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IMPROVED ORAL DELIVERY OF AGOMELATIN FROM MALTODEXTRIN BASED PRONIOSOME POWDERS

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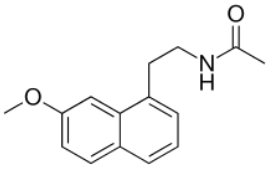
ABSTRACT

The current research was designed to improve the oral delivery of agomelatine by loading into maltodextrin based proniosome powders. proniosome powders proved to be the potential carriers for efficient oral delivery of lipophilic or amphiphilic drugs. These 'proniosomes' minimize problems of niosome physical stability such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing. The proniosome powders were fabricated by various ratios of span 60 and cholesterol and evaluated for micromeritic properties and the results indicates adequate micrometric properties. The formulation containing equimolar ratio of span 60 and cholesterol showed smaller vesicle size, high surface charge and entrapment efficiency. The formation of niosomes and surface morphology of optimized proniosome formulation was evaluated by optical and scanning electron microscopy, FT-IR, differential scanning calorimetry, and powder X-ray diffraction studies performed to understand the solid state properties of the drug reveal the absence of chemical interaction, drug transformation from crystalline to amorphous and molecular state. The drug release performance in vitro carried out in both simulated gastric and intestinal fluid demonstrate improved dissolution characteristics compared to pure drug.

INTRODUCTION:

Agomelatine is a melatonin receptor agonist MT1 and MT2 and a 5-HT2C receptor antagonist. Agomelatine resynchronises circadian rhythms in animal models of delayed sleep phase syndrome. By antagonizing 5-HT2C receptors, it increases noradrenaline and dopamine release specifically in the frontal cortex. Therefore, it is sometimes classified as a norepinephrine–dopamine disinhibitor. It has no influence on the extracellular levels of serotonin. Agomelatine has shown an antidepressant-like effect in animal models of depression as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety. In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset. Low <5% Absolute bioavailability at the therapeutic oral dose and the inter individual variability is substantial. The chemical structure of agomelatine is very similar to that of melatonin. Where melatonin has an NH group, agomelatine has an HC=CH group. Thus melatonin contains an indole part, whereas agomelatine has a naphthalene bioisostere instead.



Structure of Agomelatine

According to BCS classification, the class II drugs have low solubility-high permeability and their absorption is dissolution rate limited. Several researchers are adopted for enhancing the dissolution behavior of BCS class II drugs by particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, increasing the surface area by micronization or nanonization, spray drying and microencapsulation [1].

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% NCEs developed in pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for formulation scientist. Any drug to be absorbed must be present in the form of solution at the site of absorption. Due to its low aqueous solubility and poor bioavailability. However, not yet reported relevant studies for oral administration of agomelatin proniosomal powders. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs and can incorporate both hydrophilic and lipophilic drugs [1-2].

MATERIALS AND METHODS:

Materials:

Agomelatine was gifted from MSN Laboratories, INDIA, Maltodextrin was gifted by Sigma Aldrich Chemicals, Hyderabad, Cholesterol and Span 60 was purchased from SD Fine Chemicals, Mumbai. Methanol and Chloroform were purchased from Merck Specialties Pvt. Ltd, Mumbai.

Methods:

HPLC analysis of agomelatin

The samples were assayed for agomelatin by using a stability-indicating HPLC method reported earlier [3]. The analysis of the drug was carried out on waters instrument with PDA waters 2998 detector with Empower software and hamilton syringe with 20 µL, and a Lichrospher C18 column (150×4.6mm, 5µm). Isocratic elution was carried out at a flow rate 1 mL/min (UV detection- 236 nm). The mobile phase consisted of acetonitrile: methanol: water (55:25:20, v/v/v). The retention time was found to be 4.2 min. Aliquots of 20 µL of each sample were spiked onto the column. The assay was linear (r2 = 0.9988), in the concentration range of 1–10 µg/mL with the lowest detection.

