e-ISSN: 2349-2678, p-ISSN:2961-6050

available online on www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

NLM (National Library of Medicine ID: 101732687)

Index Copernicus Value 2022: 72.59

Volume 12 Issue 3; 2024; Page No. 42-59

Formulates and Optimizes Fast Dissolving Film of Zopiclone.

Daulat Kumar[1]* Arindam Chattrejee[2], Sunil Sain[3], Priya Sharma[4], Mayank Bansal[5], Ashutosh Sharma[6]

[1]Research Scholar, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan

[2]Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan

[3]Associate professor, Department of pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan

[4]Research Director, Axico Healthcare Pvt. Ltd., New Delhi

[5]Professor& Principal, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan

[6]Associate Professor, Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan

Article Info: Received: 20-03-2024 / Revised: 22-04-2024 / Accepted: 23-05-2024

Address for Correspondence: Daulat Kumar

Conflict of interest statement: No conflict of interest

Abstract

Background: Disturbed sleep can cause to many health problems such as cognitive impairment, depressed mood, and negative effects on cardiovascular, endocrine, and immune function. This study formulates and optimizes Fast Dissolving film of zopiclone.

Methods: Fast Dissolving film of zopiclone prepared by solvent casting method. Prepared zopiclone fast dissolving film was characterized by disintegration time, drug release, surface pH, tensile strength (TS), folding endurance and *in vitro* dissolution test. ZF15 film [(7.5) mg HPMCE 15, 40 (mg) Eudragit RL 100 , 30 (mg) PEG 40] were selected among formulation. A, B, and C are the amounts of HPMC E15, Eudragit RL 100, and polyethylene glycol, respectively were used as independent variables, their interactions, which quantify the effects on tensile strength (Y1), disintegration time (Y2), and cumulative percent of drug release after 10 minutes (Y3). Optimised zopiclone thin film undergoes 90 days of stability testing.

Results: The results indicated with a minimum thickness of 0.10 nm, maximum tensile strength of 56.73 gm, maximum folding endurance of 290, maximum drug uniformity of 99.13%, surface pH of 6.78, and minimum disintegration time of 27 seconds, formulation ZF15 demonstrated exceptional properties. Within a 10-minute period, ZF15 demonstrated the most amount of drug release. The optimal formulation was determined to be ZF15 based on its physico-chemical characteristics and the amount of medication released in vitro. disintegration time was in the range of 940 m. . All formulas exhibited acceptable uniformity content, surface pH, film thickness, and a good taste feeling.

Conclusion: Thus, employing a solvent casting method, a fast-dissolving thin film of zopiclone was created with effective taste masking and prompt in vitro drug release.

Keywords: Zopiclone , Fast dissolving oral film, HPMC E15, Eudragit RL100 , Solvent casting

Introduction

oral route is one of the most preferred routes of drug administration because of low-cost and ease of administration increases the patient compliance. Oral administration provides various benefits, including injectable simplicity, absence of discomfort, adaptability, absence of

sanitation requirements, lower cost, and patient compliance. For this reason, new methods for oral delivery have been developed [1]. It is a sort of medication that, as the name suggests, dissolving or breaks down quickly in the mouth without requiring any kind of liquid. This dose form is extremely accommodating for patients with dysphagia caused by conditions such as stroke, Shaking palsy, AIDS, neurological illness, and cerebral palsy. FDF is extremely useful for elderly and kid patients, as well as those who are travelling and do not have immediate access to water. FDF, also known as oral wafers, is a collection of thin polymeric film that is gaining increasing attention in the pharmaceutical business. It is a unique formulation that is now widely recognised for delivering vitamins and personal care items. Currently, systemic distribution of over-the-counter medications is permitted and trials are underway for prescription drugs[2].

Zopiclone activates the GABA receptor complex. There is a chemical difference between benzodiazepine drugs and zoloft, a cyclopyrrolone. But zopiclone helps keep GABA (gamma-aminobutyric acid) transmission in the brain normal by controlling GABAA receptors in the same way as benzodiazepine drugs do. Neurological functions were unaffected by zoloft. The cherry on top was that zopiclone improved my condition upon waking. You won't have to fight off those pesky nighttime awakenings and you'll have an easier time falling asleep. Insomnia may be treated using the new hypnotic drug zopiclone [3].

Materials and Methods

Zopiclone sample Hetero drug Ltd, Hyderabad. HPMC E15 , Eudragit RL 100 obtain from Nectar life Science, Hyderabad, PEG 400 obtain from Signet chemical Corporation Pvt. Ltd. Sucralose, Aspartame flavor obtained from chemical room of jaipur college of pharmacy. All chemicals and reagents used were of AR grade.

Analytical method

Spectrophotometric Method Development for Estimation of Zopiclone

An ultraviolet-visible spectrophotometer (UV 1800 Shimadzu Co; Japan) was used for the quantitative analysis of zopiclone in this investigation. A standard calibration curve and absorption maxima (λmax) for metoprolol succinate were created in a $PO_4$3-buffer with a pH of 6.8.

Determination of λmax of zopiclone in Phosphate Buffer pH 6.8

After meticulously weighing Hundred milligrammes of zopiclone, transfer it to a hundred millilitre volumetric flask. Next, dissolve the substance in one hundred millilitres of pH 6.8 PO43- buffer until a concentration of 1 mg/mL is reached. To make a stock solution with a concentration of 0.1 mg/mL, or 100 micrograms/mL, transfer 10 mL of the solution (10 mg/mL) to a volumetric flask that holds one hundred mL and top it up with water until it reaches 100 mL. The optimal the absorbance wavelength was determined by combining this stock solution with ten other components and scanning the resulting mixture employing an ultraviolet double beam spectroscopy that operates between 200 and 400 nanometers in wavelength. Scanning was performed using a pH 6.8 PO43- buffer blank solution of phosphate buffer. This stock solution was also used to create dilutions for the calibration curve.

Preparation of Calibration Curve of metoprolol succinate

Using the stock solution indicated earlier, phosphate buffer pH 6.8 was used to generate several dilutions ranging from two, four, six, eight ten, twelve sixteen, and Twenty microgram per ml. Afterwards, a UV-spectrophotometer is used to measure the absorbances of the diluted solutions at the λmax, using a control solution of PO43-buffered with a pH of 6.8. By determining the average absorbance value and standard deviation from this triplicate experiment, a calibrated curve showing the relationship between concentration in µg/ml and absorbance at Λmax was produced, along with the mathematical formula for the straight line of best fit.

Drug and Excipient Compatibility Study

Investigation of the Drug-Excipient Interaction for a Zopiclone Fast-Dissolving Film Using DSC

Scientists used DSC to check the compatibility of both the medication and the excipient before making a fast-dissolving dry film containing metoprolol succinate. DSC were brought in to carry out the probe. Thermograms of the drug and drug combination were recorded in a nitrogen atmosphere and scanned at a rate of one degree Celsius per minute from minus one hundred degrees Celsius to four hundred degrees Celsius. Reviewing the recorded thermograms allowed us to see any questionable changes in appearance or movements in peak

Assessment of Drug Excipient Compatibility via FTIR Spectroscopy

In order to learn how well drugs and excipients work together, researchers mixed the active ingredient in a 1:10 ratio with potassium bromide using agate, and then did the same with the dry formulation. Each of these mixes was then used to manufacture pellets using the IR pellet maker. Scannography in the 4000-400 cm-1 spectral region was subsequently performed on the produced pellet. A comparison was made between the spectra of the pure medication and the formulation to see whether there was any noticeable peak shift or appearance

Procedure for Film Preparation

The solvent casting procedure was used to prepare the film.

After adding 3/4 cup of distilled water, the polymer was allowed to soak in the solution overnight. The polymer solution had been stirred with the stirring magnet for approximately thirty minutes until it was evenly dispersed. Aqueous solution I was prepared by completely mixing the polymer solution with the plasticizer and then letting it rest for four hours. Using a stirrer with magnets, the polymer solution was swirled for 60 minutes. For 30 minutes, we used to sonicat to remove any air bubbles from the polymer solution. The second step was to make Aqueous solution II by combining the zopiclone, lactose, and aspartame in the prescribed amounts with the remaining water getting from distillation.

After mixing solutions I and II in water and stirring them for a few hours, they were subjected to sonication for 30 minutes. Following the lubricating process, a 9.0 cm circumference round glass dish called a petri dish was used to pour the polymer solution. Glycerin was used to coat the petri plates so they wouldn't stick. Each film was peeled and then cut into 2 cm × 2 cm pieces after being let to dry at room temperature. The desiccator was then used after wrapping them in butter paper [4].

