ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Differential Scanning Calorimetry as a tool to establish formation of Lipid Nanoparticles (NLC and SLN)

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ABSTRACT

This study was carried out to assess impact of addition a liquid lipid on the crystallinity of the product and their pharmaceutical implication. The formation of NLC/SLN with GMS and OA was investigated by DSC. Protection of loaded drug in a physically stable formulation is the major advantage NLC/SLN provides which is lacking with other colloidal systems such as liposomes. DSC had been employed to assess physical nature of formulations. Physical state in form of solid is necessary for NLC/SLN lipid matrix. DSC studies had revealed that all formulations possess melting point over 40ºC confirms solid state at room temperature. Shift in melting events in NLC was due to the interaction of solid lipid with the oil and the drug or due to the nanometric size range of the formulation which had a huge surface area per volume.

Keywords: NLC, SLN, Lipid nanoparticles, DSC, Drug loading

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ISSN: 0975-8585

INTRODUCTION

Drug delivery beyond conventional system has been continuously conceptualized and developed into dosage form ever since concept of magic bullet floated among the pharmaceutical technocrats and drug delivery scientists. It was first come in to reality polymer implants and their reservoir kinds of systems were developed in the beginning of 20th century. These polymeric systems are capable of controlling the release rate of drug but targeting to specific site of action is still not possible. Moreover, their size is too not suitable for intravenous administration.

The hypothesis that miniaturization will play a major role in pharmaceutical and pharmaceutical biotechnological products given in the start of last century come to reality as tremendous research and growth in nano structures results from their numerous potential applications in various segments of pharmaceutical and healthcare system [1]. One such area of exiting application potential is lipid based nano-scale particulate system for drug delivery synthesized by the colloidal route.

In order to overcome the drawbacks associated to the traditional colloidal systems such as microemulsions, liposomes and polymeric nanoparticles, lipid colloidal has been received a lot of attention. SLN (Solid lipid nanoparticles) were developed at the beginning of the nineties [2,3]. It consist of a matrix composed of a physiologically tolerated lipid component having property of being solid at both room and body temperatures. They have a mean particle size ranging between 50 nm and 1000 nm [4]. The first patents for SLN were filed in 1991, one by Muller and Lucks [5] describing the production of SLN by high pressure homogenization (HPH), and another by Gasco developed it via microemulsions method [6]. Nanostructured lipid carriers (NLC) were introduced to overcome the problem associated with SLN. During the last ten years different substances have been entrapped into lipid nanoparticles (both SLN and NLC), including both hydrophobic and hydrophilic compound, including labile substances, such as peptides and proteins. A lot of products come to market after their extensive research and clinical study particularly in cosmetic product category. This shows good outcome of lipid based particulate systems as compared to earlier colloidal drug delivery vehicles still facing hurdles in their commercialization.

Pure lipids possess perfect crystal habit (β form) and when used to prepare lipid nanoparticles they exhibit peculiar recrystallization characteristics. After nanoparticles formation crystals are tend to present in less perfect crystalline state with β' modification providing space for drug molecules to be accommodated. During storage these particles tend to arrange in perfect β form with less or limited space for drug molecules thus, drug expulsion is observed. When mixture of a solid lipid with a liquid lipid has been applied for the formation of lipid nanoparticles a different recrystallization behavior has been observed. In this case, after recrystallization particles tend to remains in less perfect or more precisely in imperfect β' form so that drug molecules can be accommodated for longer duration. Moreover, addition of liquid lipid in solid lipid leads to formation of additional space in crystal lattice of this 'impure or mixed lipidic system' than a pure lipid system provide higher drug loading.

Differential scanning calorimetry (DSC) has been employed as a tool to establish crystalline environment of the lipid nanoparticles. Changes in the temperature during DSC analysis provide insight in melting and crystalline behavior in the NLC/SLN formulations and hypothesis behind lipid nanoparticles formation and utility in drug loading and delivery can be established with the techniques like DSC.

MATERIALS AND METHOD

Glyceryl monostearate (GMS), oleic acid (OA) and dithranol were purchased from (Hi Media Pvt. Ltd, India). NLC and SLN were prepared using melt emulsification ultrasonication method. Briefly, 15% of lipid phase containing solid lipid GMS, oil OA, drug dithranol and stabilizer soyPC previously heated at above the melting point of solid lipid was added to surfactant solution containing Tween 80 and Poloxamer 188 preheated at the same temperature as lipid phase. After high speed homogenization resulted hot pre-emulsion was ultrasonicated to form hot nanoemulsion which upon cooling in cold water containing suitable dispersant resulted in NLC dispersion. The dispersion was then freeze dried with 5% sucrose.