FORMULATION OF PRONIOSOMAL POWDER:

The thin film deposition method was adopted for formulation of proniosome powders reported in literature [6]. Table1 represented that the different proniosomal formulations compositions. accurately weighed quantities of lipid mixture 100 µM of span 60, cholesterol and soyalecithin at various ratios and drug (25 mg) were dissolved in 20 mL of solvent mixture containing chloroform and methanol (2:1).The resultant solution was transferred into a 250 mL RB flask and maltodextrin was added to form slurry. The flask was attached to a rotary flash evaporator (Laborota 4000,Heidolph, Germany) and the organic solvent was evaporated under reduced pressure at a temperature of 45±2°C. After ensuring the complete removal of solvent, the resultant powders were further dried overnight in a vacuum oven at room temperature so as to obtain dry, free-flowing product. The obtained proniosome powders were stored in a tightly closed container at 2-8°C for further evaluation and characterization. The composition of different proniosomal formulations is represented in (Table1).

CHARACTERIZATION:

Morphological evaluation

The morphology of the niosomes was examined by optical microscopy. The proniosomes were hydrated with 7 mL of phosphate buffered saline (pH 7.4); mixed gently and final volume was adjusted to 10 mL with the same vehicle. The niosomes formed after hydration was observed at a magnification of 450X through an optical microscope (Coslabsmicro, India) and photomicrograph was taken (Fig-2)[6].

Micromeritic properties

The proniosome powder flow properties were calculated through measuring the Carr's

compressibility index, Hausner's ratio and Angle of repose. For determination of angle of repose the conventional fixed funnel method was adopted. For calculating the bulk and tapped density, Carr's compressibility index and Hausner's ratio of the proniosome powders bulk and tapped density apparatus were used.

Number of vesicles: The ample vesicle formation is influenced by the composition of proniosome formulation. The freshly prepared niosomes after hydration of proniosome powders were counted using a hemocytometer under optical microscope. The formula given below helps to find the number of vesicles per cubic mm. Total no. of vesicles per mm^3= [(total no. of vesicles counted × dilution factor × 4000)/ total no. of squares counted]

Determination of vesicle Size, Zeta Potential and Drug Entrapment efficiency

The mean size, size distribution and zeta potential (ZP) of proniosomes was determined photon correlation spectroscopy using Zetasizer NanoZS90. The proniosomal powders were hydrated with phosphate buffer (pH 7.4) and subjected to bath sonication for 3 min and the resultant dispersion was used for the determination of size, zeta potential. Each sample was diluted to a suitable concentration with phosphate buffer pH 7.4. Size analysis was performed at 25ºC with an angle of detection of 90ºC. Size, polydispersity index of proniosomes and their mean zeta potential values (±SD) were obtained from the instrument. The percentage drug entrapment of agomelatin proniosomes was calculated after determining the amount of free drug by dialysis method[38]. Accurately weighed 100mg of proniosome powders were hydrated in 10mL of phosphate buffer pH 7.4.The dialysis was performed by adding the hydrated proniosomal dispersion to a dialysis tube (donor compartment) and then dipping the tube into a receptor compartment i'e beaker containing 200 mL of PBS pH 7.4 on a magnetic stirrer, the magnetic stirrer was maintained at a contestant speed of 100 rpm, temperature of the receptor compartment was maintained at 37±2º C for 3 hours. After 3 hours, the solution in the receptor compartment was estimated for free drug at 236 nm by using HPLC[27]. The percentage drug entrapped (PDE) was determined by Ultra-centrifugation. The liposomal formulations were subjected for ultracentrifugation (ultra Centrifuge – Remi laboratories, Mumbai, India) at 5000 rpm for 15 min in an ultracentrifuge in order to separate the entrapped drug from the free drug. Then the clear supernatant was separated and analyzed for drug content after appropriate dilution by HPLC. This indicates amount of free drug. The liposomal pellet was redispersed in chloroform and analyzed for drug content after appropriate dilution by HPLC. This indicates amount of drug entrapped. The entrapment capacity of proniosomes was calculated as follows Percent Entrapment =Total entrapped Drug – free Drug /Total DrugX100

***In-vitro* dissolution study**

USP type II (paddle) dissolution apparatus was selected for *In vitro* dissolution study of agomelatin proniosomal powders and pure drug [6]. The volume of dissolution medium used was 900 mL and maintained at a temperature of 37 ± 0.5ºC with paddle speed set at 50 rpm throughout the experiment. An aliquot of 5 mL was collected at predetermined time intervals 15, 30, 60min and replaced with fresh dissolution medium to maintain constant volume and sink condation[6]. Samples were analysed for agomelatin using HPLC at 236 nm.

