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Research Article

## Formulation and evaluation of prazosin hydrochloride loaded solid lipid nanoparticles

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### ABSTRACT

Solid Lipid Nanoparticles (SLN) is rapidly developing field of nanotechnology with several potential application in drug delivery and research. Drugs having low aqueous solubility not only possess low oral bioavailability but also exhibit high inter- and intra-subject variability. The purpose of the present investigation was to study bioavailability enhancement of Prazosin Hydrochloride by formulating it into solid lipid nanoparticle. Prazosin Hydrochloride is an antihypertensive agent with limited bioavailability as a result of low aqueous solubility, hence, solid lipid nanoparticle is one of the approaches to improve the bioavailability. SLN were prepared using hot homogenization followed by solvent emulsification-ultrasonication method. Prazosin Hydrochloride loaded SLN were optimized and characterized by particle size, zeta potential, XRD and DSC. Prazosin Hydrochloride loaded SLN exhibited the particle size  $263.8 \pm 1.88$  and entrapment efficiency  $89.29 \pm 0.65\%$  showed better bioavailability and optimum stability.

**Keywords:** Prazosin Hydrochloride, Solid Lipid Nanoparticles, Bioavailability

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### INTRODUCTION

Oral bioavailability depends upon several factors such as aqueous solubility, drug permeability, dissolution rate, first pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanism.<sup>1</sup> SLN possesses advantages over other colloidal delivery system is to increase physical stability, high drug upload and absence of carrier biotoxicity.

The solid lipids were used in the preparation of SLN instead of liquid lipids to overcome the disadvantages associated with the liquid state and to improve physical stability. The successful application of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their constants and their stability in nanometer size. For *in-vivo* performance the solubility and dissolution rate are very important parameters.<sup>2</sup> About 40% of new chemical entities discovered and many existing drugs are poorly soluble compounds that leads to poor *in-vivo* bioavailability and lack of dose proportionality. Nano sized drug carriers, especially solid lipid nanoparticle can be the primary approach developed for improvement of bioavailability, due to their ability to enhance the lymphatic transport of the lipophilic drugs.<sup>3</sup>

Hypertension is the common cardiovascular diseases. In the world, about 20-50% of deaths are due to cardiovascular diseases. Prazosin Hydrochloride is an alpha blocker antihypertensive BCS class II drug. It is used for the treatment of heart failure and hypertension having low bioavailability.<sup>4</sup>

Active pharmaceutical ingredients with poor water solubility are often associated with number of *in-vivo* problems. Despite of drawbacks, advances have been made in delivery technologies to improve the bioavailability of poorly water soluble compounds. Development of new drug is not sufficient to ensure progress in drug therapy. Such advances in delivery technologies exploited by formulation scientist for bioavailability enhancement include suitable drug carrier system such as microemulsion, nanoemulsion, liposomes, self-emulsifying delivery, solid dispersion and solid lipid nanoparticles.<sup>5,6,7</sup>

### MATERIALS AND METHOD:

#### Materials:

Prazosin Hydrochloride was purchased from Swapnroop Drugs and Pharmaceuticals, Aurangabad, India, Polaxamer 407 from Research lab fine chem. Industries, Mumbai, India; Glyceryl mono stearate from Hilab chemicals,

shrirampur, India and methanol from Molychem, Mumbai, India. All other chemicals used were of analytical grade.

#### Method:

#### Preparation of Prazosin Hydrochloride loaded Solid Lipid Nanoparticles:

Prazosin Hydrochloride loaded SLNs were prepared by high pressure homogenization followed by solvent emulsification-Ultrasonication. Glyceryl monostearate (GMS) was dissolved in methanol by heating at 70-80°C and 10 mg of Prazosin Hydrochloride was dissolved by adding into this solution. In another beaker, aqueous phase was made by adding 30 ml of distilled water containing 30 mg of polaxamer 407 (P 407) and heated at

the same temperature as lipid phase Then lipid phase was added drop wise into aqueous phase by using magnetic stirrer at 1500 rpm and kept it for 2 hours. The resultant dispersion was immediately sonicated using a probe sonicator (Remi R-8C) at amplitude of 50% with the pulse of 4 sec intervals. Then high pressure homogenization (HPH) of this solution is carried out by applying 1000 bar pressure using 3-5 cycle. The prepared SLNs samples were lyophilized at -52°C for 24 hours to yield dry powder. Various formulations (A to H) were prepared using different compositions of lipid (GMS) and polymer (P407) (Table 1).<sup>8,9</sup>

