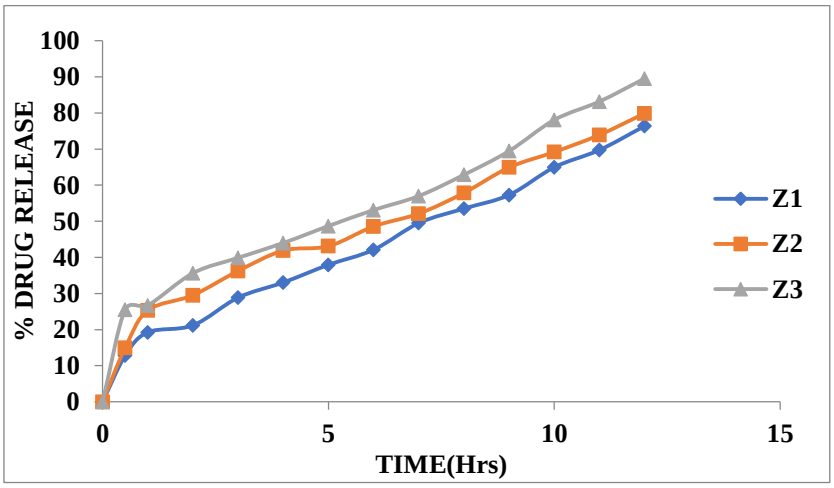

Fig 8.3: Dissolution study of Zopiclone Extended tablets (Z1 to Z3)

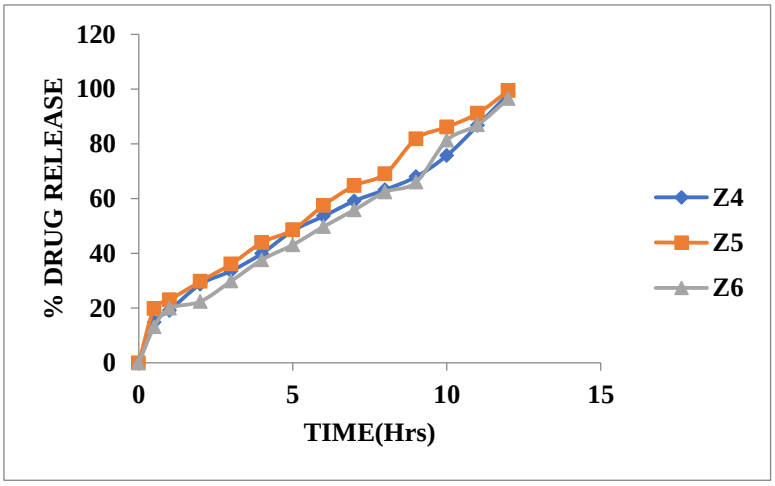

Fig 8.4: Dissolution study of Zopiclone tablets (Z4 to Z6)

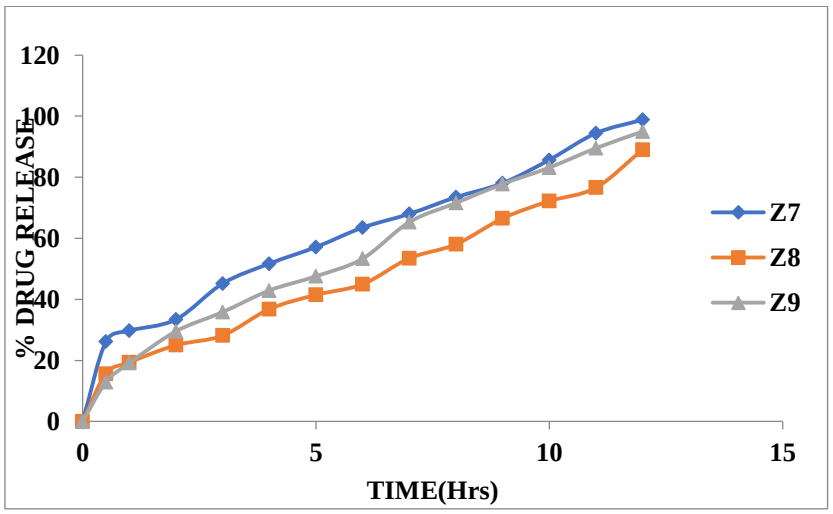

Fig 8.5: Dissolution study of Zopiclone tablets (Z7 to Z9)

From the dissolution data it was evident that the formulations prepared with Carbopol-941P as polymer were retarded the drug release more than 12 hours i.e 89.55 %.

