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Research Article

Formulation and *In-Vitro* Evaluation of Lemborexant Orodispersible Film

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Abstract

The current work focused on the formulation and in vitro evaluation of Lemborexant oral dispersible films (ODFs) loaded with nanoparticles to improve solubility, dissolution, and patient compliance in the treatment of insomnia. Lemborexant, a dual orexin receptor antagonist, has low water solubility, reducing its oral bioavailability. To overcome this limitation, nanoparticles were prepared using the solvent displacement method and incorporated into fast-dissolving polymeric films that contained hydroxypropyl methylcellulose (HPMC) and carboxymethyl cellulose (CMC) as film-forming agents, PEG as a plasticizer, and superdisintegrants for rapid disintegration. The produced films were tested for physicochemical and mechanical properties such as thickness, weight fluctuation, folding endurance, tensile strength, surface pH, drug content homogeneity, disintegration time, and in vitro drug release.The optimized formulation demonstrated uniform thickness and weight, as well as appropriate tensile strength. The films disintegrated quickly (15-30 seconds) and had considerably higher in vitro drug release than pure Lemborexant. FTIR tests verified the absence of drug-excipient interactions, while SEM revealed homogeneous nanoparticle dispersion. The findings suggested that Lemborexant-loaded nanoparticle oral dispersible films are a viable delivery platform for quick onset of action, increased bioavailability, and enhanced patient compliance, particularly in geriatric patients with swallowing issues. Additional in vivo investigations are needed to confirm the therapeutic efficacy and pharmacokinetic advantages of the proposed formulation.

Keywords: Lemborexant, Oral Dispersible Film, Nanoparticles, Solvent Casting, *In vitro* drug release studies.

1. INTRODUCTION

Lemborexant is a medication used in the management and treatment of insomnia. It is in the dual orexin antagonist class of medications. This activity outlines the indications, actions, and contraindications for lemborexant as a valuable agent in managing insomnia. This activity will highlight the mechanism of action, adverse event profile.[1]

Orodispersible films are single or multilayer sheets built of the right materials that are intended to swiftly release the loaded active ingredient in the mouth, creating a thin suspension or solution in the saliva without mastication or water intake These orodispersible films are designed in such a way that water is not necessary for administration since they immediately break apart within a few seconds, releasing the medication into the mouth. When placed on the tongue, orodispersible films quickly hydrate by soaking up saliva once the dosage form's active pharmaceutical ingredient disintegrates and/or dissolves. These thin films come in a variety of sizes and forms.[2]

2. METHODOLOGY

PRE FORMULATION STUDIES

Methods of API characterization

A. Physical properties:

The color, odour, taste of the drug was recorded.

B. Solubility studies:

- Freely soluble in dimethyl sulfoxide (DMSO), and Buffer 6.8
- Soluble in ethanol and methanol
- Insoluble in water[4]

C. Determination of melting point:

Melting Point of Lemborexant was estimated by capillary method.[6]

D. Determination of absorption maxima (λ_{max}) for Lemborexant:

A 10mcg/ml standard solution of Lemborexant was scanned on a double beam spectrophotometer against respective media blanks. An absorption maximum (λ_{max}) of 236 nm was obtained for all solutions and was selected to prepare standard curve.[7]

E. Preparation of standard curve for Lemborexant

Standard curves for Lemborexant were obtained in 6.8 pH buffers and water. Aliquots of 10, 20, 30, 40 and 50 ml of Lemborexant standard solution of 100mcg/ml (*stock*

solution-II) was taken and diluted to obtain concentrations from 10 to 50mcg/ml with appropriate media. The absorbance of solutions were determined at 236 nm against respective media as blank. The experiment was repeated five times for each buffer and a calibration curve was determined from the mean value.[8]

Determination of absorption maxima (λ_{max}) for Lemborexant

A 10mcg/ml standard solution of Lemborexant was scanned on a double beam spectrophotometer against respective media blanks.

F. Fourier Transforms Infra-Red (FTIR) Spectroscopy:

FT-IR spectra (Bruker alpha, Germany) was obtained to discover possible interactions between the drug and polymers. The ingredients were compressed with a hydraulic press to form a pellet (less than 5 k pas). The disc was put in the centre of the sample holding device and spectrum was recorded using an FT-IR spectrophotometer.[9]

Formulation design:

Solvent displacement technique is made used in preparing the drug loaded polymeric nanoparticles. 5 mg of Lemborexant and polymer were dissolved in 5 ml acetone. The organic phase with a constant flow rate of 0.3 ml/min was added up into 15 ml of aqueous phase containing 1% of PVA under magnetic stirring. With the help of a rotavapor, the organic solvent was evaporated under vacuum. The suspension was filtered by using 0.2 µm membrane and centrifuged at 15,000 rpm for 1 hr at 5°C. The sediment obtained is again dissolved in distilled water and centrifuged with the same conditions in triplicate. The final product was dried using a freeze dryer overnight.[10]