**Table 1: Experimental design for preparation of solid lipid nanoparticles**

Formulation	Drug (mg)	Water (ml)	Formulation composition	
			Lipid	polymer
A	10	40	70	20
B	10	40	70	30
C	10	40	90	30
D	10	40	90	20
E	10	40	50	25
F	10	40	60	15
G	10	40	30	10
H	10	40	60	25

#### Characterization of Solid Lipid Nanoparticles:

#### Determination of Practical yield and Entrapment efficiency

The practical yield (PL) and entrapment efficiency (EE) of the prepared SLNs for Prazosin Hydrochloride was evaluated by taking 5 ml of the resultant dispersion, and then centrifuged at 12000 rpm for 120 min at 4°C by using cooling centrifuge (Remi C-24BL). The clear supernatant layer was decanted and the remaining part was dissolved in 10 ml methanol, sonicated for 5 min then sample was filtered through filter paper no. 41 and analyzed using UV Visible spectrophotometer (Agilent Cary 60) at lambda max 248 nm. The percentage EE was calculated using following relationship.<sup>10</sup>

$$EE (\%) = \frac{\text{Mass of Drug in Nanoparticles}}{\text{Mass of Drug used in preparation}} \times 100$$

Practical yield was calculated as drug analyzed in the nanoparticle versus the total amount of product obtained and total solid used in the preparation (Table 1).

#### Particle Size Analysis of Nanoparticles:

Determination of mean average particle size of Prazosin Hydrochloride nanoparticle was carried out by using Horiba scientific instrument. The analysis was performed by introducing 0.3 ml of sample into the viewing unit the dynamic light scattering is used to measure particle size and molecule size. The particle size analysis was performed at a scattering angle of 90°C at room temperature. The diameter was averaged from three parallel measurements moving under Brownian motion, and converts this to size and a size distribution.<sup>11</sup>

#### Zeta potential Measurement:

The analysis was performed by using the Horiba scientific analyzer zetasizer. The electrophoretic mobility was converted to the zeta potential. To determine the zeta

potential, nanoparticle sample were diluted with KCL (0.1 mM) and placed in electrophoretic cell where an electrical field of 15.2V/cm was applied. All measurement was performed triplicate. The unique disposable capillary cell ensure there is no cross contamination between samples, which improves the simplicity, speed and accuracy of the measurement.<sup>11</sup>

#### Scanning Electron Microscopy (SEM):

Nanoparticles were coated with a thin gold-palladium layer by sputter coater unit (VG Microtech, United Kingdom), and the surface topography was analyzed with a Cambridge Stereoscan S 120 scanning electron microscope (SEM: Cambridge, United Kingdom) operated at an acceleration voltage of 10 kv.<sup>12</sup>

#### Fourier Transform Infrared Spectroscopy:

The FTIR spectra are used to identify the drug as well as to detect the interaction of drug with polymers. FTIR spectrum of pure drug and optimized batch of solid lipid nanoparticles was taken. Sample of solid lipid nanoparticles was kept onto sample holding surface for analysis. The spectrum was scanned over the wave number range 4000-400 cm<sup>-1</sup>.<sup>13</sup>

#### X-Ray Diffraction Analysis:

X-ray powder diffraction of pure drug and optimized batch of nanoparticles were analysed by Philips PW X-ray diffractometer. Sample were irradiated with monochromatized Cu K $\alpha$ -radiation (1.542Å) and analysed. The voltage and current used were 30k V and 30Ma respectively. The range was 5 ×10<sup>3</sup> cycle/s and chart speed was kept at 100 mm.<sup>14</sup>