Formulation and optimization of Fast dissolving zopiclone film

The solvent casting procedure was used to prepare the film. A total 27 formulation were prepared as shown in table 1.3. A design of experiment was employed to improve the zopiclne Fast dissolving Film. We used the second quadratic model to match all of the answers, and we used analysis of variance (ANOVA) tests given by Design-Expert to make sure that this model was adequate. A second-order quadratic model was fitted to each of the three answers separately, and analysis of variance was used to validate each model. We used Stat-Ease Design Expert ® software V 8.0.1 to analyse the data and get the regression equation, regression coefficients, and analysis of variance (ANOVA). results of the mathematical correlations that were established for the specified variables using multiple linear regression analysis. A, B, and C are the amounts of HPMC E15, Eudragit RL 100, and polyethylene glycol, respectively, and their interactions which quantify the effects on tensile strength (Y1), disintegration time (Y2), and cumulative percent of drug release after 10 minutes (Y3). The impact of A, B, and C on the Y1, Y2, and Y3 answers is correlated with their respective coefficient values Coefficients with higher order terms indicate a quadratic connection, while those with multiple factor terms indicate an interaction term. If the sign is positive, then the impact is synergistic, and if it is negative, then the effect is antagonistic. Data fitting to the quadratic model was accomplished using a backward elimination approach. According to the Design Expert software's instructions, an analysis of variance (ANOVA)

revealed that both polynomial equations were statistically significant (P>0.05).

Evaluation of Fast Dissolving film of Zopiclone

Physical attributes such as microscopy, weight, thickness, surface pH, folding endurance, disintegration time, tensile strength, drug release, and stability were assessed for the produced films.

Physical Appearance

Visual inspections were performed to ensure that the produced films for oral dissolution were uniform, clear, and tacky.

Weight and thickness

We measured the average and standard deviation of three films' weights before weighing them on a Sartorius electronic scale. We observed the film's thickness three times at separate locations using a micrometre. We averaged the results and reported the standard deviation. The films were sliced into 2cm X 2cm size before each measure [5].

Surface pH

After immersing the film in 0.5 ml of phosphate buffer and leaving it for 30 seconds, the pH was measured by bringing the pH meter's electrode into touch with the surface of the glass petriplate. The standard deviation and average of three film readings were collected[6].

Folding Endurance

Physically folding the films in a particular plane until a crack formed was the method used for this test. A film's folded tolerance is defined as the maximum number of folds it can sustain before shattering[7].

Tensile Strength The following formula may be used to determine the film's tensile strength, which is defined as the ultimate stress at which it ruptures:

$$\text{Tensile strength} = \frac{\text{Load at fracture}}{\text{Film thickness X film width}} \text{ X } 100$$

The results of three separate measurements were averaged and the standard deviation was obtained using a tensile strength instrument.

Disintegration test

Our disintegration test was conducted at a temperature of 37±2 using an IP apparatus with PO43- buffer at a pH of 6.8 as the medium.

In-vitro Drug Release

A modified dissolving apparatus were employed to determine the in-vitro drug release. PO43- buffer with a pH of 6.8, was used as the dissolving agent. After placing the films in a dissolving flask, they were suspended in a 50 ml beaker that contained 20 ml of PO43- buffer with a pH of 6.8. Using the dissolving apparatus II, the stirrer were set to operate at 50 rpm without the basket attachment. At 3, 6, 9, 12, 15, 18, and 21 minutes intervals, the sample was taken and the content was determined spectrophotometrically at λmax 302nm using UV 1800 [8].

Stability Study

For the ideal film formulation, the stability study will be carried out. The manufactured films were placed in a desiccator Batch ZF15 conducted over the course of 90 days at room temperature and environmental humidity. After this time, the films were tested for different parameters[9].

RESULTS AND DISCUSSION

Analytical method

The spectrum of the samples were examined using an ultraviolet spectrophotometer (UV1800) from 200-400 nm. At 302 nanometer the level of absorption was highest for the zolopiclone solution in PO43- buffer with a pH of 6.8 and a concentration of 10 microgram per mililiter as shown in figure 1.1. The 302 nm wavelength was therefore identified as the one with the highest absorption, λmax.

Using the standard calibration curve, we determined the concentration range where the drug followed Beer's law. For zopiclone, the range was determined to be 2.0 to 20.0 µg/ml. Table 1.1 and Figure 1.2 show the results of calculating the average absorbance value from three measurements together with the standard deviation (SD).A regression coefficient of 0.994 and a slope of 0.029 were determined. The linearity between the depicted values of absorbances and concentrations is shown by the coefficient of correlation value of 0.994.

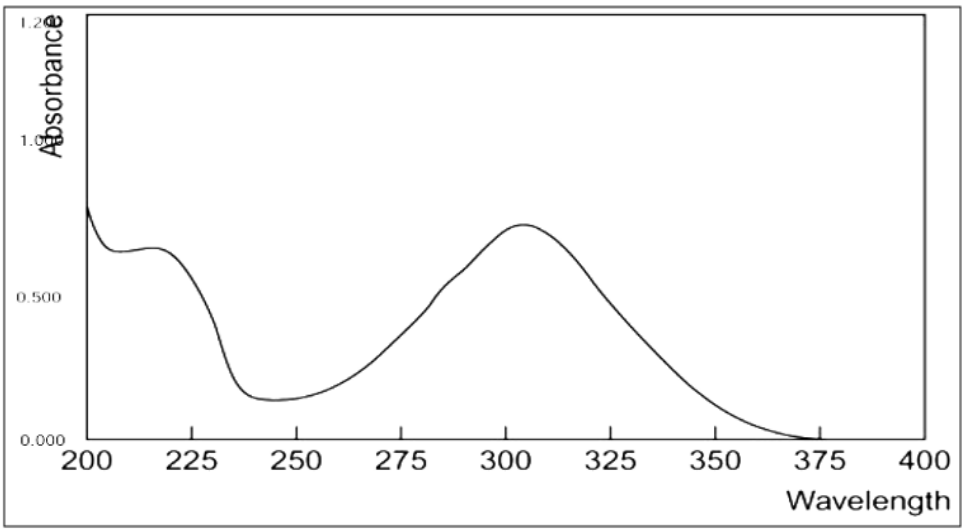

Figure 1.1: Absorbance maxima of zopiclone at 302 nm in phosphate buffer pH 6.8

Table 1.1: Standard Calibration Curve Of Metoprolol Succinate In Phosphate Buffer Ph 6.8

Sr. No.	Concentration (µg/ml	Absorbance (n=3)	SD
1	2	0.067	0.001
2	4	0.092	0.01
3	6	0.186	0.012
4	8	0.245	0.012
5	10	0.303	0.01
6	12	0.381	0.013
7	14	0.414	0.01
8	16	0.464	0.01
9	18	0.544	0.012
10	20	0.588	0.012

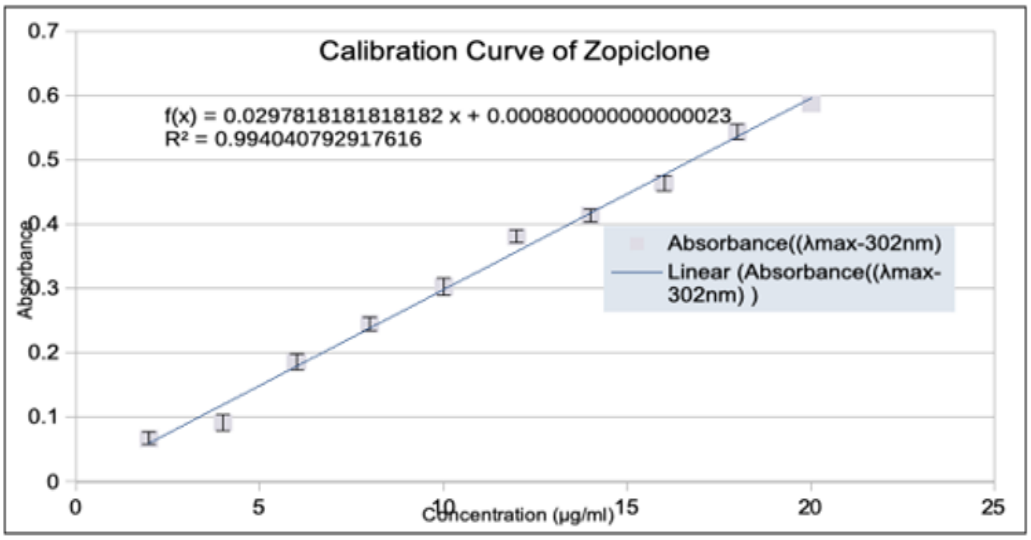

Figure 1.2: Figure 8.2: Calibration Curve for Estimation Zopiclone in pfosphate buffer pH 6.8

Drug-Excipient Compatibility Study of film of zopiclone by DSC Method

In order to verify the drug-excipient interaction, the DSC investigation were applied on both the crude drug and its combination with the suggested excipient. Displayed in Figures 1.3 and 1.4, respectively, are the DSC thermograms of Zopiclone in conjunction with excipients. It

was determined that there was no interaction between the two substances. The pure drug exhibited the peak of endothermic activity at a temperature of 177.19°C, with the beginning of the peak occurring at 176.6°C and the endset peak at 180.04°C. In contrast, the drug-excipient combination displayed endothermic peaks at temperatures of 80°C, 267°C, and 195.10°C.The endothermic peak seemed to have undergone a little shift due to the presence of polymers. There was no possibility of a conflict between the drug and the excipient since the endothermic peak remained consistently stable.