The Formulation Containing Tragacanth in 15mg Concentration Showed good retarding nature with required drug release in 12 hours i.e 99.41 %.

The Formulation Containing Lactose Bean gum in 7.5 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e 98.83 %.

Hence from the above dissolution data it was concluded that Z5formulation was considered as optimized formulation because good drug release (99.41%) in 12 hours.

8.3 Application of Release Rate Kinetics to Dissolution Data

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Zopiclone release from Extended tablets. The data was fitted into various kinetic models such as Zero, First order kinetics; Higuchi and Korsmeyer peppas mechanisms and the results were shown in below table

Table 8.6: Release kinetics data for optimized formulation (Z5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.85	0.5	0.707	1.298	-0.301	1.904	39.700	0.0504	-0.702	80.15	4.642	4.312	0.330
22.98	1	1.000	1.361	0.000	1.887	22.980	0.0435	-0.639	77.02	4.642	4.255	0.387
29.73	2	1.414	1.473	0.301	1.847	14.865	0.0336	-0.527	70.27	4.642	4.127	0.515
36.12	3	1.732	1.558	0.477	1.805	12.040	0.0277	-0.442	63.88	4.642	3.997	0.644
43.97	4	2.000	1.643	0.602	1.748	10.993	0.0227	-0.357	56.03	4.642	3.827	0.815
48.56	5	2.236	1.686	0.699	1.711	9.712	0.0206	-0.314	51.44	4.642	3.719	0.923
57.53	6	2.449	1.760	0.778	1.628	9.588	0.0174	-0.240	42.47	4.642	3.489	1.153
64.71	7	2.646	1.811	0.845	1.548	9.244	0.0155	-0.189	35.29	4.642	3.280	1.362
69.02	8	2.828	1.839	0.903	1.491	8.628	0.0145	-0.161	30.98	4.642	3.141	1.501
81.84	9	3.000	1.913	0.954	1.259	9.093	0.0122	-0.087	18.16	4.642	2.628	2.013
86.09	10	3.162	1.935	1.000	1.143	8.609	0.0116	-0.065	13.91	4.642	2.405	2.237
91.11	11	3.317	1.960	1.041	0.949	8.283	0.0110	-0.040	8.89	4.642	2.072	2.570
99.41	12	3.464	1.997	1.079	-0.229	8.284	0.0101	-0.003	0.59	4.642	0.839	3.803