Solid State Characterization Studies:

Differential scanning calorimetry (DSC):

The molecular state and thermochemical properties of the drug in optimized formulations of proniosomes and proliposomes was evaluated by performing DSC analysis of pure drug, maltodextrin and optimized proniosomal formulations. The thermogram curves of the samples were obtained by a differential scanning calorimeter (DSC Q200, TA Instruments, U.S.A.). About 2 mg of a test sample was weighed using a microbalance (Satorius), the sample was placed in an aluminium pan with a lid and the pan was sealed. An empty aluminium pan with its lid was used as a control. The samples were purged with pure dry nitrogen at a flow rate of 70 mL/min. The temperature ramp speed was set at 10 º C/ min and the heat flow was recorded from 30 to 230 º C. The temperature

scale was calibrated with high purity standards.

Powder X-ray diffractometry:

The physical states of Agomelatine, Physical mixture and optimized formulations of proniosomes were obtained using X-ray diffractometer. Diffraction patterns were obtained using a BRUKER D8 FOCUS High Resolution Powder Diffractometer (BRUKER AXS, Germany) equipped with a scintillation counter detector with a divergent beam. This beam employed a CuKα radiation source with a wavelength of λ=1.5418 containing 2 mm slits over a range of 10-50º 2-θ. X-Ray diffraction data were collected at room temperature and scanned with a step size of 5º 2-θ and a dwell time of 12 min at each step.

Fourier transforms infrared (FTIR) spectroscopy:

In order to investigate the potential interactions between the ingredients used, FTIR spectroscopy was performed using FTIR spectroscope. Samples analyzed were Agomelatine, physical mixture [span 60, cholesterol and maltodextrin] and optimized formulations of proniosomes. A small amount of sample was directly scanned over a range from 4000 to 400 wave numbers (cm^{-1}).

Scanning electron microscopy (SEM):

Shape and surface morphology of the optimized formulations of proniosomes was studied using scanning electron microscopy (S-400, Hitachi, Japan). The samples were firmly placed on a specimen stub made of brass with a two sided sticky tape. It was build conductive via coating with platinum (6 nm/min) in a vacuum (6 Pa) utilizing a Hitachi Iron Sputter (E-1030) at 15 mA for a period of 30 sec.

RESULTS AND DISCUSSIONS

Colloidal carrier drug delivery approach of proniosome has resolved many stability issues pertaining to aqueous niosome dispersions. The advantages, noisome dispersions suffer from stability problems like aggregation, hydrolysis, drug leakage and production scale up. Agomelatin loaded maltodextrin based proniosomes with span 60 as nonionic surfactant prepared by a slurry reported in the literature [7, 8]. The various ratios of cholesterol and span 60 were evaluated for the optimum composition of span 60 to cholesterol ratio by keeping the total lipid constant. The span 60 having high phase transition temperature, Highest phase transition temperature of span having high entrapment could be observed as reported in the literature [15]. Span 60 was selected as choice of nonionic surfactant due to the high phase transition temperature, it intern led's to high entrapment efficiency, to facilitate stable vesicle formation and to improve the oral delivery of agomelatin from proniosomes [20]. Maltodextrin had porous structure and high surface area and easy adjustment of amount of carrier required to support the surfactant and several researchers reported that maltodextrin based proniosomes proved to be the potential carriers for efficient oral delivery poorly soluble drugs.

Morphological evaluation of prepared proniosome powders by optical microscope

The niosomes were prepared from proniosome powder after hydration and gentle shaking with phosphate buffer pH 7.4 as shown in Fig. 2 [A-C]. Vesicles are formed after gentle agitation with and all vesicles are in spherical shape. The morphology of the proniosomes was evaluated by optical microscopy.

Micromeritic properties

The dose uniformity and ease of filling into container is dictated by the powder flow properties. The micromeritics of the proliposome powders is vital in handling and processing operations. In general, three types of flow measurements can be used to evaluate the nature of powder flow i.e. angle of repose; Carr's index and Hausner's ratio and the results were depicted in Table 3. The smaller the value of angle of repose, lesser the internal friction or cohesion between the particles and greater the flow characteristics and vice-versa. It is apparent from the results that small angle of repose (<20°) assure good flow properties for proliposome powder formulations.

