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Formulation And Evaluation of Lemborexant Niosomal Drug Delivery System

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ABSTRACT

The present investigation attempted to prepare and evaluate the Lemborexant niosomes. Lemborexant niosomes were prepared using a thin film hydration technique. The excipients compatibility was performed by using FTIR, it was found compatible with each other. Scanning Electron micrographs revealed that the formed vesicles were spherical in shape with uniform size. The prepared niosomes were evaluated with respect to entrapment efficiency (EE %), particle size, and quantity of in vitro drug released to obtain an optimized formulation. The in vitro release study suggested that there was an inverse relationship between EE% and in vitro release. The F4 formulation showed drug entraspment efficiency of 85.10% and drug release of 97.18 % sustained up to 8 hrs. The stability studies performed for 3 months at 4^0C and room temperature as per ICH guideline.

KEY WORDS:

Lemborexant, thin film hydration technique, FTIR studies, surfactant, *In-vitro* drug release studies.

1.INTRODUCTION

Novel drug delivery system aims at providing some control, whether this is of temporal or spatial nature, or both, of drug release in the body.[1] Novel drug delivery attempts to either sustain drug action at a predetermined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.[2] It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type[3].Different types of pharmaceutical carriers are present. They are particulate, polymeric, macromolecular and cellular carrier. Particulate type carrier also known as a colloidal carrier system, includes lipid particles (low and high density lipoprotein LDL and HDL, respectively), microspheres, nanoparticles, polymeric micelles and vesicular like liposomes, niosomes, pharmacosomes, virosomes, etc.[4] The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers formed, when certain amphiphilic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphilic building blocks.[5] Niosomes or nonionic surfactant vesicles are microscopic lamellar structures formed on admixture of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.[6] In niosomes, the vesicles forming amphiphile is a nonionic surfactant such as spans, tweens and brijs which is usually stabilized by addition of cholesterol and small amount of charge inducer such as dicetyl phosphate. Niosomes can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. It is reported to attain better stability than liposomes. It can prolong the circulation of the entrapped drugs.[7]

2.MATERIALS AND METHODS

Lemborexant was collected as a gift sample from Hetero labs, Hyderabad and various excipients and polymers were purchased from AR chemicals, Hyderabad.

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2.1 METHODOLOGY

Fourier transform infrared spectroscopy[8]

Fourier transform IR spectra were obtained on Shimadzu FT-IR spectrometer. Samples were prepared in KBr disks (2mg sample in 200mg KBr). The scanning range was 450-4000 cm^{-1} and the resolution was 4 cm^{-1}.

Formulation development

Table-1: Composition of Niosomal Lemborexant (F1 to F4)

S. No.	Ingredients (mg)	F1	F2	F3	F4
1	Lemborexant	100	100	100	100
2	Cholesterol	100	100	100	100
3	Span 20	5	10	-	-
4	Tween 40	-	-	5	10
5	Chloroform	10	10	10	10
6	Methanol	5	5	5	5

Preparation of Niosomes

Niosomes preparation: Lemborexant niosomes were prepared using thin film-hydration method. Accurately weighed quantities of the surfactant (Span and tween) and cholesterol in different ratios, viz. 1:1 and 1:2, were dissolved in chloroform: methanol mixture (2:1,) in a round-bottom flask. Afterwards, Lemborexant dissolved in 7.4 phosphate buffer was added to the lipid solution. The organic solvents were removed under vacuum in a rotary evaporator at 40 ◦C for 20 min to form a thin film on the wall of the flask, and kept in a desiccator under vacuum for 2 h to ensure total removal of trace solvents. After removal of the last trace of organic solvents, hydration of the surfactant film was carried out using 10mL of distilled water at 55◦C. The resulting niosomal suspension was mechanically shaken for 1 h using a horizontal mechanical shaking water bath at 55 ◦C. Then, the vesicle suspension was sonicated in 3 cycles of 1min "on" and 1min "off" leading to the formation of multi lamellar niosomes. The niosomal suspension was left to mature overnight at 4 ◦C and stored at refrigerator temperature for further studies.[9]

Evaluation of Niosomes[10,11,12]

SEM analysis

The morphology of niosomes was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminium stubs and the surface was coated with a layer of gold particles using a sputter coater. The shape of the NPs was determined by scanning electron microscopy (SEM) (XL30, Philips, the Netherlands) at 15 kV and 750 mA.