Table 1: Formulation Design of Lemborexant Nanoparticles

FORMULATION CODE	LEMBOREXANT (Mg)	ETYHL CELLULOSE (Mg)	EUDRAGIT (Mg)	PVA (%)
F1	5	100	-	1
F2	5	200	-	1
F3	5	300	-	1
F4	5	400	-	1
F5	5	-	100	1
F6	5	-	200	1
F7	5	-	300	1
F8	5	-	400	1

Preparation of fast dissolving films:·

5 mg Lemborexant ODF were prepared using a solvent casting technique. Briefly, a precisely weighed quantity of the polymers (CMC and HPMC) was added to 5 mL of double-distilled water and stirred for 1 h using a magnetic stirrer. Afterwards, Aspartame, citric acid, and menthol were added and stirred until all ingredients were completely dissolved. After that, a plasticiser (PEG), a Permeation enhancer (D-limonene), and a superdisintegrant (SSG) were added and stirred continuously for 1 h until the solution became clear. Then, the previously prepared Lemborexant nanoparticles was added to the mixture with continuous mixing for 1 h, till the formation of a homogenous mixture. The obtained mixture was left undisturbed and, after all bubbles had dissipated, was poured into a glass Petri dish and dried in a hot air oven at 60 °C for the first 2 h and at 40 °C for the following 24 h. The resulting ODF was peeled from the glass Petri dish and cut into films measuring 2 × 2 cm2, each of which contained 5 mg Lemborexant. Then, they were wrapped, utilizing airtight aluminium foil. Any film with imperfections, cuts or air bubbles was excluded.[11]

Table- 2: Formulation Design of Lemborexant Oro dispersible films loaded with nanoparticles

F. CODE	Lemborexant Nanoparticles (ml)	HPMC (mg)	Carboxy methyl cellulose (mg)	PEG (ml)	D-limonene (ml)	Aspartame (mg)	Sodium starch glycolate (mg)
F1	5	50	-	1	0.1	3	5
F2	5	100	-	1	0.1	3	5
F3	5	150	-	1	0.1	3	5
F4	5	200	-	1	0.1	3	5
F5	5	-	50	1	0.1	3	5
F6	5	-	100	1	0.1	3	5
F7	5	-	150	1	0.1	3	5
F8	5	-	200	1	0.1	3	5

Physico-chemical evaluation of oral Oro-dispersible film formulation:

1. Physical appearance:

All the prepared films were observed for color, clarity, flexibility, and smoothness.

2. Folding endurance:

A section of film is cut, and it is folded repeatedly at the same spot until it breaks, in order to measure folding endurance. The folding endurance value is calculated by how many times the film could be folded at the same spot without breaking.

3.Thickness of the film:

The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

4. Weight uniformity:

The prepared films are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance.

The average weight and standard deviation values are to be calculated from the individual weight.

5. Tensile strength:

The tensile strength is determined by measuring the force required to break a film sample under tension,The force at break and the film's dimensions are then used to calculate the tensile strength.

6. Disintegration time:

The disintegration time limit of 30 s or less for orally disintegrating films described in CDER guidance can be applied to fast dissolving oral strips.

7. Drug content:

The formulated fast dissolving film were assayed for drug content in each case. Three films from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug.

***8. In-vitro* Drug release studies:**

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The samples were analyzed for drug content spectrophotometrically.

Percentage of drug release was determined using the following formula.

Percentage drug release = Da / Dt x 100

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released.[12]

9. Release kinetics:

The zero-order, first-order, Higuchi, and Korsmeyer–Peppas models were used to assess the cumulative drug release patterns in order to determine the release mechanism. The model with the greatest correlation value (R2) was found to be the best fit. The Korsmeyer–Peppas model's release exponent (n) was interpreted as follows:

$n < 0.89 \rightarrow$ Fickian diffusion 0.45 Erosion-controlled release [25] $n \geq 0.89 \rightarrow$ anomalous (non-Fickian) transport $n < 0.45$. [13]

10. Stability studies:

To assess the stability of the drug formulation, ICH conducted stability experiments. The optimised formulation was sealed in a polyethene-laminated aluminium container. Samples were stored at 40°C and 75% RH for a month. The formulation was examined for any changes in its characteristics [14]

4. RESULTS AND DISCUSSION

In the present study 8 formulations with variable concentration of polymer were prepared and evaluated for physic-chemical parameters, in vitro release studies and stability studies.