DSC was performed in a calorimeter (Mettler Toledos R System, India) using 1-5 mg bulk of lipids, drug, physical mixtures and freeze dried formulations. Heating curves were recorded by transferring amount of different samples to aluminium pans with a scan rate of 5ºC/min from 05ºC to 200ºC using an empty aluminium plate as reference. Peak maxima of the heating curves correspond to the melting points of the samples.

RESULTS AND DISCUSSION

DSC is a tool to investigate the melting and re-crystallization behavior of crystalline materials like SLN and NLC. Figure 1 to 6 shows an over view of melting process of bulk matrix, physical mixtures of formulation components, drug loaded SLN and NLC. The DSC thermograms of different samples revealed their melting peaks as follows:

Bulk GMS – 53.64ºC
Bulk dithranol - 172.45ºC
Physical mixture of SLN components – 49.09ºC
Physical mixture of NLC components - 45.90ºC
Lyophilized drug loaded SLN formulation – 48.10ºC
Lyophilized drug loaded NLC formulation - 42.14ºC

Characterization of degree of lipid crystallinity and lipid modification is necessary for the assessment of quality and stability of NLC/SLN formulations [7,8]. This is very much important in the light of drug loading and its release behavior from the system. DSC has been used extensively to study lipid status on the fact that lipid modifications lead to variation in melting points. Freeze dried formulations were taken to avoid interference of the broad water peak at 100ºC if an aqueous dispersion was employed as sample for DSC [9].

ISSN: 0975-8585

For bulk GMS, the melting process took place with a maximum peak at 53.64ºC but upon addition of drug in physical mixture of SLN components a depression of the melting point to 49.09ºC was observed. This indicates good miscibility of dithranol in melted solid lipid and thus the crystal structure of the GMS is become less crystalline [10]. The melting point depression was more pronounced when physical mixture of lipids (oleic acid content 40% in NLC) and drug was analyzed to a value of 45.90ºC indicated a less ordered crystal lattice with a number of defects in GMS [11]. But NLC formulation melted maximum at 42.14ºC which was due to imperfection of lipid matrix and lower melting point when oil was mixed with solid lipid. An increased melting range could be correlated with impurities or less ordered crystal, so also the melting enthalpy was another characteristic of the crystal order if the influence of impurities could be ignored. For less ordered crystal or amorphous compound, the melting process did not require or just require less energy than perfect crystalline substance which needs to overcome lattice force. As a result, the higher melting enthalpy values suggest higher ordered lattice arrangements and vice versa as shown in SLN formulation melting peaks at 48.10ºC which was much higher than NLC. Absence of the peak at 172.45ºC in drug loaded NLC and SLN indicates either formation of amorphous dispersion or solubilization of dithranol in lipid matrix.