#### Differential Scanning Calorimeter Analysis:

Thermal properties of pure drug and optimized batch of nanoparticle were analyzed by DSC (TA Instruments, USA Model: SDT2960). Indium was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the

pure gas through DSC cell at flow rate of 50 ml per min. through the cooling unit. The sample was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 25 to 500°C at a heating rate of 10°C/min.<sup>15,16,17</sup>

#### **In-Vitro Drug Release Study:**

The *in-vitro* drug release experiment was developed to measure the drug release kinetics from the polymeric nanoparticle in a sink condition. Drug release study of capsules filled with nanoparticles was carried out using the USP II dissolution test apparatus (Veego VDA-8DR) under conditions at 37±0.5°C and stirred at 100 rpm. The nanoparticle formulations are tested for drugs releases for 8 hours in the dissolution medium with 0.1 N HCl+3% SLS solution. At each predetermined time intervals 5 ml of sample was taken and filtered by using by using Whatman filter paper No.41. After the appropriate dilutions the sample analyzed spectrophotometrically.<sup>18,19</sup>

#### **Stability study:**

Stability studies were carried out for the optimized batch having high entrapment efficiency and low particle size by storing (Remi SC-6 plus) the formulation at three different temperature conditions 4±2°C, 25±2°C and 40±2°C. The drug content was estimated after every 15, 30 and 45 days as per ICH guidelines to find any change in the entrapment efficiency and particle size of the SLNs.<sup>20</sup>

## **RESULTS AND DISCUSSION:**

#### **Lyophilization:**

For improving physical and chemical stability lyophilization has been mostly used. But, this process may destroy the surfactant film around the nanoparticle due to a “freeze out” effect, and lead to particle aggregation during the resolubilization or redispersion process, the sufficient protective effect can be provided. Mean particle size increased significantly after lyophilization without any cryoprotectant. Sorbitol, mannitol, maltos and dextran are examples of cryoprotectants. It will help to prevent the nanoparticle from aggregation. Mannitol works by forming film around surface of the nanoparticles, so there is no significant change in particle size after lyophilization.

#### **FTIR Analysis:**

FTIR Spectroscopy was used to investigate the interaction between lipid, drug and Excipients. From the FTIR graphs of pure drug and optimized formulation (C), it is confirmed that there are no any interaction between the lipids and drug. FTIR Spectra of pure drug (a) and formulation (b) are shown in the figure 1. The FTIR chart obtained for pure Prazosin Hydrochloride bands at the region 3150-3050 cm<sup>-1</sup> the broad intense band for C-H stretching, primary amines and primary amides is at 3100-3500 cm<sup>-1</sup>. Other peaks are at 3302 cm<sup>-1</sup> represents N-H Stretching, 1300-1000 cm<sup>-1</sup> the intense bands for C-O stretching shows carboxylic group at 1280 cm<sup>-1</sup>.

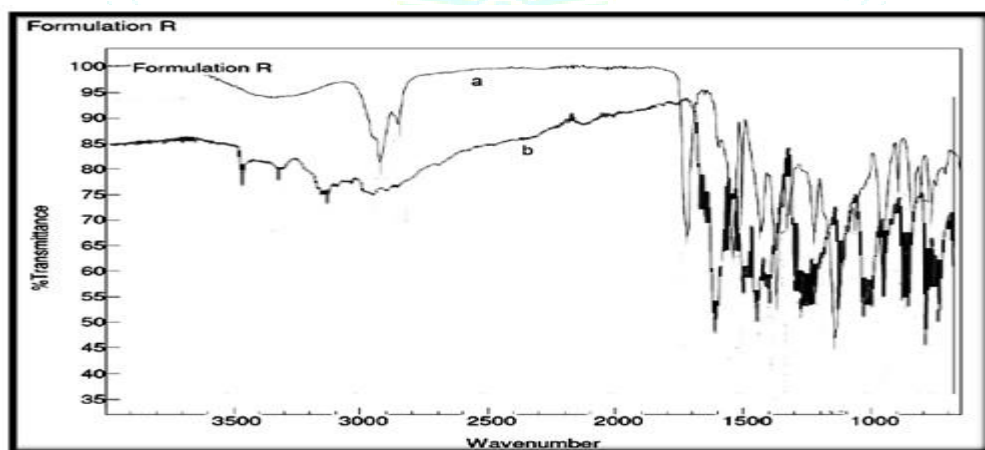


Figure 1: FTIR Spectrum of Pure Prazosin Hydrochloride (A) and Optimized Batch (B)