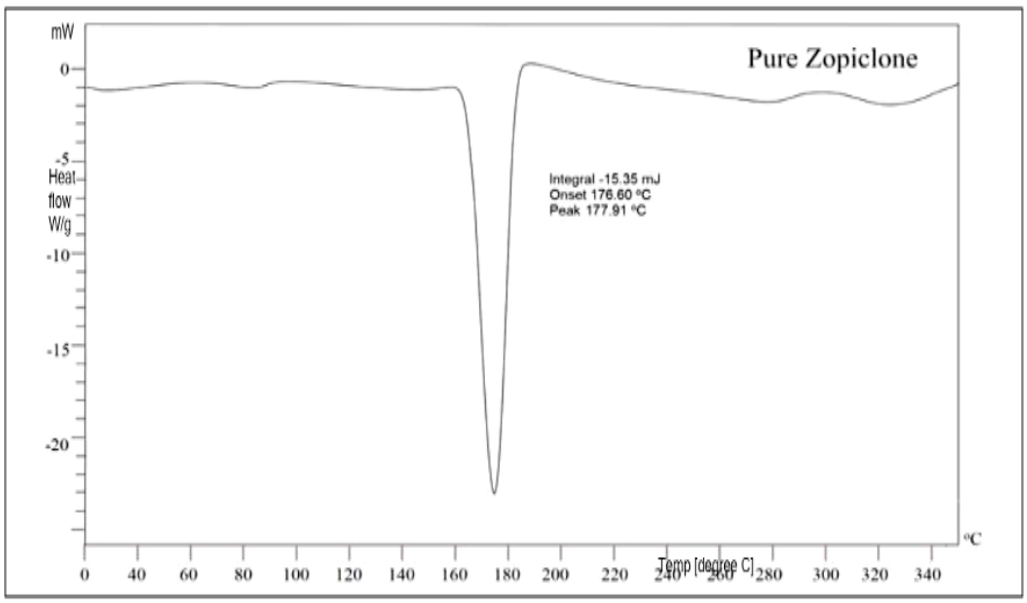

Figure 1.3: DSC Study of Zopiclone (pure drug)

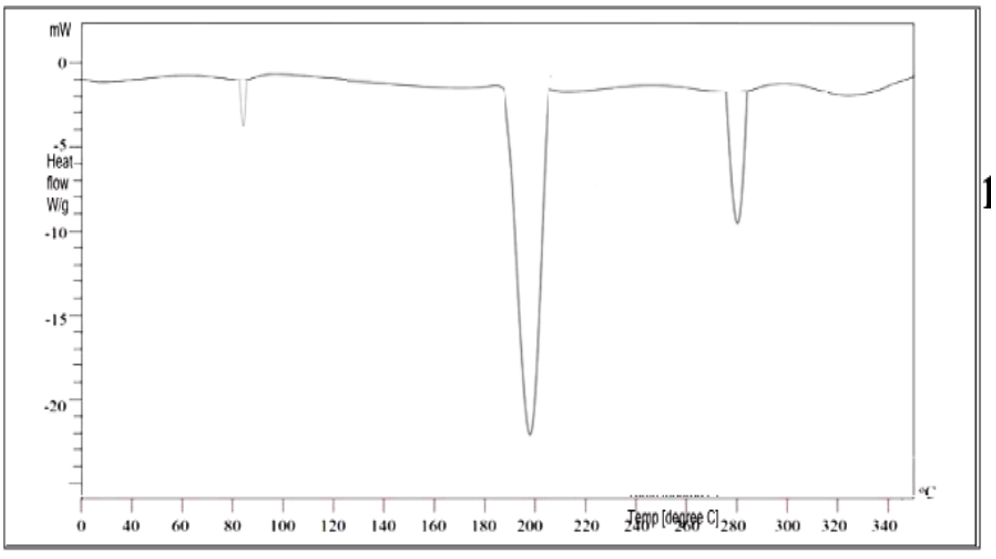

Figure 1.4: DSC Study of zopiclone (pure drug) and excipients

FTIR study for Drug–Excipient Compatibility of thin film of metoprolol succinate Formulation

Below are the infra red spectra obtained using FTIR of the medicine zopiclone in its pure form (Fig 1.5) and of the drug and excipient combination (Fig 1.6). Table 1.2 lists the drug and drug excipient combination, as well as the distinctive peaks that characterise the drug's functional groups. We compare the spectra of the drug in its pure form and of the drug mixed with an excipient. The absence of a peak or shift in the spectra indicates that the thin film of metoprolol succinate does not include any interaction between the medication and the excipient

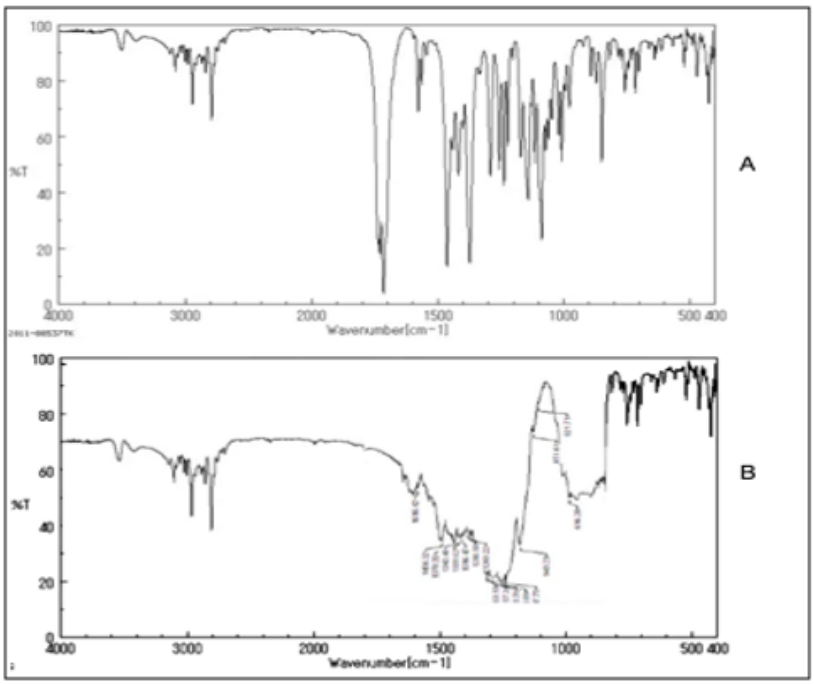

Figure 1.5: 9A) Infra Red Spectra of Zopiclone (B) Infra Red Spectra of Combination of zopiclone and excipients

Table 1.2: Interpretation of IR Spectra for Drug

Sr. No.	Functional Groups	Zopiclone (Drug) Frequency in cm-1	Peak observed (cm-1)
1	**C=Cl**	700–800	774
2	**C=O**	1690–1760	1698.66
3	CH3,CH2 and CH	2850-3000	2923.97
4	C-H (aldehyde)	2690-2840	2829.63
5	**O–C=O**	1690–1760	1692.83, 1745.76
6	CH2 and CH3	1350-1470	1385.21
7	O-H bonded	970-1250	1051.80, 1114.24 1242.23

Table 1.3: Formulation of Zopiclone fast dissolving film

Sr. No.	Zopiclone (mg)	HPMCE 15 (mg)	Eudragit RL 100 (mg)	PEG 400 (mg)	Lactose (mg)	Aspartame (mg)	Flavor (ml)	Water (ml)
ZF1	7.5	20	30	25	10	4	0.1	10
ZF2	7.5	30	30	25	10	4	0.1	10
ZF3	7.5	20	40	25	10	4	0.1	10
ZF4	7.5	30	40	25	10	4	0.1	10
ZF5	7.5	20	30	35	10	4	0.1	10
ZF6	7.5	30	30	35	10	4	0.1	10
ZF7	7.5	20	40	35	10	4	0.1	10
ZF8	7.5	30	40	35	10	4	0.1	10
ZF9	7.5	20	35	30	10	4	0.1	10
ZF10	7.5	30	35	30	10	4	0.1	10