Pre-formulation studies:

a) Organoleptic evaluation:

Table 3: Organoleptic properties of Lemborexant

Properties	Results
Description	Crystalline powder
Taste	Tasteless
Odor	odorless
Color	White to off-white crystalline powder

b) Determination of melting point:

Drug	Reference range	Observed range
Lemborexant	174-176°c	175°c

Melting point of Lemborexant was found in the range of $174\text{-}176^0$c, which complied with the standard, indicating purity of the drug sample.

c) Solubility:

Solvent	Observed solubility description	Solubility range (Mg/ml)
Water	Sparingly Soluble	11.7 mg/ml
Methanol	Soluble	45.9 mg/ml
Buffer 1.2	Sparingly Soluble	33.1 mg/ml
Buffer 6.8	Soluble	48.6 mg/ml

Spectrum of Lemborexant:

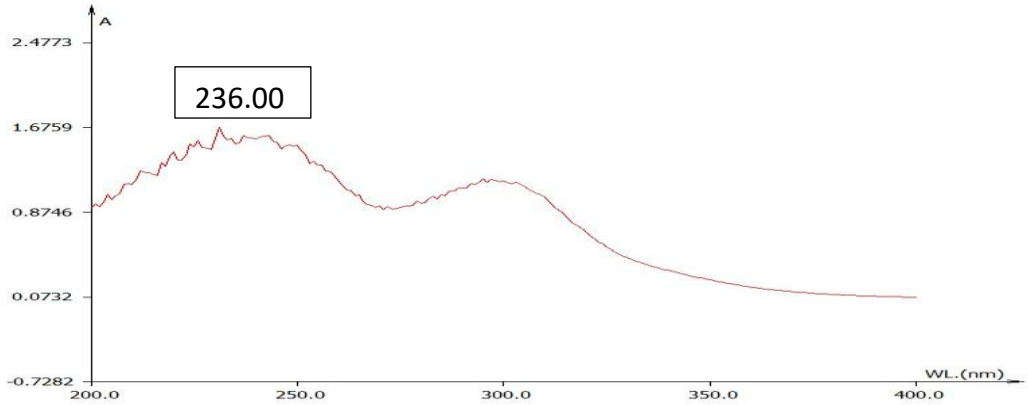

Figure 1: Spectrum of Lemborexant

d) Preparation of standard curve of Lemborexant

Standard curve of Lemborexant was determined by plotting absorbance V/s concentration at 236 nm. Using solution prepared in pH 6.8 at 236 nm. And it follows the Beer's law. The R^2 value is 0.997.

Table 4 : Calibration curve of Lemborexant

S. no	Concentration (µg/mol)	Absorbance
1	0	0
2	10	0.183±0.057
3	20	0.291±0.036
4	30	0.550±0.121
5	40	0.725±0.043
6	50	0.897±0.111

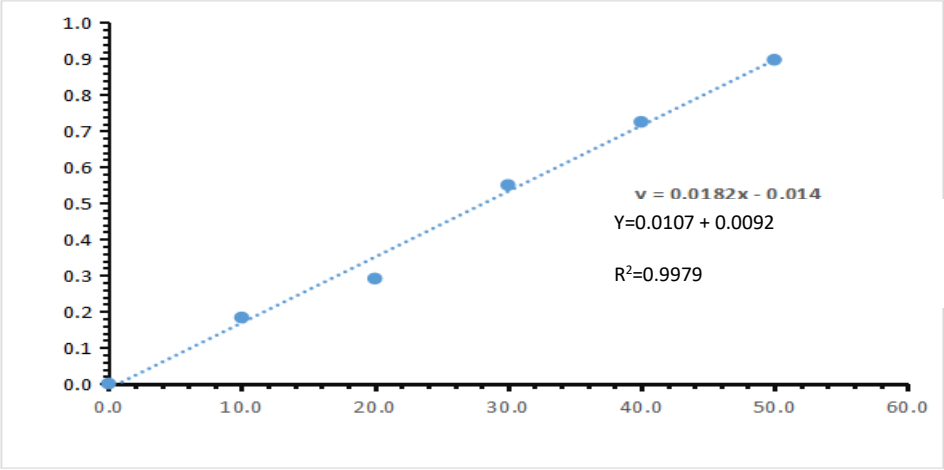

Figure 2: Calibration curve of Lemborexant

E) FT-IR Spectrum of Lemborexant :

All the formulations were uniform in drug content and the FTIR spectra of Lemborexant and its oro dispersible films are identical. The principle FTIR absorption peaks of Lemborexant oro dispersible films were observed and found to be identical with the spectra of Lemborexant pure drug. Thus from the spectra it was understood that there was no interaction between Lemborexant and polymers used in the preparation of films.