#### **Evaluation of Prazosin Hydrochloride loaded Solid Lipid Nanoparticles:**

##### **Practical yield:**

The percentage practical yield was observed ranges between 82±1.15 to 95.38±0.77. The percentage practical yield was observed to increase with the concentration of lipid (Table 2).

Table 2: % Practical yield and % entrapment efficiency of nanoparticles (batch A-H)

Formulation Code	%Practical Yield	%Entrapment Efficiency
A	90.00±1.30	86.00±0.70
B	89.39±1.52	83.42±0.90
C	95.38±0.77	89.29±0.65
D	85.83±1.66	81.71±1.29
E	92.93±1.00	77.00±1.02
F	90.97±1.79	72.57±1.12
G	82.00±1.15	65.14±1.04
H	85.24±1.01	66.28±0.84

Each value is average of three separate determination ±SD

**Entrapment efficiency:**

The percent entrapment was observed to vary within range  $65.14 \pm 1.04$  to  $89.29 \pm 0.65\%$ . The percentage entrapment efficiency was observed to enhance with the increases in lipid concentration (batch A-C). Prazosin Hydrochloride loaded SLNs of batch C showed higher percent entrapment efficiency i.e  $89.29 \pm 0.65\%$  compared to other formulations (Table 2).

**Particle Size and Zeta Potential of Prepared SLNs of Prazosin Hydrochloride:**

Particle size and Zeta potential of the all batches of Prazosin Hydrochloride SLNs was measured. The particle size was observed in the range of  $263.8 \pm 1.88$  to  $369.3 \pm 1$  nm with zeta potential  $7.5 \pm 0.32$  to  $-22.1 \pm 1.00$  mV for the prepared batches of SLN. It has been observed that an increase in lipid content (GMS) does not significantly affect the particle size. The particle size and zeta potential are depicted in Table 3.

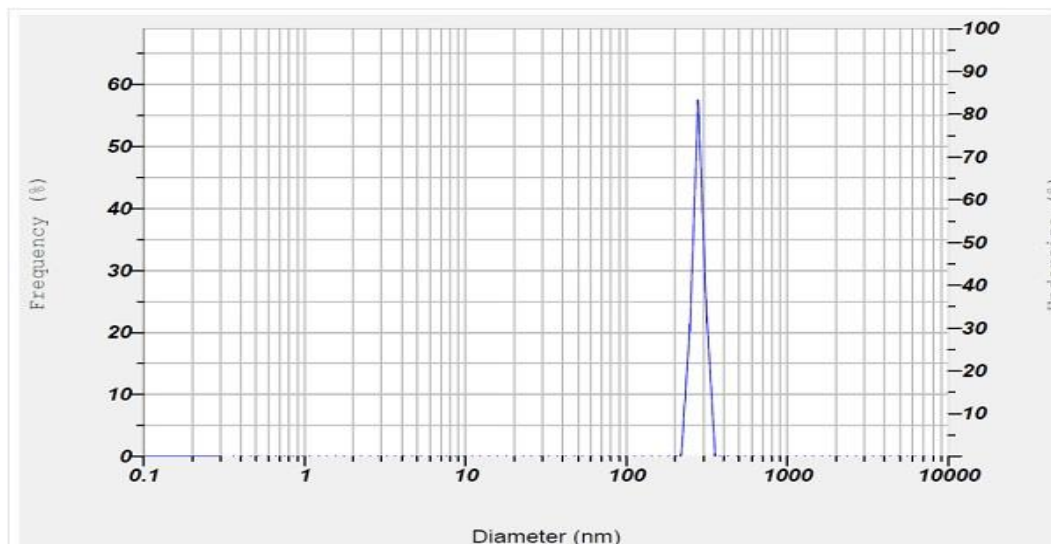
The particle size distribution has a direct influence on material properties and found to be uniform (Figure 2). Determination of mean average particle size of Prazosin