ZF11	7.5	25	30	30	10	4	0.1	10
ZF12	7.5	25	40	30	10	4	0.1	10
ZF13	7.5	25	35	25	10	4	0.1	10
ZF14	7.5	25	35	35	10	4	0.1	10
ZF15	7.5	30	40	30	10	4	0.1	10
ZF16	7.5	20	35	25	10	4	0.1	10
ZF17	7.5	25	35	30	10	4	0.1	10
ZF18	7.5	20	30	25	10	4	0.1	10
ZF19	7.5	25	40	25	10	4	0.1	10
ZF20	7.5	20	35	25	10	4	0.1	10
ZF21	7.5	25	35	30	10	4	0.1	10
ZF22	7.5	25	35	25	10	4	0.1	10
ZF23	7.5	30	35	35	10	4	0.1	10
ZF24	7.5	20	30	30	10	4	0.1	10
ZF25	7.5	25	35	35	10	4	0.1	10
ZF26	7.5	20	40	25	10	4	0.1	10
ZF27	7.5	20	35	35	10	4	0.1	10

Evaluation of Fast Dissolving thin film of Zopiclone

All of the measured metrics were within the permissible range. (Table 1.4) Because film thickness affects dosing accuracy, this is crucial for keeping film thickness consistent. The films will be uniformly thick if the SD values are lower. Changes in the viscosity of polymers may explain the observed differences in film thickness. All ZFs had an average thickness that varied from 0.10±0.11 mm to 0.20±0.40 mm. The film's ability to withstand rupture is measured by its tensile strength. All of the formulations had good results, which range from 18.5±1.48 to 56.73±1.27. The values of folding endurance, which shows how well films can resist rupture, varied from 244±1.28 to 290±1.44.

According to the findings, ZFs would remain intact in terms of folding and would not break under normal use conditions. The highest folding endurance value of 290 was seen in formulations that had a greater quantity of polymer. The homogenous distribution of the medication, as shown by drug content homogeneity, is an important aspect of ZFs. The standard deviation was modest, and the value varied from 95.25±1.01 to 99.13±0.41. To better understand potential in vivo adverse effects, the surface pH of ZFs is useful. Oral mucosa becomes inflamed by pH levels that are either too acidic or too alkaline. To ensure that the mucosal lining is not irritated, the surface pH of all ZFs falls within the range of 6.10±0.60 to 6.78±0.46. The disintegration time is impacted by the quantity of polymer as well. All of the formulations had disintegration times ranging from 27±1.85 to 77±1.51 seconds. From 70.36±1.80% to 97.29±1.87%, the drug release was different among all 27 ZFs formulations. For FF15, the maximum drug release was seen within 10 minutes, at 97.29±1.87% as shown in figure 1.6 to 1.9

Table 1.4 Evaluation of Fast Dissolving thin film of Zopiclone

F.NO	Thickness (mm)	Tensile Strength (gm)	Folding Endurance	#Content uniformity	(%) Surface pH	DT (Sec)
ZF1	0.15±0.02	33.9±1.13	263±1.10	96.21±1.03	6.23±0.37	60±1.23
ZF2	0.11±0.10	30.5±1.27	276±1.21	97.05±1.06	6.10±0.11	77±1.51
ZF3	0.18±0.26	45.9±1.10	250±1.10	98.26±1.13	6.26±0.39	50±1.40
ZF4	0.12±0.70	52.2±1.16	261±1.59	96.16±1.01	6.33±0.12	61±1.19
ZF5	0.13±0.20	40.0±1.78	244±1.18	95.31±1.12	6.38±0.19	75±1.25
ZF6	0.14±0.11	24.7±1.55	273±1.09	98.07±0.59	6.21±0.35	48±1.87

ZF7	0.16±0.61	36.1±1.34	267±1.03	95.48±1.39	6.51±0.40	55±1.63
ZF8	0.13±0.22	51.5±1.66	251±1.11	97.27±1.48	6.33±0.77	33±1.37
ZF9	0.16±0.19	18.5±1.48	264±1.08	95.95±1.13	6.27±0.11	53±1.19
ZF10	0.14±0.10	24.6±0.96	282±1.23	97.79±1.27	6.14±0.87	74±1.24
ZF11	0.15±0.10	49.5±1.75	261±1.29	96.25±1.28	6.43±0.17	43±1.19
ZF12	0.13±0.10	38.1±1.12	253±1.49	97.23±1.02	6.10±0.60	49±1.40
ZF13	0.16±0.10	22.5±1.49	266±1.19	96.15±1.17	6.24±0.89	71±1.73
ZF14	0.13±0.20	43.4±1.18	258±1.11	95.25±1.01	6.41±0.28	56±1.87
ZF15	0.10±0.11	56.73±1.27	290±1.24	99.13±0.41	6.78±0.46	27±1.85
ZF16	0.13±0.12	27.1±0.37	251±1.10	96.45±1.39	6.43±0.96	61±1.81
ZF17	0.11±0.12	38.5±1.39	275±1.28	97.86±1.24	6.33±0.29	67±1.56
ZF18	0.12±0.18	47.7±1.13	254±1.38	95.38±01.7	6.15±0.22	45±1.12
ZF19	0.17±0.10	43.9±1.14	280±1.17	97.14±1.35	6.25±0.19	55±1.33
ZF20	0.13±0.16	40.1±1.77	276±1.30	96.38±1.14	6.13±0.49	73±132
ZF21	0.14±0.29	26.2±1.30	254±1.19	97.53±0.87	6.33±0.41	32±1.27
ZF22	0.12±0.49	20.5±1.19	262±1.41	96.57±1.81	6.10±0.85	41±1.61
ZF23	0.19±0.58	26.7±1.10	272±1.31	97.25±1.38	6.21±0.62	54±1.49
ZF24	0.16±0.88	20.9±1.14	259±1.23	96.31±1.52	6.14±0.46	39±1.31
ZF25	0.12±0.36	43.2±1.37	256±1.21	97.31±1.45	6.60±0.14	51±1.39
ZF26	0.17±0.39	54.5±1.44	284±1.34	95.28±1.42	6.31±0.25	61±1.40
ZF27	0.20±0.40	34.6±1.58	252±1.30	96.59±1.33	6.26±0.51	34±1.77