Table No 1: Formulation Table for Agomelatin Proniosomes

Ingredients	APN1	APN2	APN3	APN4	APN5	APN6	APN7
Drug (mg)	25	25	25	25	25	25	25
Span 60(mg)	175	150	125	100	75	50	25
Cholesterol(mg)	25	50	75	100	125	150	175
Maltodextrin (mg)	150	150	150	150	150	150	150
Chloroform and Methanol (mL) (2:1)	20	20	20	20	20	20	20

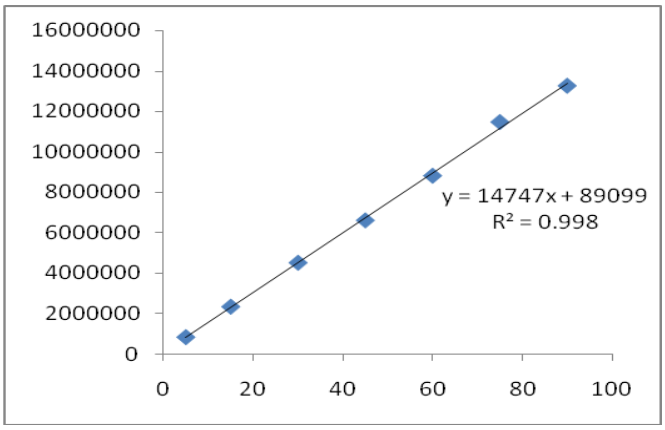
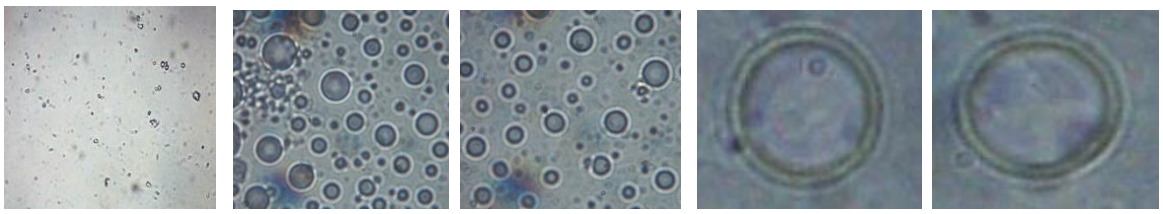


Fig. 1 : Standard Graph of Agomelatin



A B C

Fig.2. Optical microphotographs showing (A) proniosome powder, (B) formation of vesicles on maltodextrin after hydration with phosphate buffer (pH 7.2), (C) Niosome dispersion from proniosome powder (APN4) upon gentle agitation

Table 3: Micromeritic properties of various proniosome powder formulations.

Formulation	Angle of repose (θ)	Compressibility index	Hausner's ratio
APN1	17.0±0.20	10.2±0.06	1.06±0.15
APN2	18.1±0.25	11.1±0.06	1.16±0.19
APN3	19.2±0.30	14.5±0.29	1.22±0.10
APN4	18.0±0.35	15.2±0.33	1.17±0.20
APN5	19.0±0.26	15.3±0.23	1.20±0.12
APN6	19.8±0.10	16.7±0.26	1.22±0.14
APN7	19.3±0.25	16.9±0.40	1.12±0.09

Table No 4: Particle size of proniosome formulations

S. No	Formulation	size (nm)	PI	Zeta potential (mV)	Entrapment efficiency ± SD (%)	No. of vesicles per mm^3 x 10^3
1	APN1	424±22	0.359	35.1 ± 3.8	65.90±0.24	3.00
2	APN2	333±10	0.282	25.6 ± 4.2	68.10±1.32	3.80
3	APN3	255±05	0.265	33.3 ± 2.1	77.02±0.42	3.21
4	APN4	200±11	0.165	42.4 ± 2.8	85.60±0.20	4.00
5	APN5	334±28	0.283	33.1 ± 3.0	72.50±0.24	3.23
6	APN6	402±15	0.320	29.0 ± 5.2	67.00±1.48	3.41
7	APN7	450±25	0.352	25.5 ± 2.6	60.00±2.18	3.70