Hydrochloride solid lipid Nanoparticles was carried out by using Horiba instrument. Average particle size of all SLN preparations was found to be within range of  $263.8 \pm 2$  to  $295.3 \pm 1.15$ . Determination of Zeta potential of prepared SLNs (Table 3) was found in the range of  $7.5 \pm 0.32$  to  $-22.1 \pm 1$  shown in the Figure 3. It was found that higher the zeta potential, less will be the particle aggregation, due to electric repulsion and hence more will be the stability of SLNs.

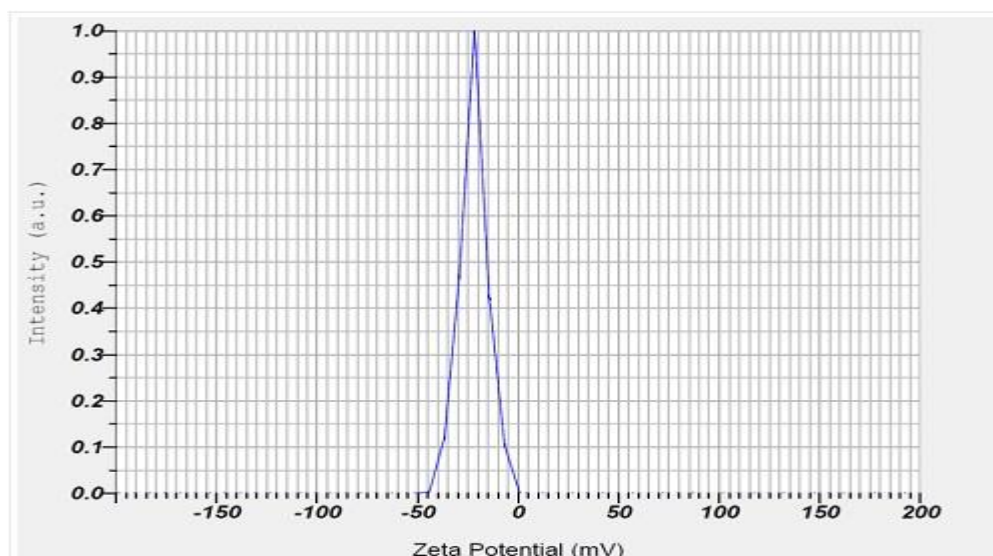
**Table 3: Mean particle size or average zeta potential of prazosin hydrochloride SLNs**

Formulation Code	Size (nm)	Average Zeta Potential (mV)
A	$283.5 \pm 2.0$	$7.5 \pm 0.32$
B	$282.02 \pm 1.60$	$13.4 \pm 0.2$
C	$263.8 \pm 1.88$	$-22.1 \pm 1.00$
D	$295.3 \pm 1.55$	$8.7 \pm 0.41$
E	$299.4 \pm 0.90$	$9.2 \pm 0.15$
F	$304.6 \pm 1.52$	$10.3 \pm 0.30$
G	$348.9 \pm 1.91$	$13.4 \pm 0.15$
H	$369.3 \pm 1$	$17.7 \pm 0.87$

Each value is average of three separate determination  $\pm$ SD



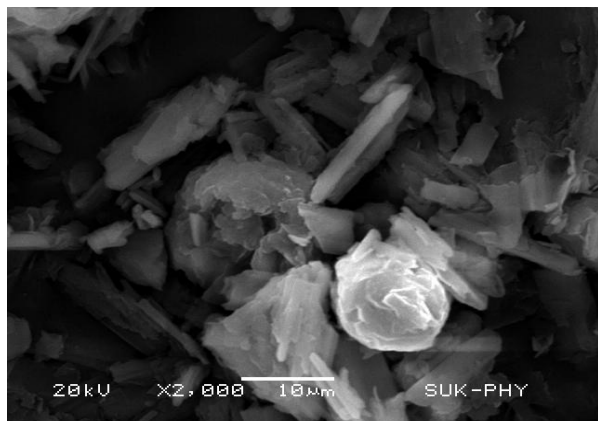
**Figure 2: Size Distribution Report of Optimized Batch**



