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Preparation And Evaluation of Melatonin Solid Lipid Nanoparticles for Targeted Drug Delivery to The Brain

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Abstract

Melatonin has low solubility and permeability, which result in limited and variable bioavailability; its low stability makes it difficult to develop stable aqueous liquid formulations. The Melatonin solid lipid nanoparticles were created using the Sonicator to apply ultrasonic energy during the emulsification solvent evaporation process. The numerous formulations with varied drug-lipid and surfactant ratios were analyzed and improved. Melatonin solid lipid nanoparticles containing soy lecithin were created using the solvent evaporation method, then the particle size was decreased by sonication. Particle size, surface morphology by SEM, drug excipient compatibility by FTIR, and in-vitro drug release experiments were used to characterise the produced nanosuspensions. The formulation with the best encapsulation efficiency was (F-3) A drug encapsulation effectiveness of up to 83.56% has been attained in this study. It was discovered that the efficiency of encapsulation improved along with the soy lecithin content.

Keywords

Melatonin drug, solid lipid Nano Particles, solvent evaporation technique, lipid, FTIR, invitro drug release

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1.INTRODUCTION

An alternate carrier system to conventional colloidal carriers such emulsions, liposomes, and polymeric micro and nanoparticles is the solid lipid nanoparticle (SLN), which was first introduced in 1991.[1] As an innovative colloidal drug carrier for intravenous applications, nanoparticles synthesized from solid lipids are gaining significant attention. They have been suggested as an alternate particulate carrier system.[2]Sub-micron colloidal carriers, or SLN, have a size between 50 and 1000 nm and are made of physiological lipid that has been disseminated in water or an aqueous surfactant solution. Because of their potential to enhance the efficacy of pharmaceuticals, SLN are appealing due to their distinctive qualities, which include their tiny size, vast surface area, high drug loading, and phase interaction at the interface.[3] Phospholipids are a crucial component of lipid and lipid-based drug delivery systems due to their range of characteristics, including their amphiphilic nature, biocompatibility, and multifunctionality.[4] However, the complex manufacturing process, low percentage entrapment efficiency (% EE), and challenging large-scale manufacture of liposomes, lipospheres, and microsimulation carrier systems, as well as their other shortcomings, have led to the development of the SLN delivery system.[5]SLNs typically have a spherical shape with a diameter between 50 and 1000 nm. Lipids, which are solid at room temperature, emulsifiers, and occasionally a combination of both, active pharmaceutical

ingredients (APIs), and a suitable solvent system are the main components of SLN formulations.[6] Drug delivery systems based on nanocarriers can be divided into different categories according to factors like administration method, degree of degradation, etc. Nanoparticles for protein peptide delivery, oral, ophthalmic, and topical administration, as well as parenteral administration, are all forms of administration that can be used.[7]

2.1 MATERIALS

Melatonin was collected as a gift sample from Hetero laboratories, Hyderabad polymers and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY

Formulation development

Table 1: Formulation Table

Ingredients	F1	F2	F3	F4
Melatonin	10	10	10	10
Phosphatidylcholine	500	500	500	500
Poloxamer 407	100	200	300	400
Solvent (Methanol)	10	10	10	10
Chloroform	20	20	20	20

Drug excipient compatibility studies[8]

FTIR analysis was performed in order to study the compatibility of ingredients used in the preparation of nanoparticles, using a Shimadzu FTIR spectrophotometer (Prestige21, Shimadzu Corporation, Kyoto, Japan).melatonin and Excipients their mixture with ratio (1:1) was evaluated using FTIR spectrophotometer using potassium bromide disc technique where 1mg of the sample is mixed with 100 mg of dry powdered KBr; the mixture is pressed into a transparent disc and was inserted in the apparatus for IR scan.

Evaluation of Melatonin loaded nanoparticles [9,10,11,12]:

Particle size:

All of the generated batches of nanoparticles were observed under a microscope to establish their sizes. The average size of the nanoparticles was determined by measuring the size of each batch's nanoparticles in a small drop of nanoparticle dispersion on a slide.

SEM analysis

The morphology of nanoparticles was examined using the scanning electron microscope (SEM, Hitachi, Tokyo, Japan). After being properly diluted (1:100) in double-distilled water, Melatonin -freeze-dried SLNs were added to a drop of the nanoparticle formulation and left to air dry. The sample was then observed under various magnifications and a 15,000-volt accelerating voltage. The imaging was performed in a high vacuum.