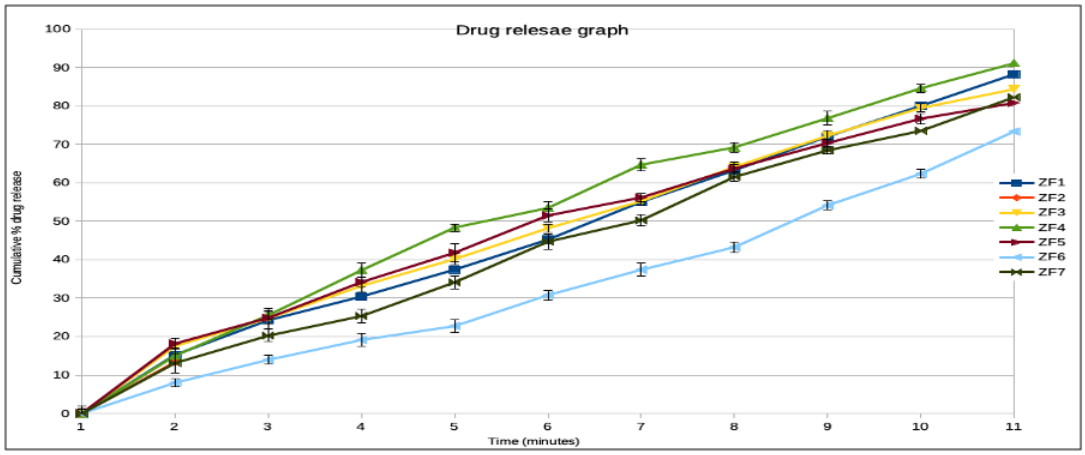

Figure 1.6: Comparative Dissolution profile of ZF1-ZF7

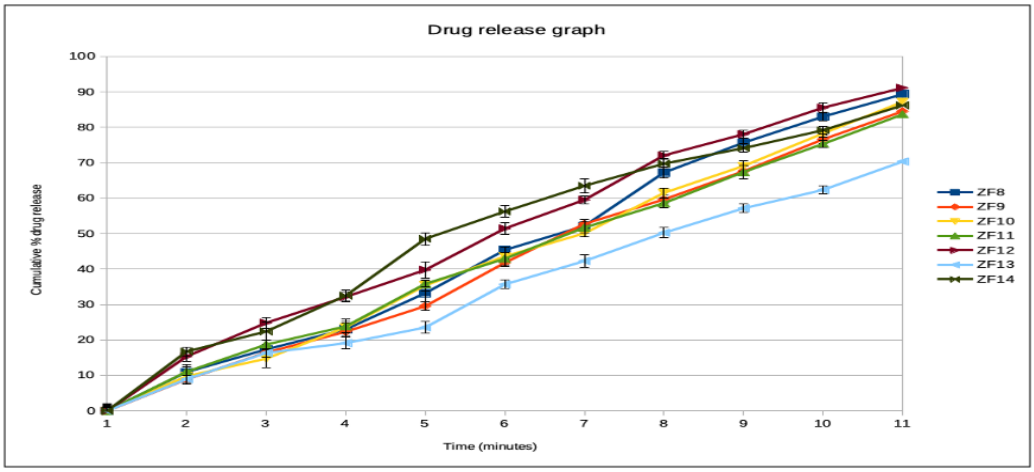

Figure 1.7: Comparative Dissolution profile of ZF8-ZF14

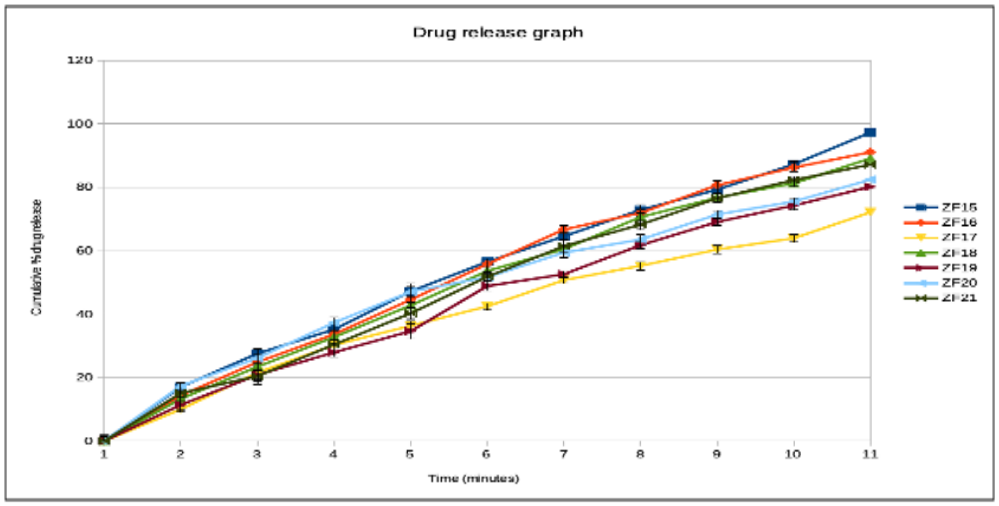

Figure 1.8: Comparative Dissolution profile of ZF15-ZF21

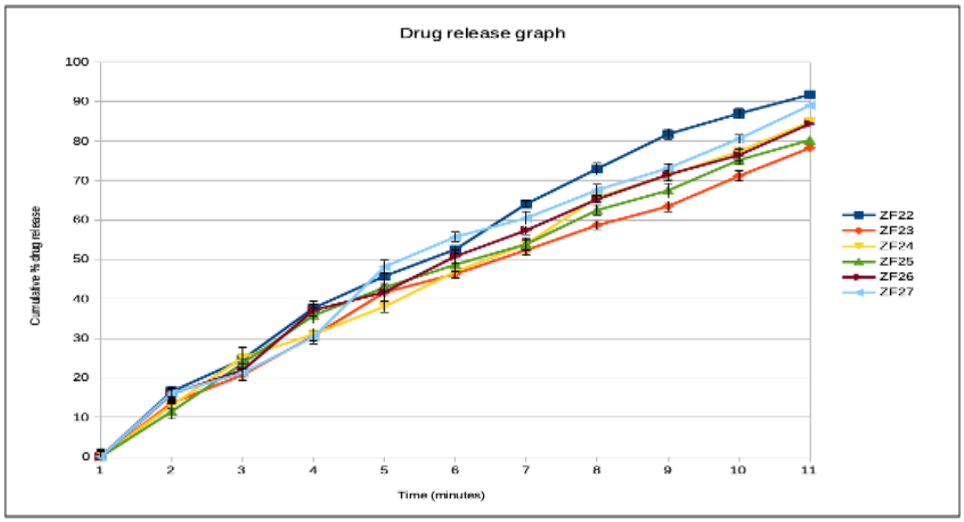

Figure 1.9: Comparative Dissolution profile of FF22-FF27

ANOVA Analysis

The impact of independent factors on dependent variables may be understood via the mathematical connections created by multivariate linear regression analysis. The reaction is enhanced when the coefficient is positive, and it is suppressed when the coefficient is negative. According to a Design Expert's recommendation, we used ANOVA with a 5% significance level to estimate the model's efficacy. If the probability of an error is less than 0.05, the model is deemed to be significant[10].

The reduced model was created by leaving out the factors that were found to be statistically unimportant ($p>0.05$). Below, we provide the condensed models for each answer:

Tensile Strength $Y1 = 13.38+08.75\ X_1- 6.30\ X_2- 1.05\ X_3 - 0.48\ X^2_1+1.59X_1X_3+13.52X^2_2-3.15X^2X_3+2.69X^2_3$

Disintegration Time $(Y2) =17 + 9X_1 + 12\ X_2 +5X_3 + 3X^2_1 – 5\ X_1\ X_3 – 11\ X^2_2 – 2\ X_2\ X_3 - 3X^2_3$

% Cumulative drug release (%CDR) $Y3 = 70.32 – 2.74\ X_1 + 21.08\ X_2 – 18.26\ X_3 + 0.47\ X^2_1 – 12.19\ X_1\ X_3 + 0.67\ X^2_2 – 34.45\ X_2\ X_3 + 2.30\ X^2_3$

Tensile strength (%)

The films' tensile strengths were determined to be between 18.5 and 56.73 nm. The results of the quadratic model show that the tensile strength is significantly affected by the amounts of hydroxy propyl methyl cellulose E15 (A), Eudragit RL 100 (B), and Polyethylene Glycol (PEG 400). The theoretical (anticipated) and

practical outcomes were rather consistent with one another. A statistically significant computational framework for Tensile Strength (Y1) was established, as shown by an F-value of 979.10. Such a large "Model F-Value" could only occur by chance (with a mere 0.01% likelihood). The independent factors A, B, and C, along with the quadratic term of AB, BC, A2, and B2, all significantly affect the Tensile Strength, as shown in Table 1.5, which comprises the major model components. The reason behind this is that the P values are smaller than 0.05.With a "Lack of Fit F-value" of 0.0213, the absence of a fit is statistically significant when compared to the pure error. A "Lack of Fit F-value" of this size is likely caused by noise 01.34% of the time. A large mismatch is ideal since we want for a model that fits the data well. Based on the equation's results, B is more influential than A and C. The factorial equation and droplet size were strongly associated (r=0.9987). To better understand the relationship between the independent and dependent variables, 3D response surface plots and accompanying contour plots were utilised. demonstrated in figures 1.10A and 1.10B.

Table 1.5: ANOVA was conducted on the quadratic model to analyse the relationship between the response variable, Tensile Strength (Y1).