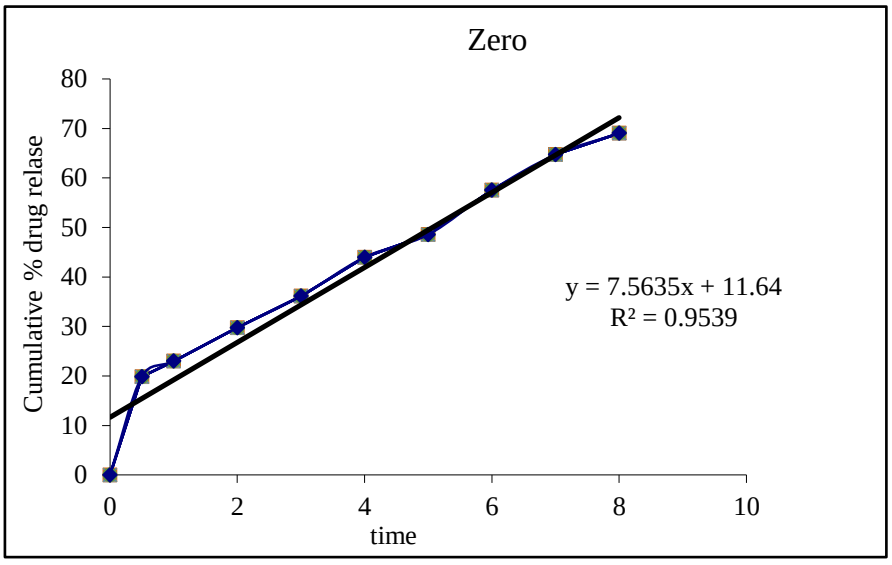

Fig 8.6: Graph of zero order kinetics

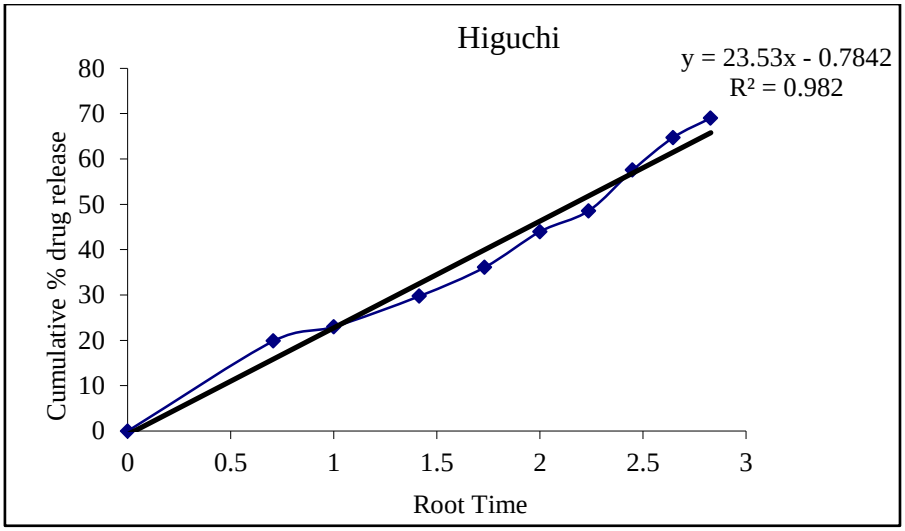

Fig 8.7: Graph of higuchi release kinetics

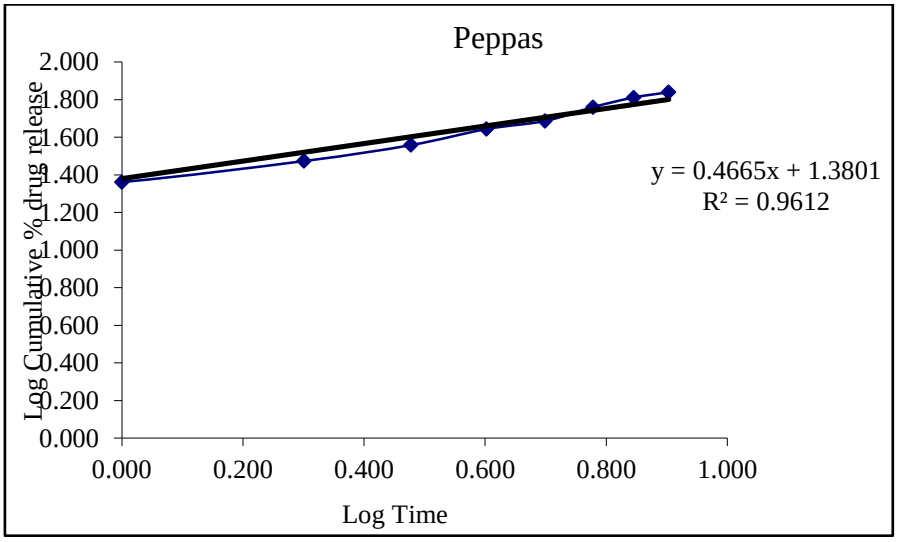

Fig 8.8: Graph of peppas release kinetics

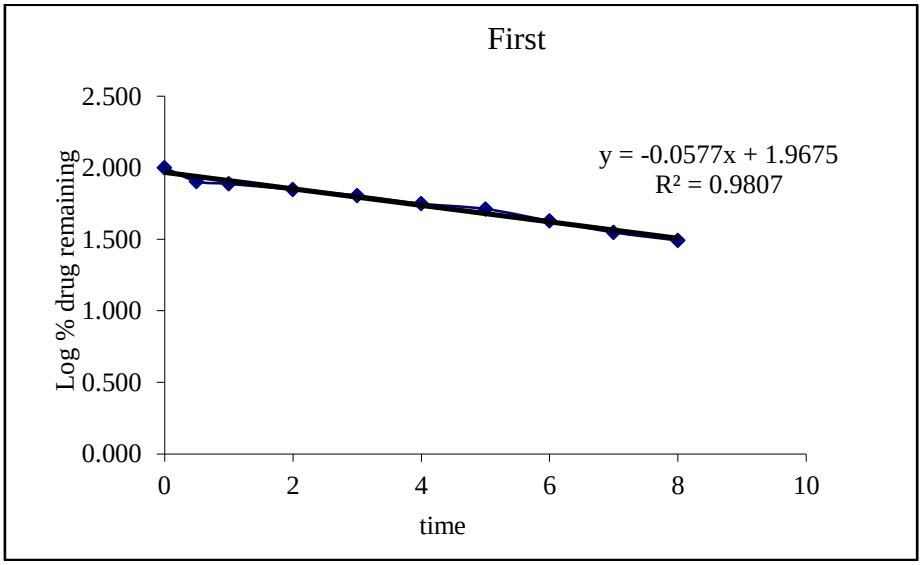

Fig 8.9: Graph of first order release kinetics

Optimised formulation NV9 was kept for release kinetic studies. From the above graphs it was evident that the formulation NV9 was followed zero order mechanism.

