INTRODUCTION

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterilization constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral dosage forms. In addition, the effective lipid based colloidal carriers which were introduced as an alternative to the conventional carriers such as microemulsions, liposomes, microparticles and nanoparticles based on synthetic polymers or natural macromolecules. Typically they enhance the oral bioavailability of the low aqueous soluble drugs due to their potential to enhance gastrointestinal solubilization and absorption via selective lymphatic uptake. These properties can be harvested to improve the therapeutic efficacy of the drugs with low bioavailability, as well as to reduce their effective dose requirement.

MATERIALS AND METHODS

Materials: Phospholipon-80H was received as a gift sample from Lipoid GmbH, Friesenstrasse 4, D-67065, Ludwigshafen. Ibuprofen was purchased from local supplier, stearic acid (Central Drug House (P) Ltd. New Delhi); Tween-80 (Finar Chemicals Limited, Ahmedabad, India); Dichloromethane (Merck Specialties Private Limited, Worli, Mumbai, India); Potassium Dihydrogen Ortho Phosphate (Finer Chemicals Limited, Ahmedabad-380006, India) and Sodium Hydroxide (Central Drug House (P) Ltd. New Delhi-110002, India) and all other required chemicals were procured from the suppliers.
Particle size of the solid lipid nanoparticles was analyzed by Particle size determination

Solid Lipid Nanoparticles of Ibuprofen were produced using Preparation of Ibuprofen SLN by Hot Homogenization technique: 

Solid Lipid Nanoparticles of Ibuprofen were produced using preparation technique:

In vitro drug release study:

The release of Ibuprofen from the solid lipid nanoparticles was compared with the pure drug using a dissolution system comprising of a HiMedia Dialysis Membrane-70 mounted over a jacketed dialysis beaker. The dialysis membrane was filled with 2 ml of solid lipid nanoparticles, clipped and exposed to diffusion medium containing Phosphate buffer pH (7.2), stirred magnetically & maintained at a constant temperature of 37°C ± 0.5°C. Aliquots were drawn at specified time intervals and analyzed using a UV spectrophotometer (Shimadzu-1700).

Drug Entrapment Efficiency:

The percentage of incorporated Ibuprofen (entrainment efficiency) was determined spectrophotometrically at 221 nm. After centrifugation of the aqueous suspension, amount of the free drug was detected in the supernatant and the amount of incorporated drug was determined as the result of the initial drug minus the free drug. The entrainment efficiency can be calculated using the following formula:

\[
\text{Entrapment efficiency (EE)} = \frac{W_{\text{initial drug}} - W_{\text{free drug}}}{W_{\text{initial drug}}} \times 100
\]

Differential Scanning Calorimetry (DSC):

DSC scan of about 5mg, accurately weighed ibuprofen and physical mixture (lipids and surfactant) and the SLN formulation were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) Sealed and perforated aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10°C/min from 25-300°C.

Lyophilization:

The SLN were lyophilized using an MAC Lyophilizer. The cryoprotectant was added to the SLN liquid. The SLN liquid was frozen at a temperature of –40°C for 4 h in cold trap and lyophilized for 24 h. The freeze-dried powder was re-suspended in water and characterized.

Stability Testing Studies:

The intermediate stability testing studies for SLN-3 was performed for 6 months according to the ICH Guidelines. The SLN of Ibuprofen was kept at 30°C ± 2°C and 65% ± 5% Relative humidity in stability chamber. Particle size measurement, Drug entrapment and Drug release were fixed as physical parameters for stability testing.

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>[ Drug ] Ibuprofen (mg)</th>
<th>[ Lipid ] Stearic acid (mg)</th>
<th>[ Surfactant ] Phospholipon-80H (mg)</th>
<th>Dichloromethane (ml)</th>
<th>Water (ml)</th>
<th>[ Stabilizer ] Tween-80 (ml)</th>
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<tr>
<td>SLN-1</td>
<td>300</td>
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<td>300</td>
<td>10</td>
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</table>

<table>
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<tr>
<th>No of month</th>
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<th>Particle size in nano range</th>
<th>Drug entrapment</th>
<th>Drug release up to 6 hr.</th>
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<td>30°C ± 2°C</td>
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<td>80.35%</td>
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<td>3</td>
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<td>37 volume %</td>
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<td>30°C ± 2°C</td>
<td>35 volume %</td>
<td>79.85%</td>
<td>74.31%</td>
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</table>
Figure 1: FTIR Spectra of pure Ibuprofen

Figure 2: FT-IR Spectra of Physical Mixture of Ibuprofen with Stearic acid and Phospholipon 80H

Figure 3: Particle size distribution of SLN-3 containing optimum stabilizer (Tween 1.5%)

Figure 4: Particle size distribution of SLN-6 containing higher ratio of surfactant.
Figure 5: Particle size distribution of SLN-10 containing lower ratio of Lipid

Figure 6: Comparison of In-Vitro release of Ibuprofen from different SLNs having different stabilizer concentration with pure drug.

Figure 7: In-vitro release profile of Ibuprofen from different SLNs having different lipid, drug and surfactant ratio.

Figure 8: Trmg Entrapment efficiency of different SLN formulations.

Figure 9: DSC thermogram of the pure drug Ibuprofen.
Particle Size determination:
The FTIR Spectra of pure Ibuprofen and the physical mixture (1:1:1) of drug with Stearic acid and Phospholipon80H given in the Fig.1 and Fig.2 respectively. The IR spectra of pure drug shows principle peaks at 1721 cm\(^{-1}\) (C=O stretching vibration of –COOH group), 870, 779 cm\(^{-1}\) (Aromatic stretching bending vibration). The mixture physical on the other hand shows peaks at 1720.72, 865.51 and 779.83 cm\(^{-1}\). Thus, it is concluded that the physical mixture of the drug, Ibuprofen does not show any major interactions with the formulation components like lipid (Stearic acid) and surfactant Phospholipon80H.