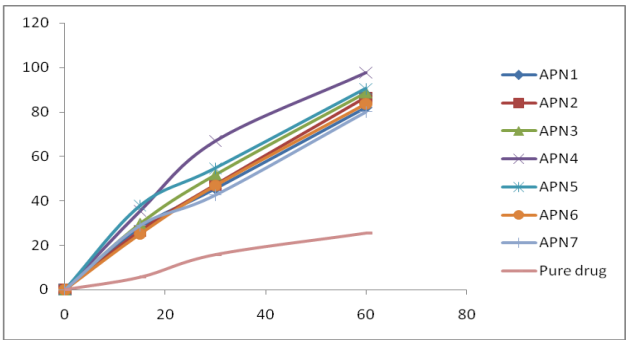


Fig.3A: Dissolution profile of Agomelatin from proniosome powder formulations in pH 1.2 media

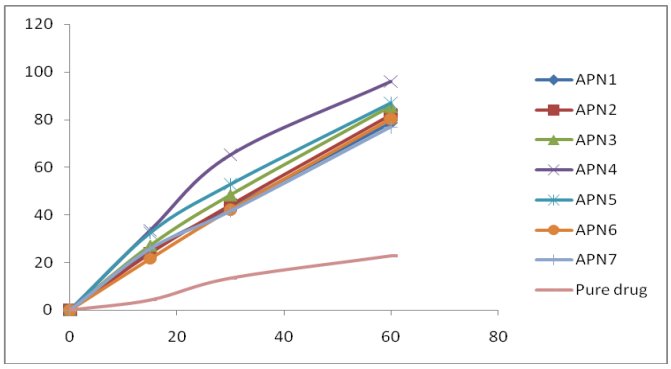


Fig.3B: Dissolution parameters of Agomelatin from proniosomal powder in pH 4.5 Phosphate buffer

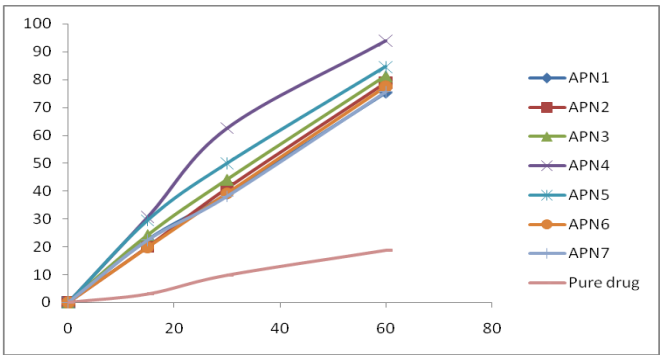


Fig.3C: Dissolution profile of Agomelatin from proniosomal powder in pH 6.8 Phosphate buffer

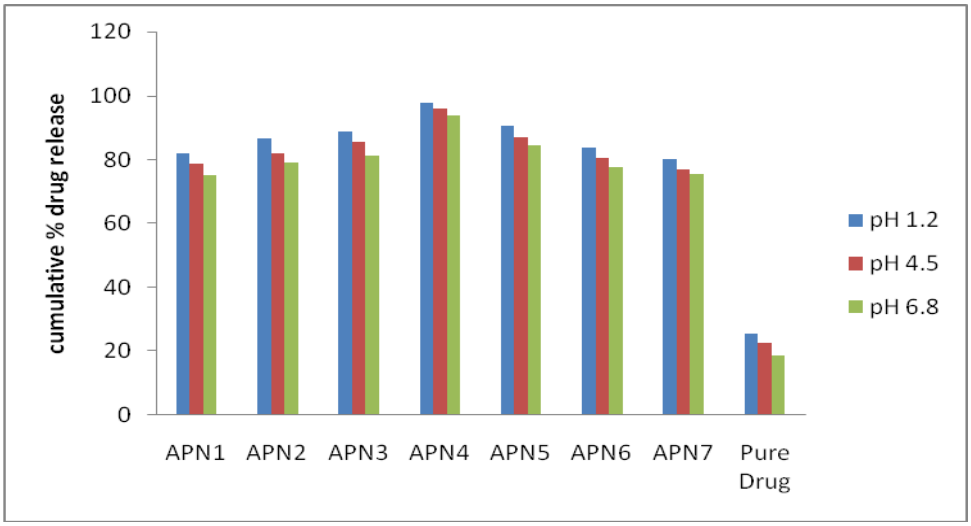


Fig 4: Drug Release profiles of various Proniosome formulations of agomelatin after 60 min

In addition to angle of repose, Carr's index and Hausner's ratio were also less than 17 and 1.23 respectively ensuring acceptable flow for proniosomes powder formulations and results are reported below table (Table 3).