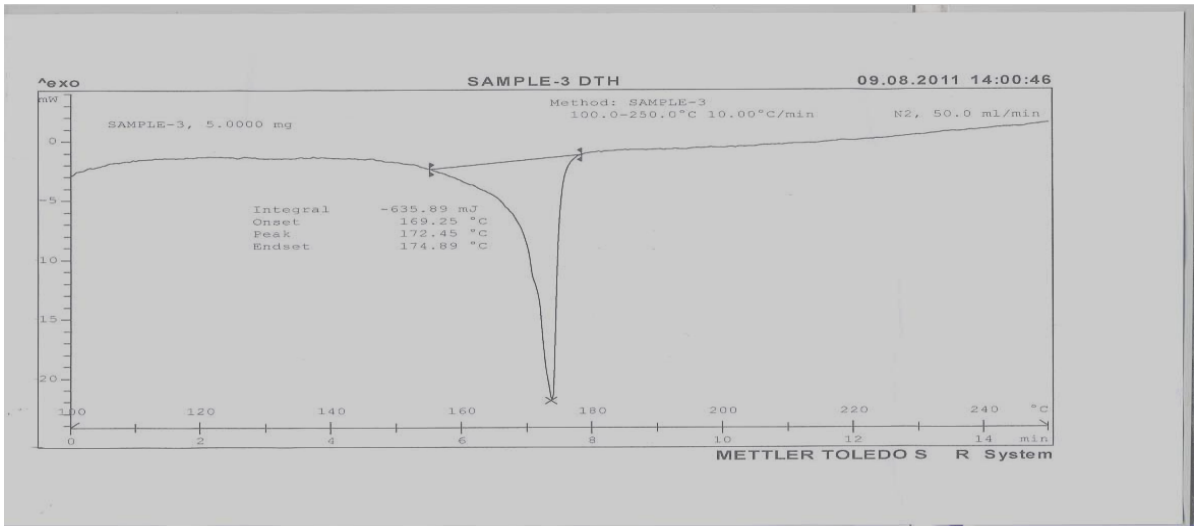

FIGURE 1: DSC thermogram of dithranol

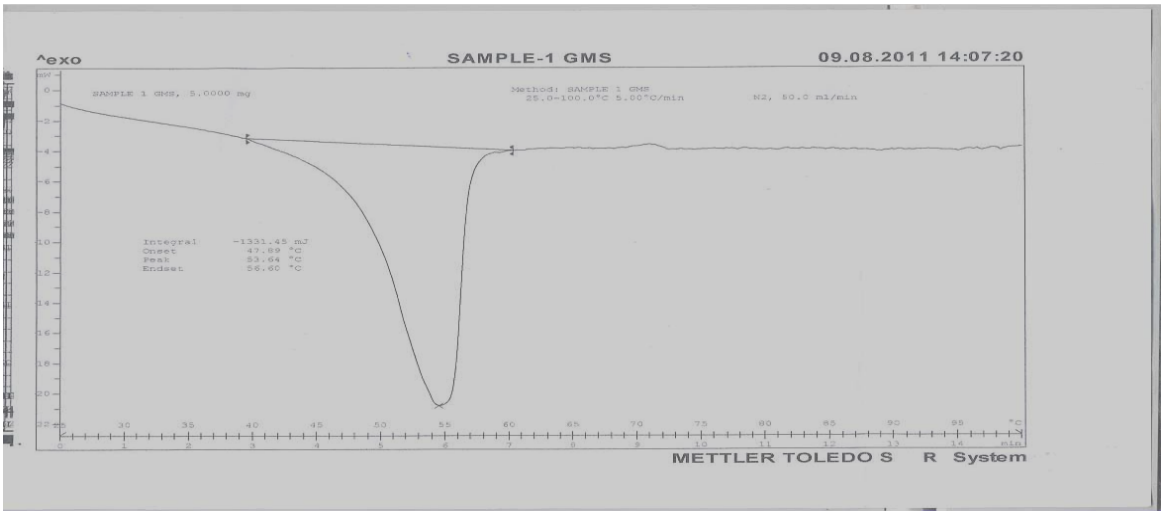

FIGURE 2: DSC thermogram of GMS

ISSN: 0975-8585

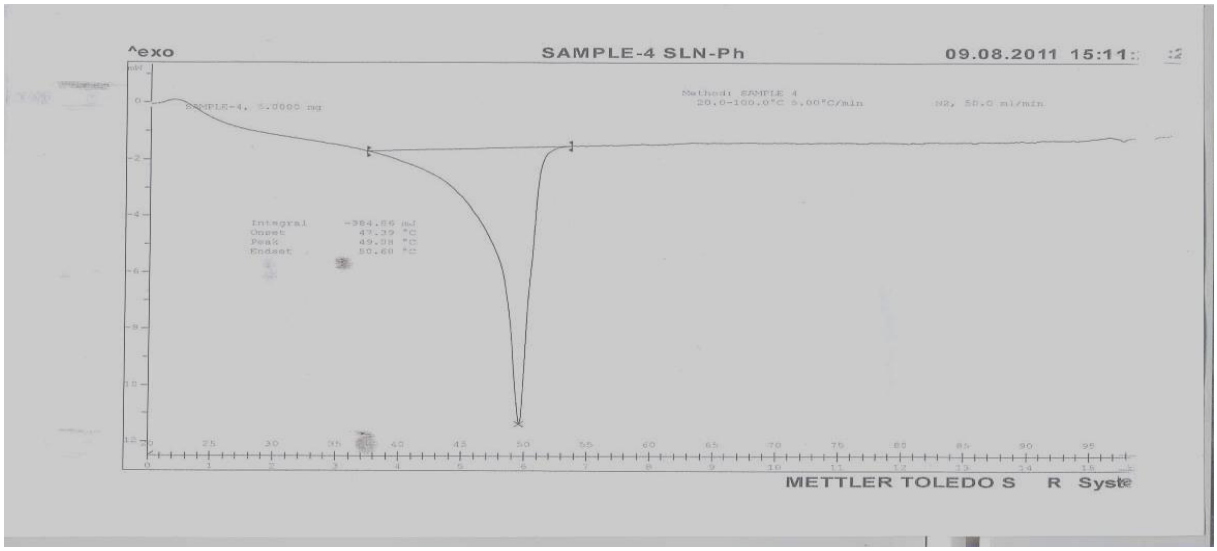

FIGURE 3: DSC thermogram of physical mixture of SLN components

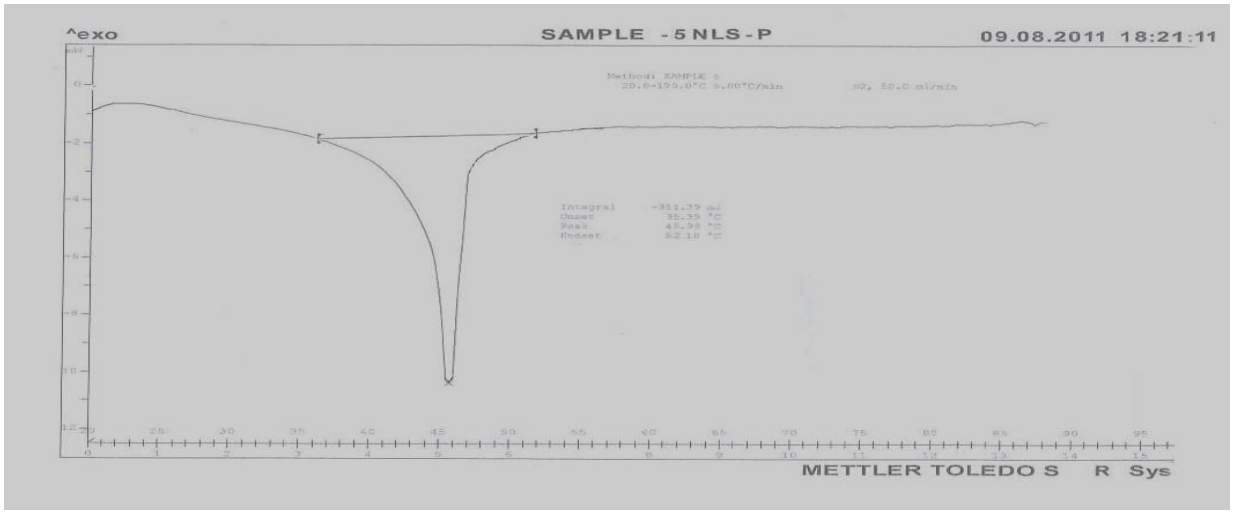

FIGURE 4: DSC thermogram physical mixture of NLC components

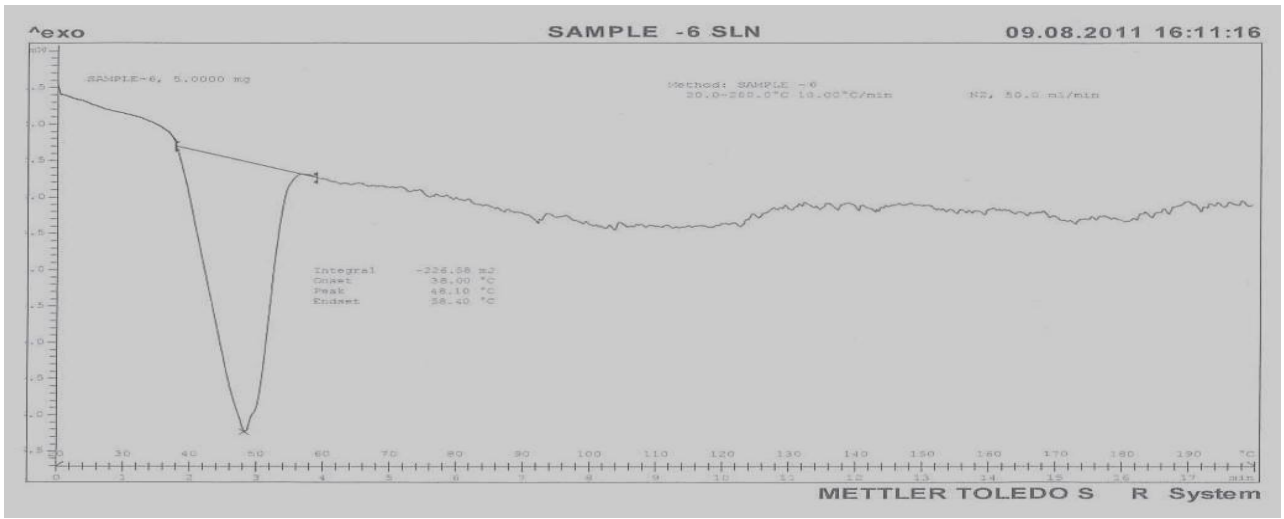

FIGURE 5: DSC thermogram of drug loaded SLN

ISSN: 0975-8585

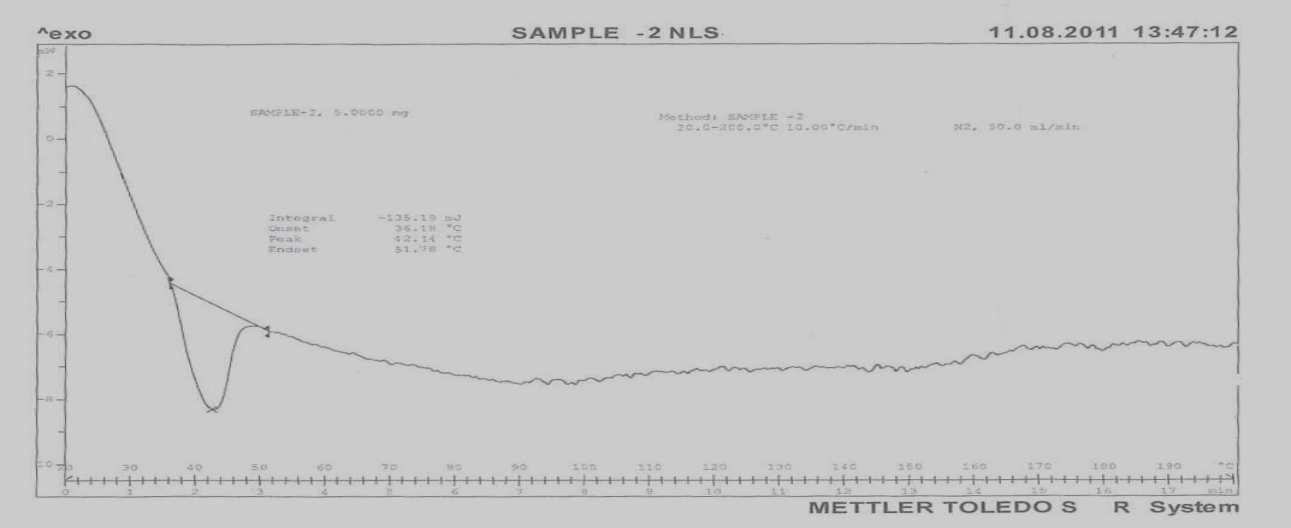

FIGURE 6: DSC thermogram of drug loaded NLC

SUMARRY AND CONCLUSION

The formation of NLC/SLN with GMS and OA was investigated by DSC. Protection of loaded drug in a physically stable formulation is the major advantage NLC/SLN provides which is lacking with other colloidal systems such as liposomes. DSC had been employed to assess physical nature of formulations.