Drug encapsulation efficiency:

A set volume of the SLNs dispersion (10 ml) was poured into a centrifuge tube at room temperature, and it was spun at 18,000 rpm for 20 minutes (Remi Instruments Pvt. Ltd, India). The drug's absorbance in the supernatant was measured spectrophotometrically at a maximum wavelength of 243 nm after the lipid component was removed (Shimadzu 1800, Japan).

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug loaded}} \times 100$$

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

Utilizing the dialysis bag approach, in vitro release tests were carried out. Prior to the release trials, the dialysis membrane (molecular weight cutoff between 12,000 and 14,000) was immersed in double distilled water for an overnight period. As releasing media, phosphate buffer pH 6.8 and hydrochloric acid (0.1 N) were also employed. A donor compartment and a receptor compartment make up the experimental unit. A boiling tube that was cut open at one end and tied with a dialysis membrane at the other end serves as the donor compartment, into which 3 ml of SLN dispersion was injected for the release research. The receptor compartment is made up of a 250 ml beaker that contains 100 ml of release media and was kept at a temperature of 37 0.5 °C. Every 3 ml sample was taken out of the receiver compartment and replaced with the same amount of release medium at the 1, 2, 3, 4, 5, 6, 7 and 8h time periods. The collected samples were appropriately diluted before being examined at 243 nm with a UV-visible spectrophotometer.

Percentage of drug release was determined using the following formula.

$$\textbf{Perentage drug release} = \frac{\textbf{Da}}{\textbf{Dt}} \times \textbf{100}$$

Where, Dt = Total amount of the drug
Da = The amount of drug released

Stability studies:

Over the course of 90 days, the stability of Melatonin nanoparticle dispersion in screw-capped glass vials was assessed. Six samples were split into two groups and kept at 4°C and 25°C, respectively. At the end of the 90 days, the amount of drug leaking from nanoparticles and the average particle size of the samples were calculated.[13]

3.RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

FT-IR Spectra of Melatonin and excipients were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Drug and lipids. It also confirmed that the stability of drug during encapsulation process.