8.4 Drug and Excipient Compatibility Studies

FTIR STUDY

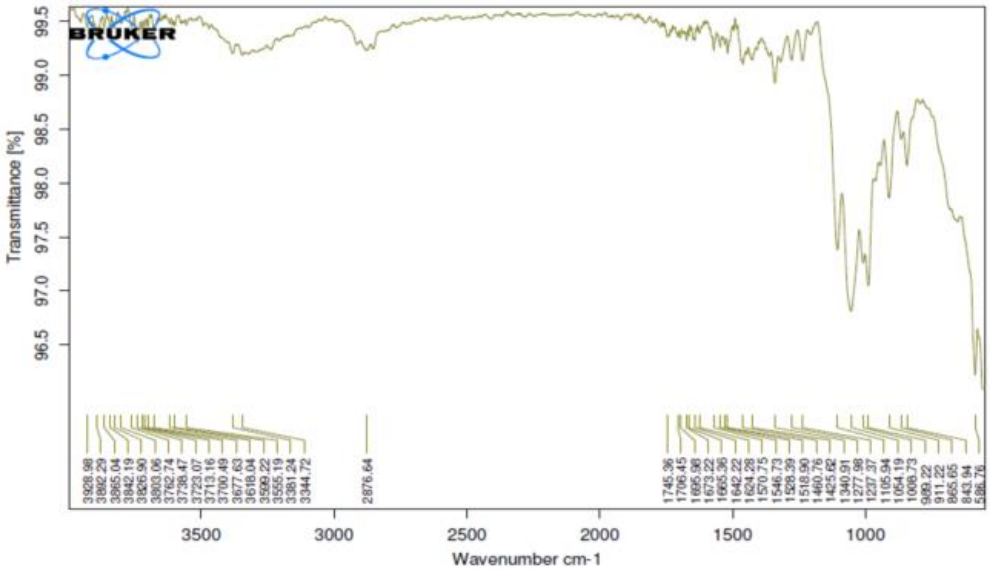

Fig 8.10: FTIR graph of pure drug of Zopiclone

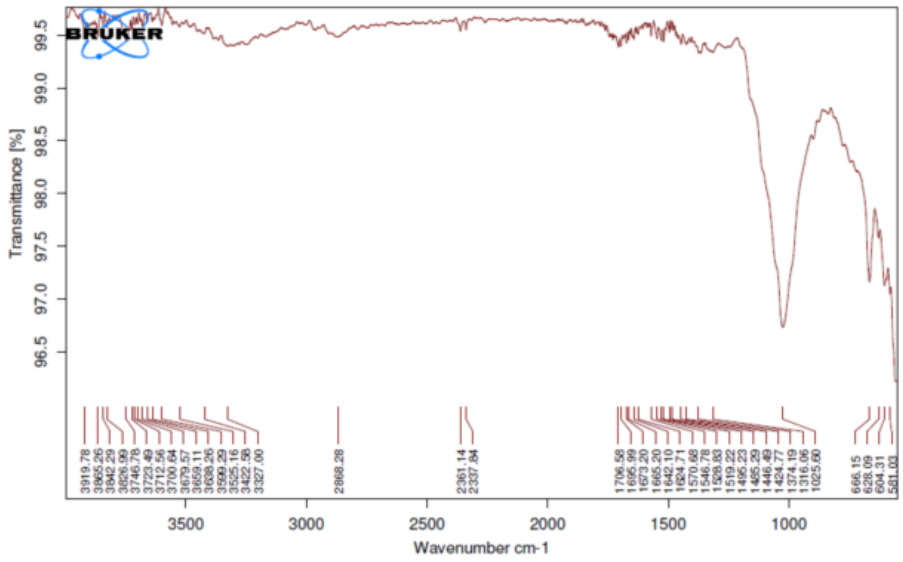

Fig 8.11: FTIR Spectrum of optimized formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Zopiclone and excipients used in the preparation of different Zopiclone extended release formulations. Therefore, the drug and excipients are compatible to form stable.

Formulations under study, The FTIR spectra of Zopiclone and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence, they were compatible.

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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