Outputs	Degree of Freedom (DF)	Sum of Square (SS)	Mean of Square (MS)	**F**	P-value Prob > F		
Model	6	979.10	161.52	0.011	< 0.05		
A-Amount of HPMC E15	1	122.77	122.77	0.024	< 0.05		
B-Amount of Eudragit RL 100	1	63.35	63.35	0.0310	< 0.05		
C-Amount of Polyethylene Glycol	1	33.78	33.78	0.017	< 0.05		
AB	1	373.25	373.25	0.011	< 0.05		
AC	1	245.42	245.42	0.035	< 0.05		
BC	1	136.12	136.12	0.020	< 0.05		
Residual	6	2127.63	101.02	-			
Lack of Fit	8	952.88	115.86	0.0213	< 0.05		
Response	**P Value**	**R^2**	**Adjusted R^2**	**Predicted R^2**	**Adequate precision**	**SD**	**CV%**
Y_1	<0.05	0.9987	0.9963	0.9933	93.4194	0.692	0.738

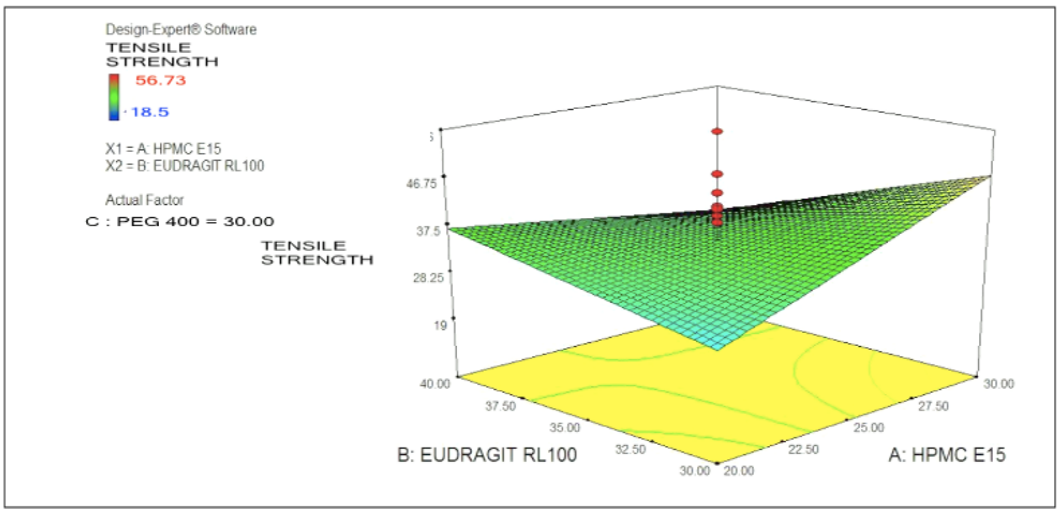

Figure 1.10 A: A three-dimensional surface map showing how different concentrations of C-value for tensile strength are affected by a constant amount of Hydroxypropyl methylcellulose E15 and Eudragit RL 100

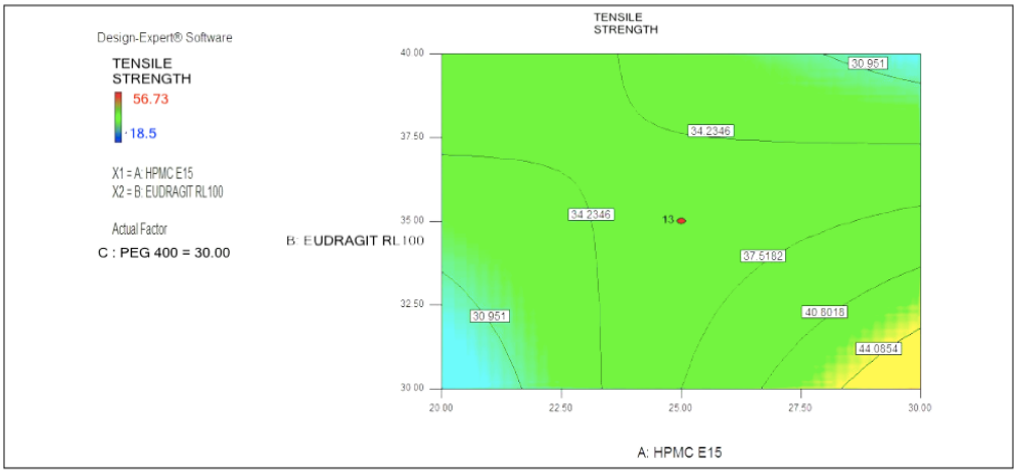

Figure 1.10 B: An exploded view of the tensile strength at a fixed C-level as a function of various concentrations of Hydroxypropyl methylcellulose E15 and Eudragit RL 100

Both polymers used in the formulations have high tensile strengths, thus any impact from PEG 4000 is small. Consequently, the formulations' tensile strengths are unaffected.

8.6.2.2 Disintegration Time

According to the created quadratic model, the amounts of eudragit RL 100 and polyethylene glycol significantly affect the disintegration time. Reasonable agreement existed between the theoretical (predicted) values and the observed values. A statistically significant model was created for Disintegration Time (Y2), as indicated by an Fisher-Snedecor distribution value of 0.0133. The only way for such a massive "Model F-Value" to occur is by chance; the likelihood of this happening is approximately 0.85%. The significance level of model terms is determined by whether the value of "Prob > F" is less than 0.05. A, B, and C are crucial elements of this philosophy. This is exhibited in Table 8.14. To be statistically significant, the "Lack of Fit F-value" must be greater than or equal to the pure error, which in this case is 0.0192. For a "Lack of Fit F-value" of this size, the chance that it is due to noise is 1.26%. A value of 0.0192 is considered significant, meaning that the model does not fit the data as expected. Compared to A and C, B's effect is much larger, according to the equation. The correlation value of 0.9992 was displayed by the factorial equation of Disintegration Time. We utilised 3D response surface plots and accompanying contour plots to better understand the relationship between the independent and dependent variables. With C held constant, the influence of A and B on Disintegration Time is illustrated in Figure 1.11A. These contour plots are shown in Figure 1.11 B.

Response Y2, which represents disintegration time, showed that the linear model was the best match according to the ANOVA results. For answer Y2, the programme produced the polynomial equation that may be found in Table 1.6. The disintegration time was discovered to be agonistically affected by X1 and X2, which were determined to be important determinants. Disintegration time reduces with increasing polymer concentration and rises with increasing plasticizer content, according to the data.

Table 1.6: Analysis of variance (ANOVA) using a quadratic model to predict disintegration time (Y2)

Outputs	Degree of Freedom (DF)	Sum of Square (SS)	Mean of Square (MS)	**F**	P-value Prob > F
Model	6	2241.57	356.63	0.013	< 0.05
A-Amount of HPMC	1	166.46	166.46	0.008	< 0.05

E15							
B-Amount of Eudragit RL 100	1	25.10	25.10	0.013	< 0.05		
C-Amount of Polyethylene Glycol	1	661.63	661.63	0.0251	< 0.05		
AB	1	221.12	221.12	0.0156	< 0.05		
AC	1	980.12	980.12	0.044	< 0.05		
BC	1	161.12	161.12	0.0145	< 0.05		
Residual	20	5351.39	264.37	-			
Lack of Fit	8	1359.39	161.15	0.0192	< 0.05		
Response	**P Value**	**R^2**	**Adjusted R^2**	**Predicted R^2**	**Adequate precision**	**SD**	**CV%**
Y_2	<0.05	0.9992	0.9864	0.9514	25.9499	3.36	4.04

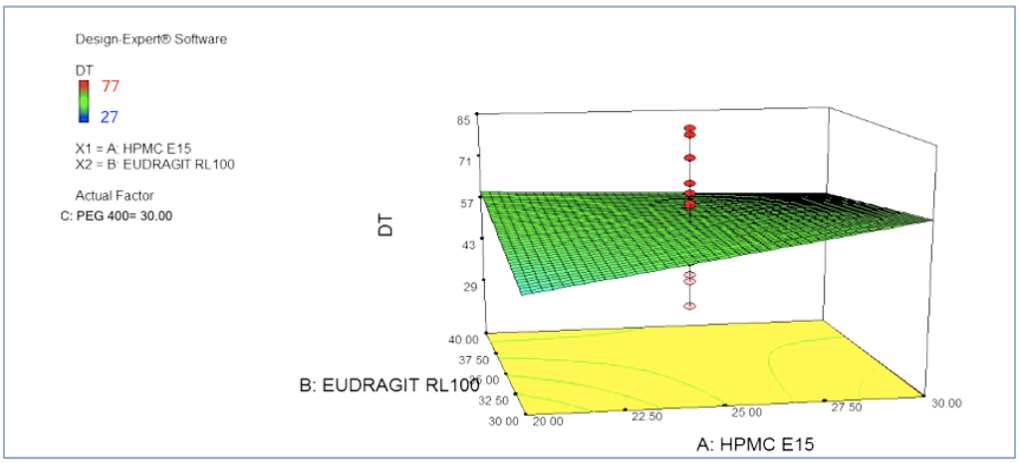

Figure 1.11A: The response 3D surface map shows how different concentrations of Hydroxypropyl methylcellulose E15 and Eudragit RL 100 affect disintegration time at a fixed concentration of C.