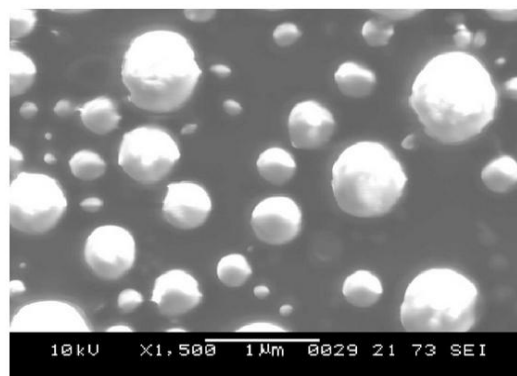
**Figure 3: Zeta Potential Report of Optimized Batch**

### Scanning Electron Microscopy Analysis:

Scanning electron microscopy (SEM) is an electron optical imaging technique that provides photographic images and elemental information. The signals that derive from electron sample interaction reveal information about the sample including external morphology (texture), crystalline structure, and orientation of materials making up the sample. The Prazosin Hydrochloride appeared as smooth surfaced, irregularly flat shaped and crystalline in nature (Figure 4). SLNs were observed to be small sized, spherical in shape and porous in nature (Figure 5).



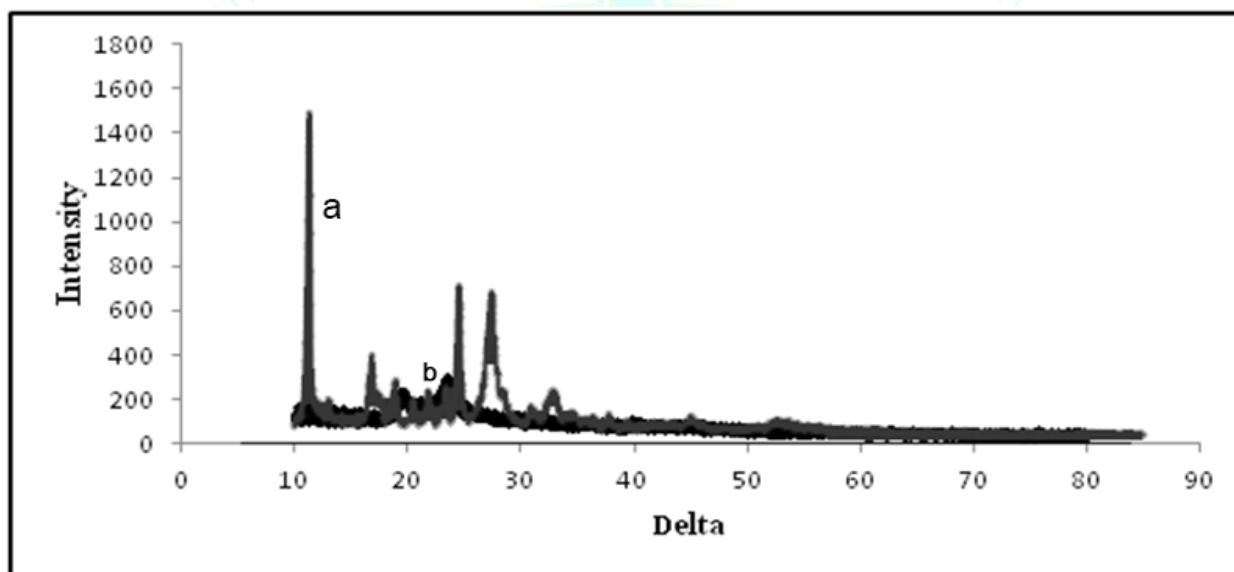
**Figure 4: Scanning Electron Microscopy of Pure Prazosin Hydrochloride**



**Figure 5: Scanning Electron Microscopy of Optimized Batch**

### X-ray diffraction study:

The XRD study of Solid Lipid Nanoparticle showed in Figure 6. Pure Prazosin Hydrochloride powder showed prominent diffraction peaks in the range of 1-40 of  $2\theta$ . But, no obvious peaks representing crystalline nature of Prazosin Hydrochloride was seen for the SLN, indicating the conversion to amorphous nature of Prazosin Hydrochloride in the formulation. It revealed that quite amorphization has occurred during SLNs preparation of Prazosin Hydrochloride.