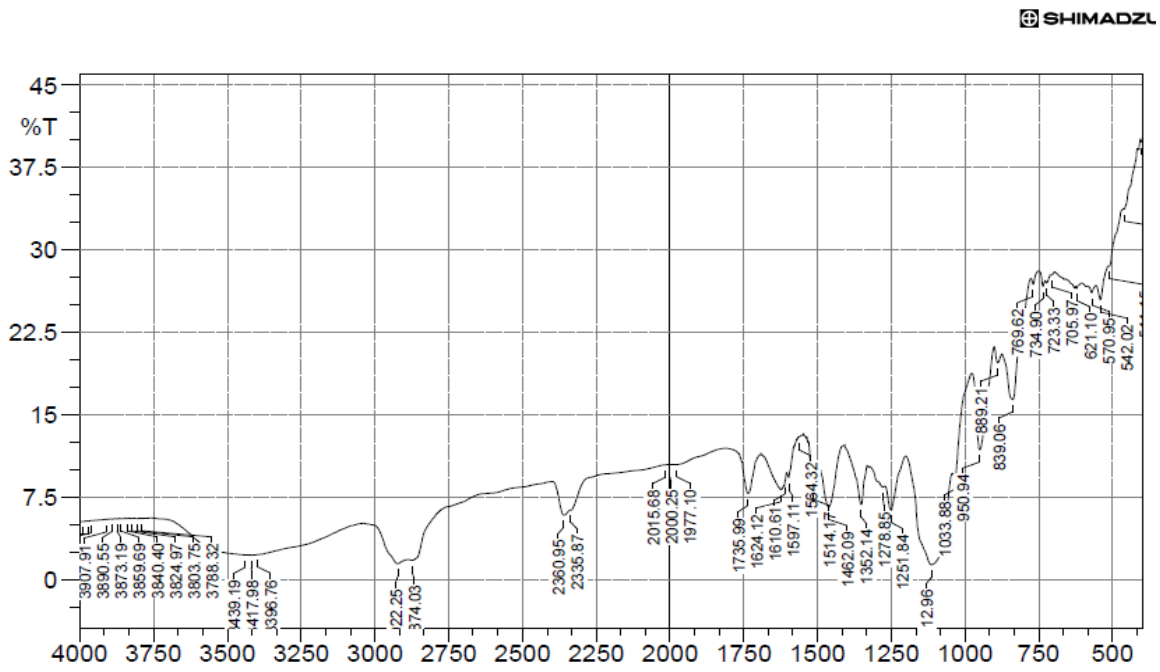

Figure 3: FTIR Studies of Lemborexant

Table 5: Characteristic Peaks for Lemborexant

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3972.18
2	OH Bending	3500-3000	3396.76
3	C-H stretching	2750-2250	2360.95
4	C=O stretching	1500-1000	1352.14

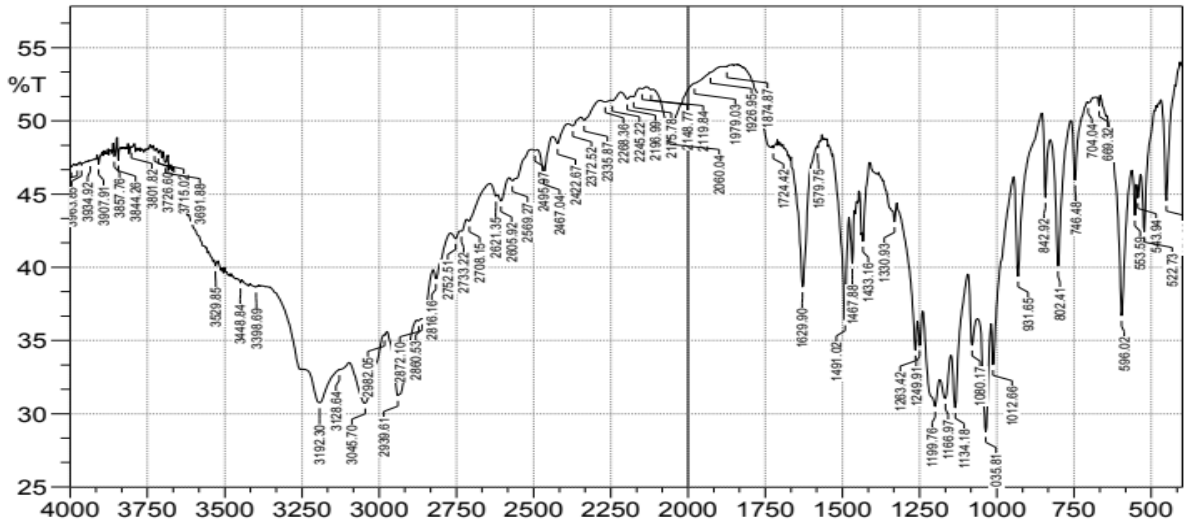

Figure 4: FTIR Studies of Lemborexant nanoparticles

Table 6: Characteristic Peaks for Lemborexant nanoparticles:

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3857.76
2	OH Bending	3500-3000	3192.30
3	C-H stretching	2750-2250	2569.27
4	C=O stretching	1500-1000	1263.42

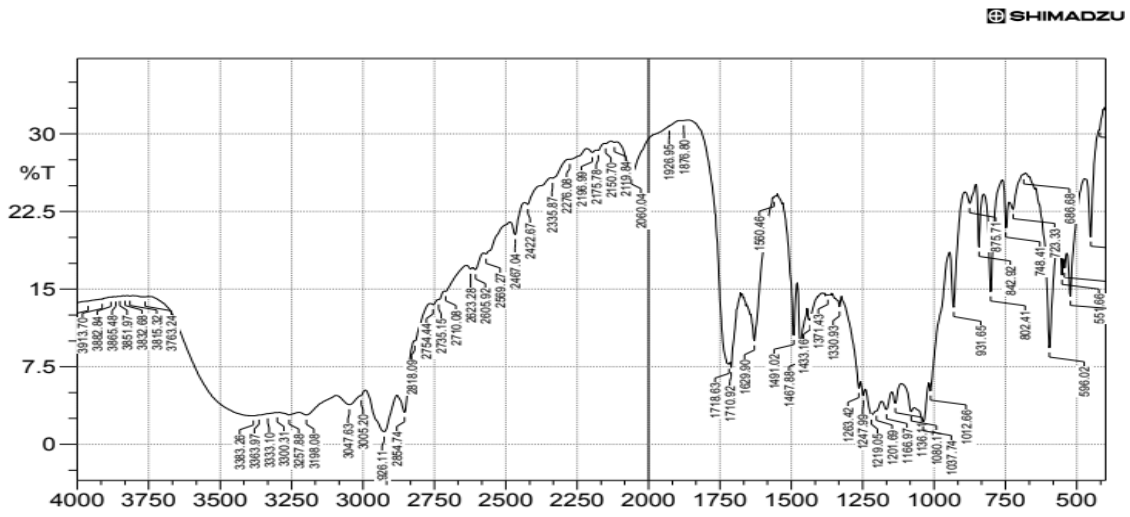

Figure 5: FTIR Studies of Lemborexant Oro dispersible films loaded with nanoparticles.

Table 7: Characteristic Peaks for Lemborexant Oro dispersible films loaded with nanoparticles :

S.No.	Characteristic Peaks	Frequency range (cm-1)	Frequency (cm-1)
1	OH stretching	4000-3500	3865.48
2	OH Bending	3500-3000	3363.97
3	C-H stretching	2750-2250	2623.28
4	C=O stretching	1500-1000	1330.93

CHARACTERIZATION:

Particle size:

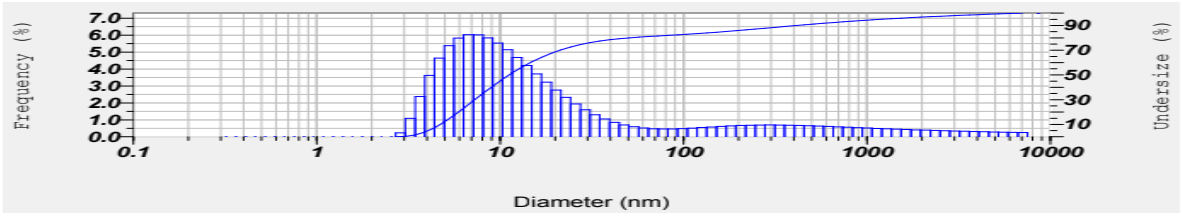

Figure 6: Particle size of Polymeric nanoparticles

The mean particle size of optimized Nanoparticles was found to be 68 nm.

Zeta potential:

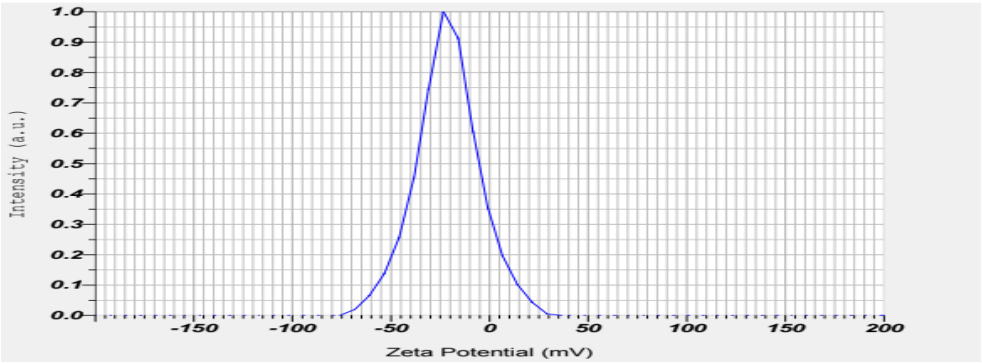

Figure 7: Zeta potential analysis of Optimized Nanoparticles

The ZP or change in the surface of colloidal particles in Nanoparticles was studied to determine the charge on the particles to avoid agglomeration. Figure indicates the ZP of the optimized formulation as -23 mV.

Table 8: Evaluation Studies of particle size and Zeta potential Nanoparticles :

F. No	Particle size (nm)	Zeta potential
F1	83	-26
F2	72	-20
F3	80	-21
F4	75	-23
F5	82	-21
F6	68	-21
F7	76	-25
F8	81	-19

Surface morphology:

According to scanning electron microscopy (SEM), the polymeric nanoparticles were round, smooth, and free of any aggregation.

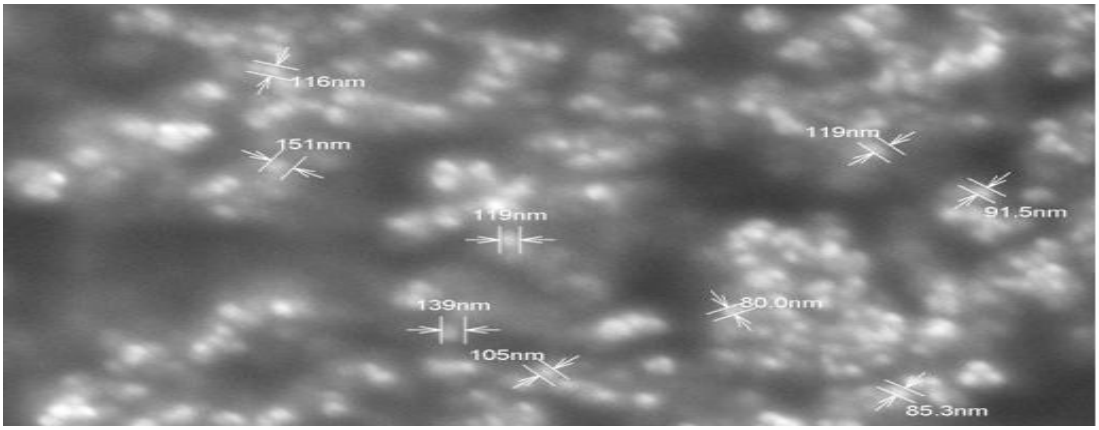

Figure 8: SEM analysis of Optimized polymeric nanoparticle

EVALUATION PARAMETERS OF NANOPARTICLE INCORPORATED IN ORODISPERSIBLE FILMS

Evaluation of Orodispersible film formulation

Physical appearance:

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance:

The folding endurance numbers of all the Nanoparticles oro dispersible films are 142-157. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the oro dispersible film

Thickness was changed from batch to batch in individual strips of medicated orodispersible film carry uniform thickness, which indicates that total medicated film carries uniform thickness.

Weight uniformity:

The weights are in the range of 126-138. The F5 formulation patches showed maximum weight.

Drug content:

The drug content analysis of the prepared formulations has shown that the process employed to prepare the films was capable of giving uniform drug content with minimum batch variability.

Tensile strength

For ODFs, an ideal tensile strength range is usually 13.6–24.8 MPa

Disintegration Time

The disintegration time of optimized formulation was found to be 16sec.

Table 9: Physicochemical evaluation of nanoparticle oro-dispersible films

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	Tensile strength(Mpa)	Disintegration time (sec)
F1	138±0.03	0.39±0.02	142	75.69±0.43	13.6	24
F2	132±0.08	0.41±0.06	146	78.10±0.24	24.1	26
F3	129±0.05	0.43±0.03	150	80.12±0.51	23.9	29
F4	135±0.04	0.47±0.07	153	79.68±0.62	14.7	18
F5	131±0.02	0.45±0.06	149	82.36±0.17	19.6	16
F6	128±0.09	0.42±0.05	157	80.15±0.29	23.8	20
F7	126±0.07	0.40±0.02	153	79.58±0.54	24.8	22
F8	136±0.06	0.45±0.07	148	80.22±0.46	15.1	25

***In vitro* release study:** Phosphate buffer pH 6.8 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.997. the drug release was governed by polymer nature and content.