Entrapment efficiency

To 0.2 g of Niosomes, weighed in a glass tube, 10 ml phosphate buffer pH 7.4 were added. The aqueous suspension was then sonicated. Niosomes containing Lemborexant were separated from untrapped drug by centrifugation at 9000rpm for 45 min at 4 ◦C. The supernatant was recovered and assayed spectrophotometrically using UV-spectrophotometer.

The encapsulation percentage of drug (EP) was calculated by the following equation

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$$EP = [(C_t - C_r)/ C_t] * 100$$

Where,
Ct, concentration of total Lemborexant,
Cr, concentration of free Lemborexant.

In- vitro drug Release Study

In vitro drug release studies were carried out using unjacketed vertical Franz diffusion cells with a diffusional surface area of 6.154 cm^2 and 20 mL of receptor cell volume. Prior to the study, the dialysis membrane (Himedia laboratories Pvt Ltd., Mumbai) was soaked in phosphate buffer pH 7.4 Formulation equivalent to 5mg of Lemborexant was placed in the donor compartment. The receptor compartment consisting of PB pH 7.4 was maintained at 37±2°C under constant stirring up to 8 hrs. The donor chamber and the sampling port were covered with lid to prevent evaporation during the study. Aliquots of 5 mL were withdrawn periodically at different time intervals (1, 2, 3, 4, 5, 6, 7, 8 hrs) and replaced with equal volume to maintain constant receptor phase volume. At the end of the study, the samples were suitably diluted and the amount of drug was determined spectrophotometrically.

Stability Studies

The formulations stored in glass vials covered with aluminium foil were kept at room temperature and in refrigerator (4◦C) for a period of 90 days. At definite time intervals samples were withdrawn and hydrated with phosphate-buffered saline (pH 7.4) and observed for any sign of drug crystallization under optical microscope. Furthermore, the samples were also evaluated for particle size and percent retention of Lemborexant[13].

3.RESULTS & DISCUSSION

Drug- Excipient compatibility studies (FT-IR):

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

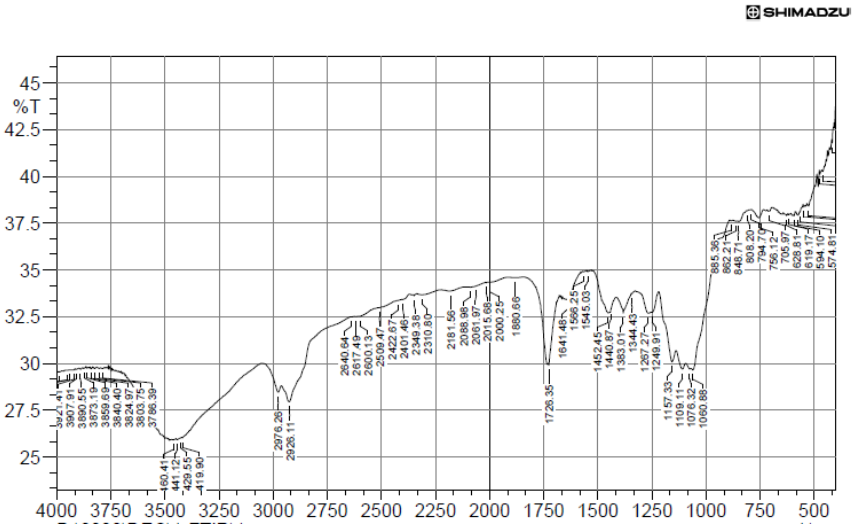

Fig 1: FTIR spectra of Lemborexant

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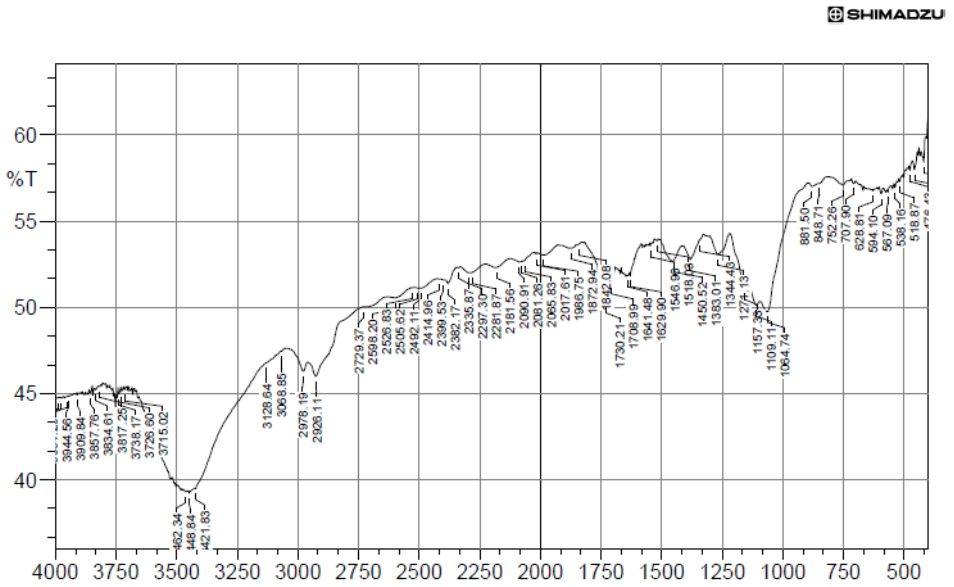