**Figure 6: X-RAY Diffraction Pattern of Pure Prazosin Hydrochloride (A) and Optimized Batch (B)**

### Differential Scanning Calorimetry:

Thermogram of Solid lipid Nanoparticle has been depicted in Figure 7. In the case of pure Prazosin Hydrochloride a sharp endothermic peak was observed at 283.31°C,

corresponding to its melting point. In the SLNs, endotherm was observed at near about 79.07°C with the sharp appearance. It reveals that is no polymeric transition during Nanoparticles preparation of Prazosin Hydrochloride.

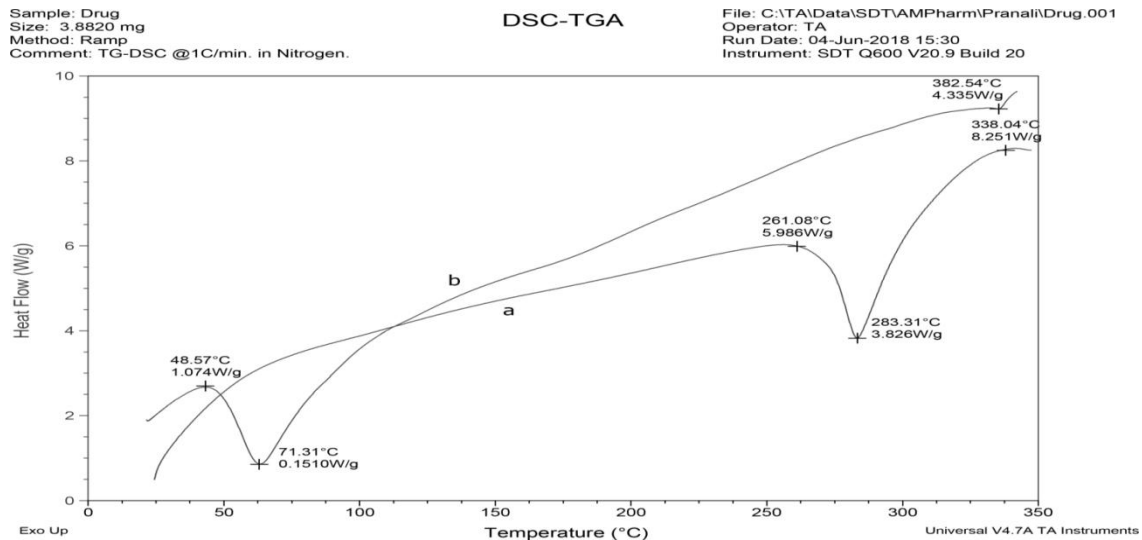


Figure 7: DSC Thermogram of Pure Drug Prazosin Hydrochloride (A) and Optimized Batch (B)

**In-Vitro release studies:**

*In vitro* drug release study of the all SLNs (A-H) was carried out depicted in Figure 8. The SLNs exhibited biphasic release pattern with initial release in 2 hours by sing 0.1N HCl + 3% SLS followed by sustained release for 8 hours. About 25-28% of incorporated amount of drugs was found to be released during first 2 hours, followed by a slowed release profile of the drug up to 8 hours (Table 4). The prolonged release at 8 hours can be attributed to slow diffusion of drug from lipid matrix.