Table10: *In vitro* drug release profiles of Nanoparticles Oro dispersible film(F1-F8)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.25±0.32	18.86±0.43	20.21±0.38	23.57±0.11	19.86±0.64	16.96±0.17	18.15±0.54	17.67±0.43
2	27.46±0.12	30.29±0.62	31.37±0.47	32.86±0.51	30.39±0.28	29.46±0.36	28.36±0.62	25.46±0.37
3	35.19±0.46	33.48±0.58	37.29±0.61	39.53±0.25	44.48±0.56	41.55±0.73	38.47±0.43	35.52±0.28
4	42.12±0.33	43.83±0.22	46.27±0.54	50.12±0.43	52.34±0.53	49.68±0.65	46.29±0.37	41.22±0.48
6	56.93±0.51	55.42±0.73	58.38±0.34	60.13±0.63	64.39±0.23	62.95±0.48	59.37±0.51	59.19±0.44
8	65.39±0.23	68.10±0.44	70.79±0.18	72.25±0.27	80.18±0.54	76.36±0.37	74.58±0.29	71.64±0.53
10	78.68±0.71	80.21±0.38	81.25±0.60	83.59±0.65	87.43±0.29	84.35±0.61	81.15±0.46	75.33±0.28
12	81.25±0.14	82.36±0.53	84.38±0.27	91.35±0.29	97.56±0.37	85.99±0.18	86.37±0.29	84.87±0.41

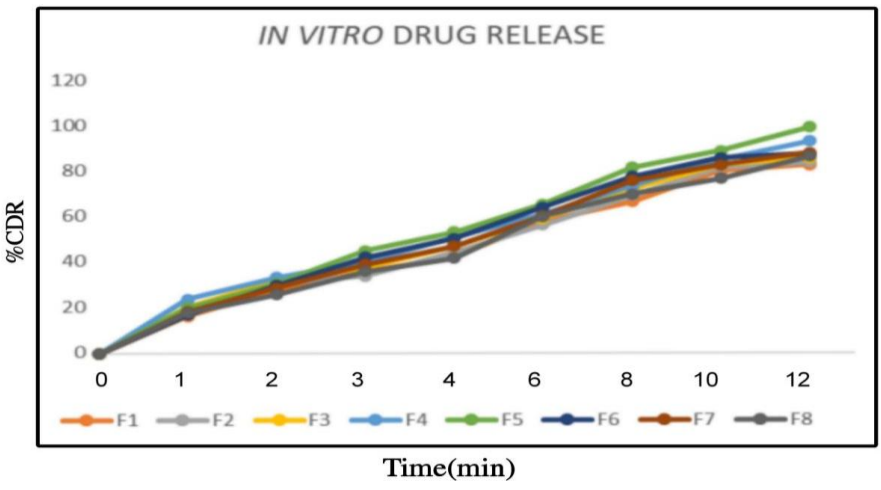

Figure 9: Drug release for (F1-F8) formulations

Kinetic models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table 11: Drug Release Kinetics of Formulation F5

Time (hrs)	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	100	0
1	17.86	1	0	1.251881455	82.14	0
2	25.39	1.41421	0.29103	1.404662701	74.61	0.15051
3	37.48	1.73205	0.45712	1.573799582	62.52	0.23856
4	50.34	2	0.62689	1.701913211	49.66	0.30103
6	62.39	2.44949	0.70815	1.795114986	37.61	0.38908
8	75.18	2.82843	0.91031	1.876102321	24.82	0.45154
10	85.43	3.16228	0.96025	1.931610406	14.57	0.5
12	97.56	3.4641	1.07449	1.989271792	2.44	0.53959