Fig 2: FTIR Spectra of physical mixture of drug and excipients

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

EVALUATION PARAMETERS:

Entrapment Efficiency:

$$\%\ Entrapment\ efficiency = \frac{Amount\ of\ drug\ entrapped}{Total\ amount\ of\ drug\ added} \times 100$$

Table-2: Drug entrapment efficiency of all formulation

F. No	Drug entrapment efficiency
F1	80.12
F2	82.59
F3	79.86
F4	85.10

Determination of Vesicle morphology and Size

The morphological characteristics of formulated niosomes were carried by using Scanning electron microscopy (SEM). A small drop of niosomal suspension was placed between two rivets fixed on a gold-plated copper sample holder. The whole system was slushed under vacuum in liquid nitrogen. The sample was heated to -85^{0}C for 30 min to sublime the surface moisture. Finally, the sample was coated with gold and allowed the SEM to capture the images at a temperature of -120^{0}c and voltage of 5kV.

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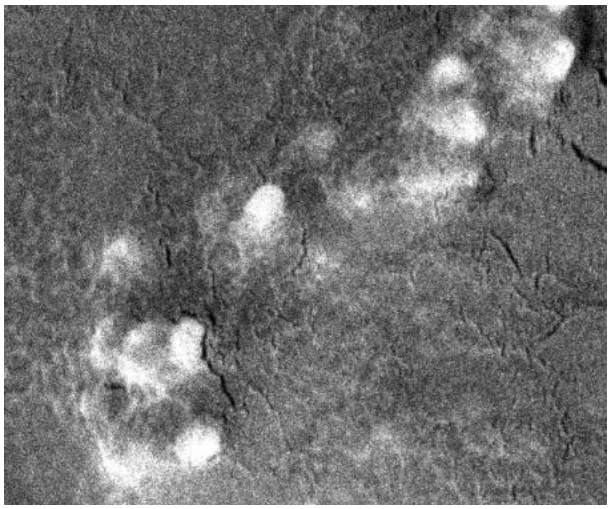

Fig 3: SEM analysis of Optimized Niosomes

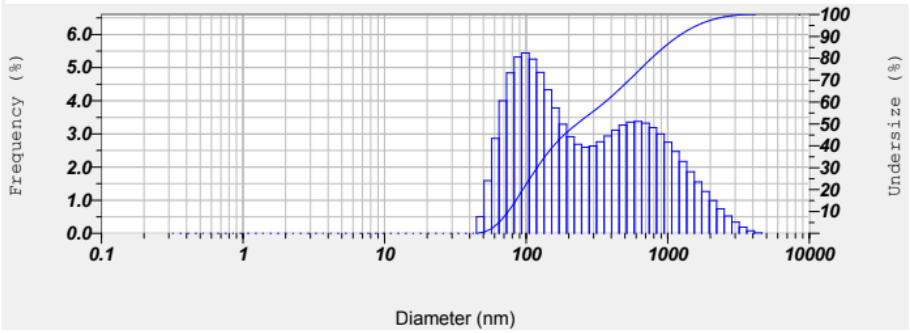

Fig 4: Particle size analysis of optimized formulation

Table-3: Evaluation Studies of Vesicle size Niosome

Batch No	Particle size (nm)
F1	196
F2	220
F3	189
F4	224

***In vitro* drug release studies:**

The release of drug from niosomal suspension was investigated using dialysis tubing method. All the formulations were separately placed in a dialysis membrane of 5cm length with closed ends which was washed and soaked in phosphate buffer pH 7.4 for about 15min. The membrane was suspended in a beaker containing 500ml of phosphate buffer pH 7.4 as diffusion medium maintained at a temperature of 37 ± 0.5^0 C and stirred continuously by means of magnetic stirrer at a constant speed. At a regular time interval of one-hour 5ml of diffusion medium was withdrawn periodically for about 8hrs and immediately replaced with same amount of fresh diffusion medium to maintain sink condition. The collected samples were measured spectrophotometrically at 259 nm.