Table 4: percentage drug release of SLNs of batch A-H

Formulation code	% Drug Release at 8 hr
A	95.16±1.590
B	95.35±1.130
C	97.35±0.790
D	90.00±0.009
E	95.46±0.019
F	93.94±0.017
G	92.88±0.010
H	89.77±0.010

Each value is average of three separate determination ±SD

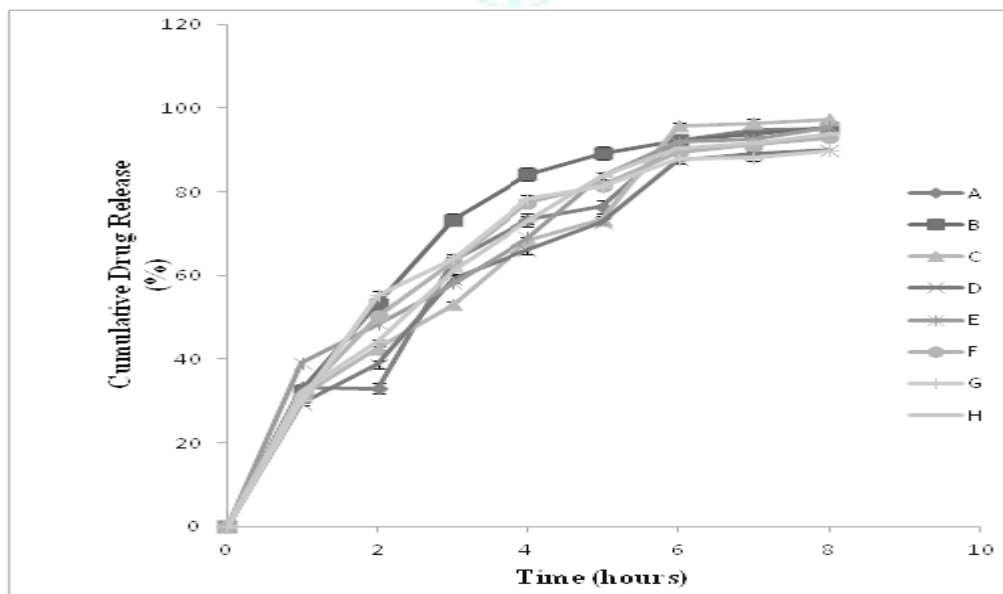


Figure 8: Drug Release Profile of Nanoparticles Batches (A-H)

**Stability study:**

Stability studies were carried out for the optimized batch having high entrapment efficiency and low particle size by storing the formulation at three different temperature conditions as 4°C, 25±2°C and 40±2°C. The drug content

was estimated after every 15, 30 and 45 days as per ICH guidelines to find any change in the entrapment efficiency and particle size of the SLNs. The result was shown in the Table 5. SLNs were found to be stable over the above mentioned period as per ICH guidelines.

Table 5: stability study for solid lipid nanoparticles of prazosin hydrochloride (batch-C)

Storage Condition	Particle Size (nm)				Entrapment Efficiency (%)			
	Initial	15 days	30 days	45 days	Initial	15 days	30 days	45 days
4°C	263.8±1.88	263.80±0.54	262.13±0.01	257.81±0.56	89.29±0.65	88.47±0.59	87.4±0.60	87.1±1.00
25°C	263.8±1.88	261.00±0.81	259.14±0.04	256.46±0.61	89.29±0.65	88.36±0.38	87.1±0.04	85.1±0.01
40°C	263.8±1.88	261.39±1.09	260.15±0.02	256.17±0.02	89.29±0.65	88.10±0.25	86.1±0.03	84.2±0.15

## CONCLUSION

Hot homogenization followed by solvent emulsification-ultrasonication method was a useful method for the successful incorporation of the poor water soluble drug Prazosin Hydrochloride with good entrapment efficiency. The Preformulation study showed the compatibility of Prazosin Hydrochloride with the other formulation ingredients and the drug is molecularly dispersed into the lipid. The particle size distribution shows the particle size in the nano range. *In-vitro* drug release through the dialysis membrane from the prepared SLNs is much higher than the pure drug. The Stability study showed that formulations did not changed their performance on storage. Hence formulation of Prazosin Hydrochloride in SLNs can enhance the bioavailability of the drug which could be stabilized during storage.

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**Conflicts of interest:** Nil

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