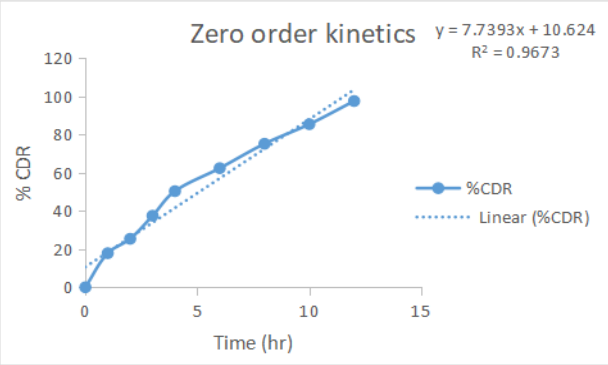

Figure 10: Zero order kinetics of optimized formulation

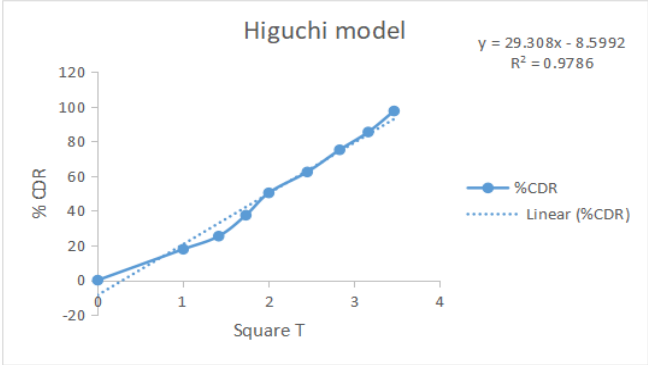

Figure 12: Higuchi model of optimized formulation

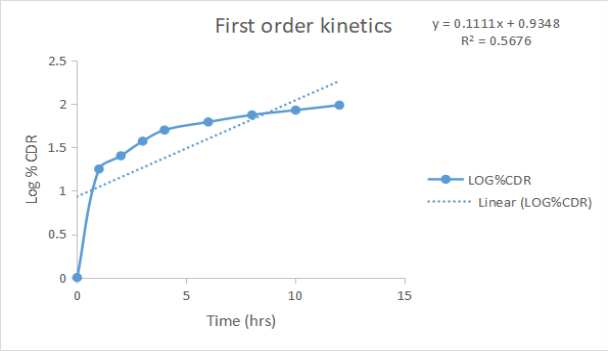

Figure 11: First order kinetics of optimized formulation

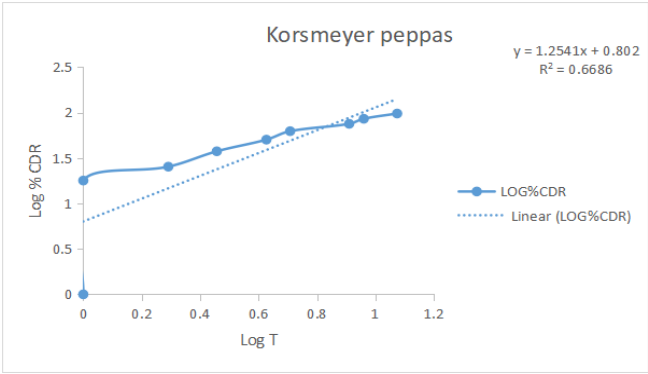

Figure 13: Korsmeyer Peppas of optimized formulation

Discussion: Regression values are higher with zero-order release kinetics. Therefore, all orodispersible film follows zero-order release kinetics.

Table 12: Regression equations of optimized formulation

F. No	In vitro release in phosphate buffer P^H 6.8 Regression values			
	Zero order	First order	Higuchi Plot	Korsmeyerpeppas
F5	0.967	0.567	0.978	0.668

Table 13: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months :

Time in days	Drug content (%)	Physical appearance	% Cumulative drug release
0	82.36±0.27	No change in color	97.56±0.32
30	82.21± 0.21	No change in color	97.32±0.34
60	81.90±0.24	Faint yellow in color	97.09±0.39
90	81.59±0.26	Slight yellowish color	96.30±0.36

Phosphate buffer pH 6.8 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.997. The drug release profiles of Orodispersible film containing Carboxy methyl cellulose. It was clear from the release profiles of formulations that the drug release was governed by the polymer nature and content.

CONCLUSION

The present work was focused on the formulation and in vitro evaluation of Lemborexant oral dispersible films (ODFs) loaded with nanoparticles to enhance the solubility, dissolution, and bioavailability of the poorly water-soluble drug. Nanoparticles were prepared using the solvent displacement technique and incorporated into polymeric oral films using film-forming agents such as HPMC and PVA, along with plasticisers, superdisintegrants, and stabilisers.

The prepared films were evaluated for physicochemical parameters, including thickness, weight variation, surface pH, folding endurance, disintegration time, and drug content uniformity. Further, in vitro drug release studies revealed rapid disintegration with sustained drug release, confirming the synergistic effect of nanoparticle incorporation and film formulation. FTIR studies confirmed the absence of primary drug–excipient interactions.

Overall, the nanoparticle-loaded ODFs showed improved dissolution rate and enhanced drug release profile, indicating their potential in providing better patient compliance, especially in populations with swallowing difficulties, such as elderly patients suffering from insomnia.

The study successfully demonstrated that nanoparticle-loaded oral dispersible films of Lemborexant can be prepared using the solvent-casting technique. The optimized formulation showed desirable physicochemical characteristics, rapid disintegration in the oral cavity, and significantly enhanced in vitro release compared to pure drug.

Thus, Lemborexant ODFs loaded with nanoparticles offer a promising approach for improving solubility, onset of action, and patient compliance, especially for the management of insomnia in geriatric patients.

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