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Table-4: *In- vitro* drug release studies of (F1-F4) formulation

Time	F1	F2	F3	F4
0	0	0	0	0
1	15.89	16.37	17.70	18.16
2	27.56	28.15	26.35	27.10
3	38.15	37.69	38.10	37.55
4	48.90	49.10	48.16	49.18
5	57.83	58.16	57.89	58.36
6	67.58	68.39	65.44	67.89
7	76.35	77.15	78.19	81.20
8	92.19	93.67	95.22	97.18

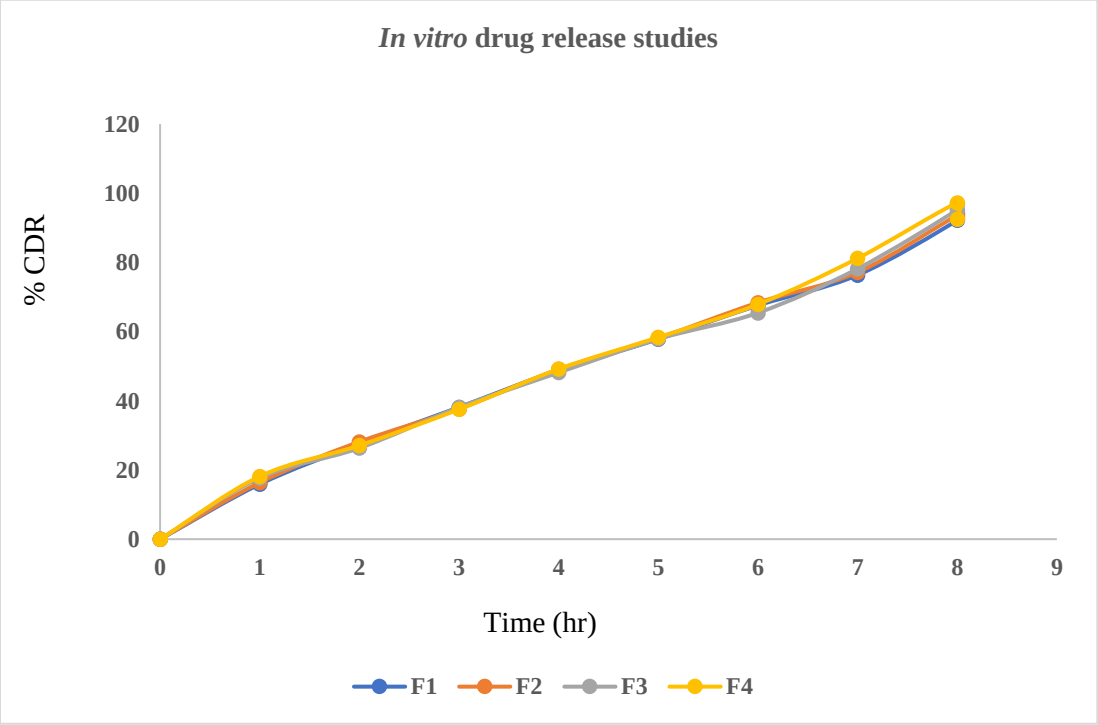

Fig-5: *In vitro* drug release studies of (F1-F4) formulation

Stability studies:

There was no significant change in physical and chemical properties of the Niosomal formulation F-4 after 3 months. Parameters quantified at various time intervals were shown.

Table5: Results of stability studies of optimized formulation F-4

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	**25^{0}C/60%RH % Release**	97.18	96.58	95.78	94.66	**Not less than 85 %**
F-4	**30^{0}C/75% RH % Release**	97.18	96.52	95.53	94.50	**Not less than 85 %**
F-4	**40^{0}C/75% RH % Release**	97.18	96.20	95.16	94.52	**Not less than 85 %**

4.CONCLUSION

Bilayer vesicles can be prepared with the combination of non-ionic surfactants and cholesterol in order to efficiently entrap Lemborexant. The IR spectra of all studied niosomes revealed that Lemborexant was entrapped in the vesicles. Nonionic surfactants and cholesterol these vesicles were thermally stable compared to Lemborexant able to efficiently entrap Lemborexant and the membrane was more deformable and yet stable. A higher Lemborexant entrapment was observed with non-ionic surfactant/cholesterol at molar ratios, and the maximum Lemborexant entrapment was observed with tween 40, as non-ionic surfactant. The role of these Lemborexant niosomes, obtained in this study, can only be settled following future in vitro drug release studies.

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