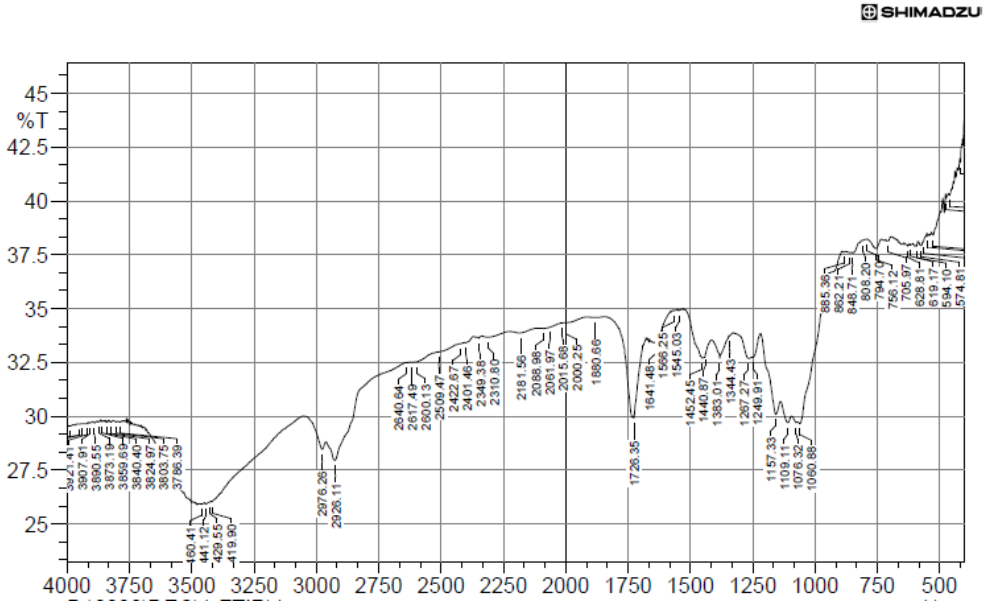

Fig 1: FTIR spectra of Melatonin

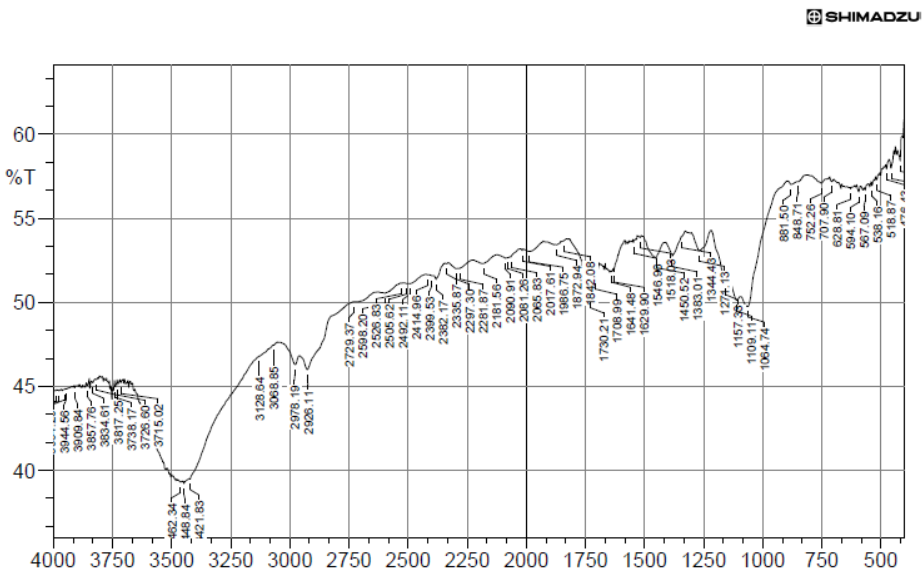

Fig 2: FTIR Spectra of physical mixture of drug and excipients

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

Particle size:

With an increase in lipid concentration, the particle size increased. based on entrapment effectiveness and particle size distribution.

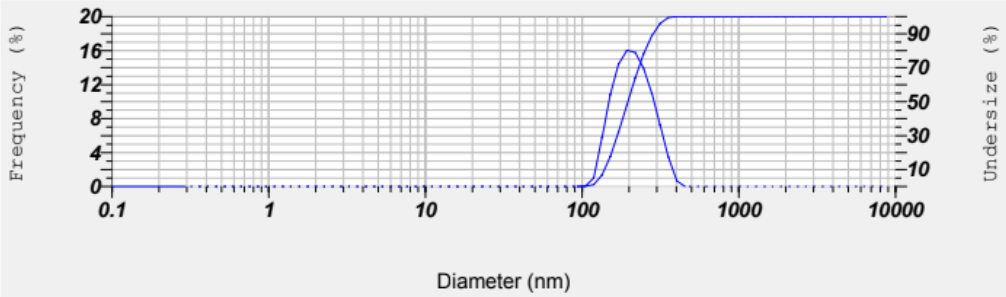

Fig 3: Particle size of optimized formulation

Surface morphology:

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

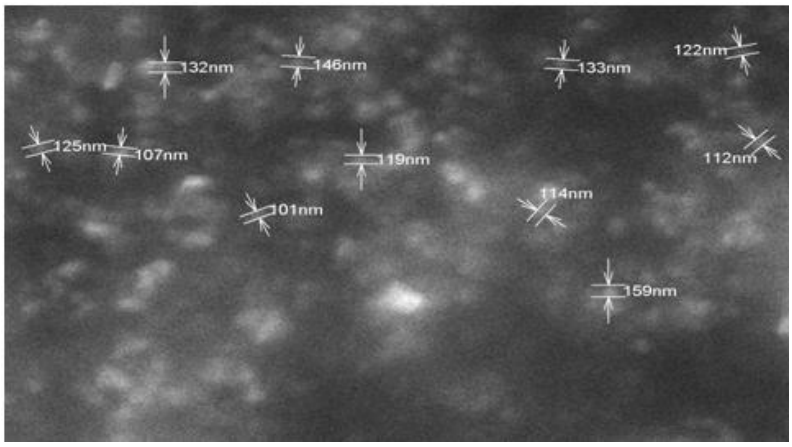

Fig 4: SEM analysis of Optimized Solid lipid nanoparticle

Drug entrapment efficiency:

Optimizing the lipid concentration to be used in the creation of solid lipid nanoparticles was the first step of the work plan. Based on the particle size and entrapment effectiveness of the discovered solid lipid nanoparticles, the lipid content was optimized.