Characterization studies

Formation of vesicle was observed in hydrated niosomes, Results of average vesicle size and distribution were calculated for count and distribution. Among all the formulations, The proniosome formulation containing span 60 and cholesterol at a ratio of 1:1 (APN4) has observed good number of vesicles which is min well correlation with the size and entrapment efficiency results. Vesicle size and size distribution is an important parameter for the vesicular systems [25]. The mean size of the vesicles was in the range of 200–450 nm. Small value of polydispersity index (PI) (<0.1) indicates a homogenous population, while a PI (>0.3) indicates a higher heterogeneity. The zeta potential and entrapment efficiency of the formulations was between 25.5 and 35.5 mV and 60– 86%, respectively. Determination of entrapment efficiency is an important parameter in case of proniosome as it majorly effects the drug release. Entrapment efficiency is expressed as the fraction of drug incorporated into proniosome relative to total amount of drug used. The size and surface charge of the vesicles seems to be dependent on the cholesterol concentration. We could notice small sized vesicles with high zeta potential when equimolar ratio of formulation containing span 60 and cholesterol (APN4) and also (Table 4). The haemocytometer was used for counting of hyderated niosomes by optical microscope. The niosomes in 80 small squares were counted, calculated and tabulated (Table 4).

***In – vitro* Dissolution studies**

The dissolution profiles of proniosomes formulation were shown in figure 3[A-C]. The amount of agomelatin released from proniosomes was ranging between 18 to 96% in 60 min and was higher compared to control (18 %) (Table 5 [A-C]) at all multimedia dissolution. The dissolution efficiency of insoluble drug agomelatin has been significantly improved in proniosomes (Table 5 [A-C]). This might be due to the improved solubility of agomelatin by non-ionic surfactant molecules. However, there was no significant change in the drug release in dissolution with different proliposome formulations. The proniosome formulation (APN4) has higher drug release of agomelation compared to remaining proniosome formulations. The surface area available for dissolution of drug molecules is may be higher in the proniosome powder formulations. APN4 formulation has selected as optimized formulation which is used for further study based dissolution results. The dissolution profiles and cumulative dissolution of agomelatin from proniosome powder formulations (APN1-APN7) and control (pure drug) in pH 1.2, pH 4.8 and pH 6.8 are represented in Figs. 3[A-C], respectively.

Solid state characterization

Differential scanning calorimetry, Fourier transform infrared spectroscopy, X-ray powder diffraction and Scanning electron

microscopy used evaluation of the molecular interactions between drug and carrier. The DSC studies were conducted for agomelatine, unloaded proniosomes, loaded proniosomes,. The DSC thermogram of agomelatine, indicated a sharp endotherm at 111.2°C [Fig No 5]. The disappearance of drug peak in DSC thermogram of proniosome over the melting range of agomelatine explains the transformation of the physical state of the drug from crystalline to amorphous. PXRD studies were carried out for pure drug, maltodextrin, optimized formulations APN4. The graphs [Fig No 6] of pure drug, Maltodextrin and optimized formulation APN4 indicate that the characteristic agomelatine peak were reduced in intensity or absent when compared to proniosomal formulation. The drug peak at 18.6 2-Theta was seen in proniosomal APN4 peak at 18.8 2-Theta indicating that there may be presence of small traces of unentrapped drug. The disappearance of peak in proniosomal formulation unravels the transformation of the physical state of the drug from crystalline to amorphous. FT-IR spectroscopy sample of agomelatine, physical mixture containing span 60, cholesterol and optimized (APN4) formulations of proniosomes were subjected to FT-IR analysis. A spectrum was collected for each sample within the wave number region 4,000-400cm-^{1}. The optimized proniosome(APN4) formulation exhibit characteristic peaks at 1047.12 cm^{-1},1087.96 cm^{-1} (C-N Stretch (alkyl)),1249.84 cm^{-1},1302.02 cm^{-1} (C-N Stretch (aryl)),1047.12 cm^{-1} (C-O-C Stretch), 1047.12 cm^{-1}, 1087.96 cm^{-1} (Fig. 6C). All these peaks have appeared in physical mixture at 1047.12 cm^{-1},1087.96 cm^{-1} (C-N Stretch (alkyl)),1249.84 cm^{-1},1302.02 cm^{-1}(C-N Stretch (aryl)),1047.12 cm^{-1} (C-O-C Stretch),1047.12 cm^{-1},1087.96 cm^{-1}(Fig. 6B), indicate no chemical interaction between agomelatin, physical mixture, and optimized (APN4) formulations. In all proniosome powders Maltodextrin was chosen as a carrier. It is evident from the SEM images that the maltodextrin have porous surface with high surface area which enables it to be used as an efficient carrier for the lipid loading (Fig. 7). The SEM images reveal the absence of native crystalline structures of agomelatin in the proniosome powder (Fig. 7C).