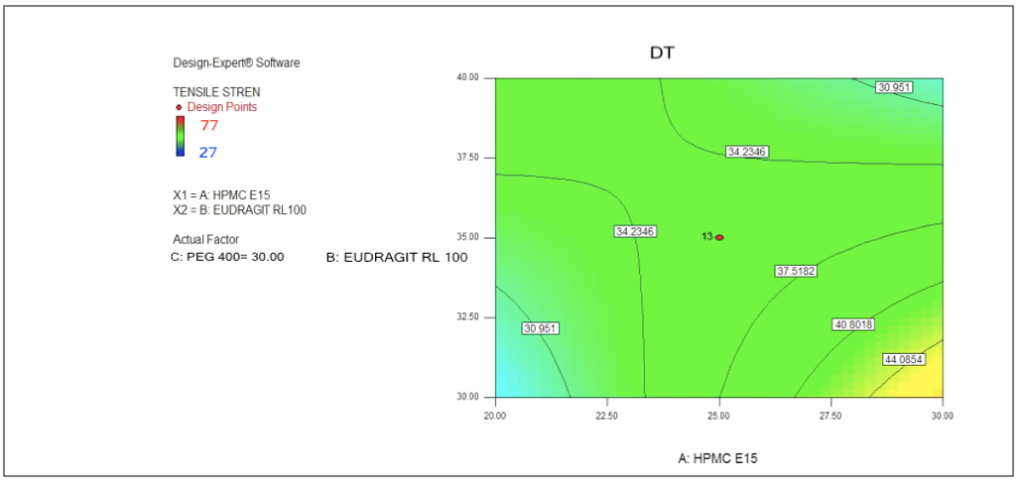

Figure 1.11B: A contour plot showing the impact of different concentrations of Hydroxypropyl methylcellulose E15 and Eudragit RL 100 on disintegration time at a constant temperature C

Cumulative percent drug released

Results showed that the mouth dissolving films had a cumulative percent release of medication ranging from 70.3% to 97.29% after 10 minutes. According to the quadratic model that was created, the Cumulative percent drug is significantly affected by the amounts of Hydroxypropyl methylcellulose E15, Eudragit RL 100, and Polyethylene Glycol 400.

The results show that the theoretical (expected) and actual figures were quite close to one another. The mathematical model for the proportion of drug release in 10 minutes (Y3) is significant, as shown by an F-value of 0.0163. A "Model F-Value" this high is very unlikely to occur by coincidence, with a probability of less than 0.01%. For the model terms to be considered significant, the "Prob > F" values must be lower than 0.05. In this case, the appropriate model terms are A, B, AB, AC, BC, A2, and B2, as shown in table 1.7. For model terms, values greater than 0.05 do not indicate significance. A statistically significant "Lack of Fit F-value" of 0.0295 in comparison to the pure error suggests that the Lack of Fit is worth noting.

Figures 1.12A and 1.12B show 3D response surface plots and accompanying contour plots, which further revealed the link between the independent and dependent variables. One of the key reasons the formulation's cumulative percentage of drug release increased was the quantity of plasticizer and polymers. The formulations' films that dissolve in the mouth primarily increased cumulative drug release because the drug is instantly dispersed in the medium upon film disintegration. Because of this, the film is able to absorb more water, which breaks the interface and speeds up the release rate. Incorporating the penetration enhancers also increased the cumulative proportion of drug released

Table 1.7: ANOVA was conducted using the quadratic model to analyse the response variable, Cumulative percent drug released (Y3).

Outputs	Degree of Freedom (DF)	Sum of Square (SS)	Mean of Square (MS)	**F**	P-value Prob > F		
Model	9	567.66	62.20	0.0163	< 0.05		
A-Amount of HPMC E15	1	40.33	40.33	0.0211	< 0.05		
B-Amount of Eudragit RL 100	1	97.60	97.60	0.0357	< 0.05		
C-Amount of Polyethylene Glycol	1	2.05	2.05	0.0194	< 0.05		
AB	1	0.90	0.90	0.0241	< 0.05		
AC	1	84.89	84.89	0.0239	< 0.05		
BC	1	124.34	124.34	0.0160	< 0.05		
Residual	17	713.80	42.56	-			
Lack of Fit	5	52.41	10.47	0.0295	< 0.05		
Response	**P Value**	**R^2**	**Adjusted R^2**	**Predicted R^2**	**Adequate precision**	**SD**	**CV%**
Y_2	<0.05	0.9997	0.9945	0.9814	25.9499	3.16	4.01

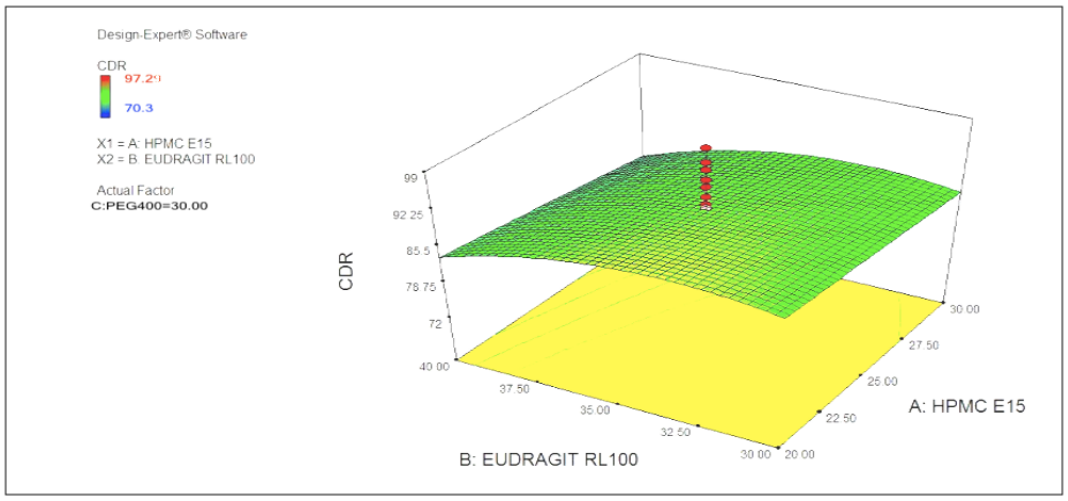

Figure 1.12A: A 3D surface map is generated to illustrate the impact of the quantities of Hydroxypropyl methylcellulose E15 and Eudragit RL 100 on the cumulative percentage of medicine released at a constant level of C.

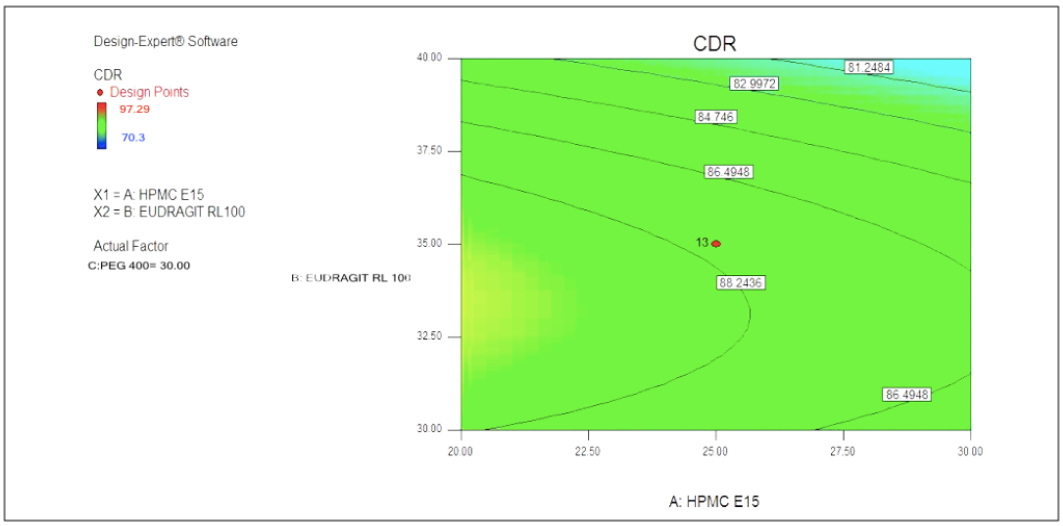

Figure 1.12B: A contour figure is shown to illustrate the impact of varying quantities of Hydroxypropyl methylcellulose E15 and Eudragit RL 100 on the cumulative percentage of drug released at a constant level of C.

There is a fairly noticeable influence of polyethyl glycol 400 on % cumulative drug release, as seen in the following graph, which examines this effect. The in vitro drug release investigation found that the percentage of drug release reduced with increasing polymer concentration and rose with increasing plasticizer concentration. However, in order to visualise the data graphically, a response surface plot was created based on the forecast of the drug release percentage. Thus, the figure demonstrated the shared impact of the concentration of plasticizer and polymer. From the contour plot of formulation batches FF1–FF27, we can deduce that the percentage of drug release decreased with increasing polymer concentration and rose with increasing plasticizer concentration.