Physical state in form of solid is necessary for NLC/SLN lipid matrix. DSC studies had revealed that all formulations possess melting point over 40ºC confirms solid state at room temperature. Shift in melting events in NLC was due to the interaction of solid lipid with the oil and the drug or due to the nanometric size range of the formulation which had a huge surface area per volume [12]. Presence of surfactant in the formulation may also have impact on lipid matrix crystallinity [13]. Shift of melting point of GMS in physical mixture with OA was observed. It has been therefore assumed that the shift of melting temperature to lower temperatures is consequence of liquid lipid incorporation. Further loss of crystal lattice in lipid matrix was found with incorporation of drug with shift in melting peaks towards lower value indicating significant effect of dithranol on the lipid matrix crystallinity and also provided evidence that dithranol was dissolved in the lipid matrix [9]. For the less ordered crystal or amorphous state, the melt of the substance did not require or just required less energy than the perfect crystalline substance which needed to overcome lattice force. As a result, the higher melting values should suggest higher ordered lattice arrangement and vice versa [14]. Crystallinity of NLC is expected to be lower than that of bulk material or SLN prepared from pure lipids only. Depression of melting point and broadening of the peak of melting event is more pronounced in NLC as compared to SLN [15,16]. Endothermic event in drug loaded NLC was broader and lower than the SLN formulation again confirmed effect of drug on crystallinity of the NLC system and anticipated that dithranol was solubilized (it is in amorphous form) within the lipid matrix which is also in agreement with the outcomes of study performed by various researchers. The amorphous form was thought to have higher energy with increased surface area, subsequently higher solubility, dissolution rates and bioavailability of the drug loaded [17,18].

ISSN: 0975-8585

ACKNOWLEDGEMENT

Mr. Gaurang K. Das is acknowledged for his effort in manuscript preparation.

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