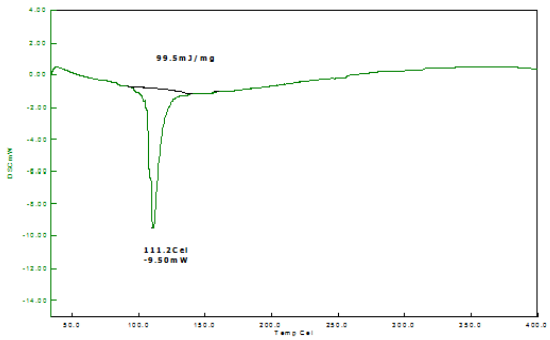


Fig. 5A. *DSC thermogram of Agomelatin*

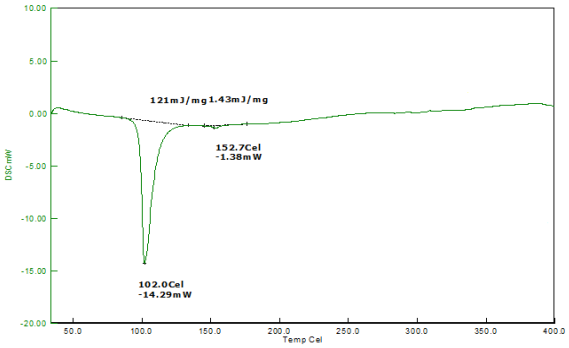


Fig. 5B. *DSC thermogram of unloaded proniosomes*

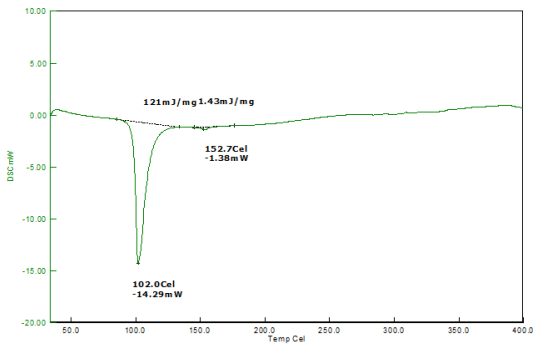


Fig. 5C. *DSC thermogram of optimized proniosomes APN4*

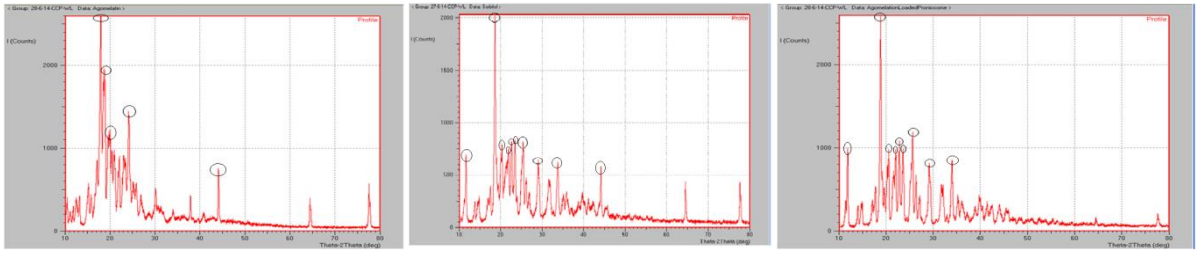


Fig.**5. [A]***Powder X-ray diffraction pattern of Agomelation, [B]Maltodextrin, [C]optimized formulation APN4*