Optimization By Desirability Function

To optimise all three replies at once, an optimisation procedure was carried out using a desirability function. The following answers were converted into the desirability scale: tensile strength (Y1), disintegration time (Y2), and cumulative percentage of medication released in 10 minutes (Y3). Y3 had to be maximised, whereas Y1 and Y2 had to be minimised. Equation (3) was used to get the highest objective function (D) for each answer, which was then used to determine the individual

desirability functions Ymax and Ymin. After a thorough grid search and feasibility search over the domain, the global desirability value was computed using the geometric mean of the individual desirability functions. This process was carried out using the Design-Expert programme. The highest value for the function was achieved at X1:25, X2:35, and X3:30. We created three batches of formulations with the optimal mix and tested all three responses to ensure the model was adequate for prediction. You may see the results in Table 1.8. The model was validated since the anticipated and actual outcomes were quite close to each other. It is evident that the experimental values closely matched the anticipated values, suggesting that the assessment and optimisation of formulations for mouth dissolving films was successfully accomplished using the central composite design in conjunction with a desire function.

During the optimisation process, we prioritised minimising the disintegration time and optimising the drug release of the zopiclone fast-dissolving film. The programme offered a number of alternatives, but only the batch ZF15 formula produced a desirable outcome. Because of its optimal combination of rapid disintegration and sustained drug release, batch ZF15 was chosen as the best formulation.

Table 1.8: Results for Y1, Y2, and Y3 after optimising for the restrictions

Independent variable	Nominal Values %	Predicted values			Observed values			
		Tensile Strength (Y1) (nm)	Disintegration Time (Sec) (Y2)	%CDR (Y3)	Batch	Tensile Strength (Y1) (nm)	Disintegration Time (Sec) (Y2)	Percent drug released in 10 min (Y3)
Amount of HPMC E5 (A)	25	17.5	29	98.29	1	19.3	32	97.29
Amount of Eudragit RL 100 (B)	35				2	20.8	35	96.23
Amount of PEG 400 (C)	30				3	22.5	31	97.17

Microscopy of the Optimized Formulation.

The surface topography of the 2cm X 2cm fast-solving Zopiclone film was examined under a scanning electron microscope (Fig. 1.13), and the results showed that the film was smooth and adequate.

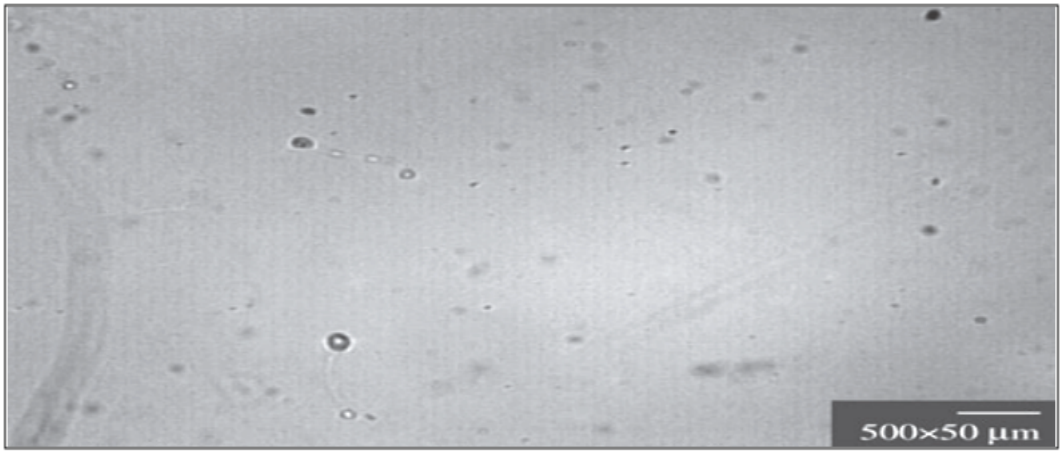

Figure 1.13: The Improved Formulation Under the Microscope.

Stability Study

For nintey days at ambient temp and humid condition stability study was carried out on the optimised batch ZF15 of zopiclone film. The results of the stability tests are shown in Table 8.17. Findings from the stability studies indicated that the finished product remained unchanged and did not degrade or interact with any contaminants.

Table 8.17 Results of Stability Testing on the Optimised ZF15 Formulation

Evaluation parameters	Initial days	30 days	60 days	90days
Physical observation	Transparent film	Transparent film	Transparent film	Transparent film
Thickness (mm)	0.10±0.11	0.10±0.11	0.10±0.06	0.10±0.04
Folding endurance	290±1.24	290±1.24	285±1.02	270±1.5
Surface pH	6.78±0.46	6.78±0.6	6.56±0.6	6.50±0.6
In vitro disintegration time (s)	27±1.85	27 ±1.01	26.0 ±0.1	25.0 ±0.08
% Drug release at 10 min	97.29±1.87	97.20 ± 1.55	97.1 ± 1.55	96.2 ± 1.32

Conclusion

A zopiclone film that dissolves quickly was created using a solvent cast technique. This might make administration simpler for patients with dysphagia or who are old. Using the Design of Experiment programme, twenty-seven formulations (ZF11-ZF27) were developed using the solvent casting process. The formulations were tested at low, medium, and high concentrations of the polymers HPMC E15, Eudragit RL 100, and Polyethylene Glycol 400. The Response surface method was also used. Using Design Expert Software, the batches of formulation were optimised with success. With a disintegrating duration of 27 sec and release of medicine from dosage form is approximately 97.29% at the end of 10 minutes, formulation ZF15 was determined to be the most optimal batch. So, if you're looking for an alternative that works quickly to alleviate insomnia, a film of zopiclone might be a good option.

References

1. Alqahtani, M.S., Kazi, M., Alsenaidy, M.A. and Ahmad, M.Z., 2021. Advances in oral drug delivery. *Frontiers in pharmacology*, *12*, p.618411.
2. Shah, K.A., Li, G., Song, L., Gao, B., Huang, L., Luan, D., Iqbal, H., Cao, Q., Menaa, F., Lee, B.J. and Alnasser, S.M., 2022. Rizatriptan-Loaded Oral Fast Dissolving Films: Design and Characterizations. Pharmaceutics, 14(12), p.2687.
3. Al-Kubati, S.S., Ahmed, M.A. and Emad, N.A., 2022. Palatable Levocetirizine Dihydrochloride Solid Dispersed Fast-Dissolving Films: Formulation and In Vitro and In Vivo Characterization. The Scientific World Journal, 2022(1), p.1552602.
4. Shah, K.A., Gao, B., Kamal, R., Razzaq, A., Qi, S., Zhu, Q.N., Lina, S., Huang, L., Cremin, G., Iqbal, H. and Menaa, F., 2022. Development and characterizations of pullulan and maltodextrin-based oral fast-dissolving films employing a box–behnken experimental design. Materials, 15(10), p.3591.
5. Suruse, P.B., Deshmukh, A.P., Barde, L.G., Devhare, L.D., Maurya, V.K., Deva, V. and Priya, N.S., 2023. Rimegepant embedded fast dissolving films: A novel approach for enhanced migraine relief. Journal of Survey in Fisheries Sciences, pp.2071-2084.
6. Arif Muhammed, R., Yalman Othman, Z., Rashid Noaman, B., Visht, S., Jabbar, S. and Sirwan Salih, S., 2023. Innovations In Formulation And Evaluation Of Oral Fast

Dissolving Film. Eurasian Journal of Science and Engineering, 9(2).
7. Suruse, P.B., Deshmukh, A.P., Barde, L.G., Devhare, L.D., Maurya, V.K., Deva, V. and Priya, N.S., 2023. Rimegepant embedded fast dissolving films: A novel approach for enhanced migraine relief. Journal of Survey in Fisheries Sciences, pp.2071-2084.
8. Gandhi, N.V., Deokate, U.A. and Angadi, S.S., 2021. Formulation, optimization and evaluation of nanoparticulate oral fast dissolving film dosage form of nitrendipine. AAPS PharmSciTech, 22(6), p.218.
9. Butkevych, T., Polova, Z. and Savchenko, S., 2023. Development of the composition and technology of an orodispersible film with melatonin and magnesium citrate.
10. Martínez-Cortés, D.M., Vera-Pérez, J. and Gómez-y-Gómez, Y., 2022. Ultrathin oral films with extracts of Agastache mexicana and its hypnotic activity as a potential treatment for insomnia. TIP. Revista especializada en ciencias químico-bi*ológicas*, *25*.