Table 2: Evaluation Studies of Prepared solid lipid nanoparticles: Entrapment Efficiency and Particle size

Batch No	Particle size (nm)	Entrapment Efficiency (%)
F1	182	82.36
F2	118	81.24
F3	107	83.56
F4	110	80.19

In vitro drug release studies

Using a dialysis membrane and a pH 7.4 buffer, the in vitro diffusion investigations were carried out for eight hours. This resulted from the drug's release from the surface of the solid lipid nanoparticles. Later, for 8 hours, a consistent and gradual medication release was seen. The lipid and surfactant ratio in the F3 formulation was shown to be the most effective one.

Table 3: *In vitro* drug release profiles of SLN (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	23.72	26.36	25.18	28.98
2	35.42	37.89	37.82	35.16
3	43.56	41.29	44.25	43.25
4	53.56	54.59	52.95	50.92
5	60.16	62.49	64.50	61.25
6	70.42	79.86	75.53	74.88
7	81.93	82.63	86.91	85.52
8	93.52	94.28	96.86	94.69

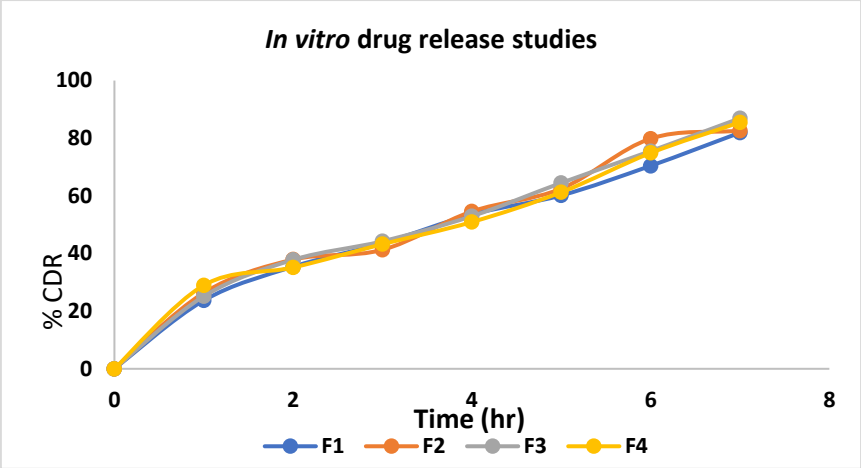

Fig 5: Drug release for all formulations

Stability studies:

After three months, the physical and chemical characteristics of the nanoparticles of formulation F-3 had not significantly changed. The parameters quantified at various times were displayed.

Table 4: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	**25^{0}C/60%RH % Release**	96.86	95.81	94.60	93.67	**Not less than 85 %**
F-3	**30^{0}C/75% RH % Release**	96.86	95.75	94.28	93.50	**Not less than 85 %**
F-3	**40^{0}C/75% RH % Release**	96.86	95.46	94.20	93.56	**Not less than 85 %**

4.CONCLUSION

The current study suggested a unique Melatonin solid lipid nanoparticle formulation for regulated release. Investigation into the solid lipid nanoparticles' production, characterization, and in-vitro release was done. The numerous formulations with varied drug-lipid and surfactant ratios were analyzed and improved. A drug encapsulation effectiveness of up to 83.56 % has been attained in this study. Melatonin solid lipid nanoparticles containing soy lecithin were created using the solvent evaporation method, then the particle size was decreased by sonication. formulations using solid lipid nanoparticles performed well in terms of medication content and encapsulation effectiveness. This shows that the formulation procedure was suitable and reproducible in nature, and it provided a good yield. The formulation with the best

encapsulation efficiency was (F-3) It was discovered that the percentage of encapsulation efficiency rose along with the soy lecithin concentration. According to the method described, permeation studies with dialysis membrane were conducted. The in vitro drug release profiles of all the formulations indicated an initial burst effect, followed by a gradual drug release. The formulations demonstrated good drug release from the lipid. These solid lipid nanoparticles contained more Melatonin and released it more quickly.

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