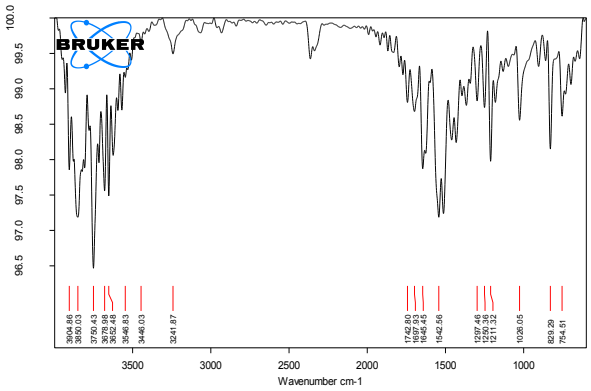


Fig.6. [A] ***FT-IR spectra of pure Agomelatine,***

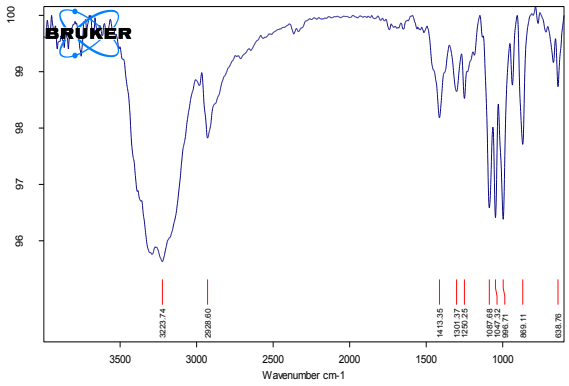


Fig.6. [B] ***FT-IR spectra of physical mixture***

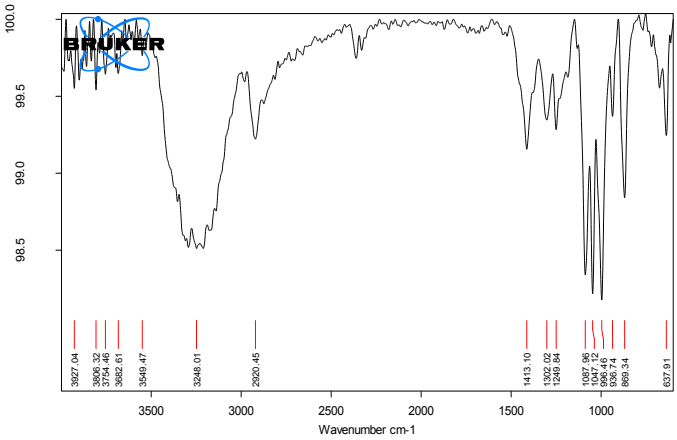


Fig.6. [C] ***FT-IR characteristic peaks of physical mixture***

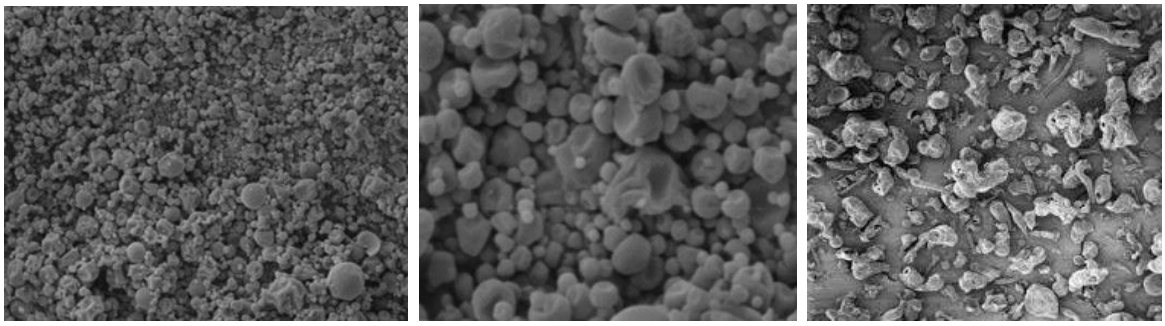


Fig.7. SEM images of (A) Agomelatin (B) Maltodextrin (C) Proniosome powder (APN4).

CONCLUSION

Systematic studies were conducted with various concentrations of cholesterol, maltodextrin and span 60 to optimize proniosomal powder. All formulations were evaluated for the different Physico-chemical characteristics. Formulated proniosomes gave satisfactory results for various evaluation parameters like particle size, Zetapotential, Powdered XRD, DSC, Scanning electron Microscopy, FTIR entrapment efficiency and In vitro Dissolution studies. The optimized proniosomal system could be screened with in-vivo studies to evaluate efficacy of the system.

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