RESULTS AND DISCUSSION
Compatibility study by FT-IR
The FTIR Spectra of pure Ibuprofen and the physical mixture (1:1:1) of drug with Stearic acid and Phospholipon80H given in the Fig.1 and Fig.2 respectively. The IR spectra of pure drug shows principle peaks at 1721 cm\(^{-1}\) (C=O stretching vibration of –COOH group), 870, 779 cm\(^{-1}\) (Aromatic stretching bending vibration). The mixture physical on the other hand shows peaks at 1720.72, 865.51 and 779.83 cm\(^{-1}\). Thus, it is concluded that the physical mixture of the drug, Ibuprofen does not show any major interactions with the formulation components like lipid (Stearic acid) and surfactant Phospholipon80H.

Particle Size determination:
Particle size of the solid lipid nanoparticles was analyzed by laser diffractometry using a Mastersizer 2000 instrument (Malvern) equipped with a Hydro 2000MU (A) dispersing unit. The particle size distribution of SLN-3 showed[Fig. 3] that about 36% volume of the particles are in nano range (below 1µ) and the rest of the particles are in between 1 to 100µ. Further modification in the formulation SLN-6 (increase in surfactant ratio) cause higher volume % of particle fall in nano size (56 volume %) as shown in Fig. 4. but when the lipid ratio is increased in SLN-10 the particle size distribution becomes less in nano range only 27% volume in Fig. 5.

In-vitro drug release study:-
In-vitro drug release study of ibuprofen from various SLN formulations was done by using dialysis membrane. Cumulative % drug release when plotted against time for pure drug (PD) and formulation SLN- 1 to SLN-5 with different stabilizer concentration (0.5-2.5%) in the [Fig. 6] it has been found that from the SLN formulations the drug release is much higher than the pure drug and SLN-3 with the stabilizer concentration 1.5% gives 75.58% drug release up to 6 hr period with higher dissolution rate in the initial period than other four formulations. Hence 1.5% stabilizer concentration (Tween 80) is considered as an optimum concentration for this type of formulations. Keeping the stabilizer concentration (1.5%) fixed in the formulations SLN-6 to SLN-11 drug lipid and surfactant ratio is changed. The formulation SLN-12 is prepared without the drug which is also studied for diffusion and the samples were taken as blank. Cumulative % drug release from SLN-6 to SLN-11 is compared against the optimum formulation SLN-3 and plotted against time [Fig. No 7]. The effect of surfactant concentration was studied by changing the ratio of surfactant (Drug: Lipid:Surfactant=1:1:1 in SLN-3) in the SLN-6 (Drug: Lipid:Surfactant=1:1:2) and SLN-9 (Drug: Lipid:Surfactant=1:1:0.5). There is slight enhancement in the release (82.56%) with increasing the surfactant (SLN-6) and also the release is decreased (74.87%) with decrease in concentration of surfactant (SLN-9). The effect of drug loading is found in SLN-8 (Drug: Lipid:Surfactant=2:1:1) and in SLN-11 (Drug: Lipid:Surfactant=0.5:1:1). Change in drug loading cause no further increase in release of drug. Lipid ratio is changed in SLN-7 (Drug: Lipid:Surfactant=1:2:1) and SLN-10 (Drug: Lipid:Surfactant=1:0.5:1). Increase in the lipid ratio in SLN-7 cause decrease (69.58%) in the release of drug.

Drug Entrapment Efficiency: The percentage of entrapped Ibuprofen in different SLN formulations with different drug, lipid, surfactant and stabilizer ratio was found spectrophotometrically. The results are given in the following Fig.8. Highest entrapment 86.32% is found in SLN-8 (Drug: Lipid: Surfactant=2:1:1) and the lowest 43.3% is found in SLN-11 (Drug: Lipid: Surfactant=0.5:1:1). Hence increase in drug loading increase the percentage of drug entrapped and decrease in drug loading cause decrease in entrapment efficiency.

Differential Scanning Calorimetry (DSC)
DSC thermogram of pure drug, Ibuprofen (Fig.9) exhibits a sharp endothermic peak at 82.76°C. The DSC curve for physical mixture of lipid (Stearic acid) and the surfactant (phospholipion 80 H) showed the presence of endothermic peaks at about 62.71°C and 111.43°C (Fig.10). On the other
hand, the SLN thermogram of Ibuprofen (Fig.11) displayed complete disappearance of characteristic peak Ibuprofen, but it shows both the characteristic peaks of lipid (Stearic acid) and the surfactant (Phospholipion 80 H) at 67.53°C and 112.65°C with minimum shifting. The disappearance of the characteristic peak of Ibuprofen is due to the fact that the drug is molecularly dispersed within the lipid matrix as found for rizatriptan by Rahul Nair et al. 10.

**Lyophilization**

In recent years, lyophilization has been widely used to improve the chemical and physical stability of SLN over a long period of time. However, it may destroy the surfactant film around the nanoparticles due to a “freezeout” effect, and lead to particle aggregation during the resolubilization or redispersion process. The polymers could not provide a sufficient protective effect. The mean particle size increased significantly after lyophilization without any cryoprotectant, so effective cryoprotectants should be chosen to avoid these problems associated with lyophilization. There are many kinds of cryoprotective agents that can be used for lyophilization, such as sorbitol, glucose, fructose, mannose, mannitol, maltose, dextran, and trehalose. The most effective cryoprotectant in all is mannitol. It could prevent the nanoparticles from aggregating effectively during the lyophilization process. Mannitol could form a film around the surface of the nanoparticles, which prevents nanoparticles from aggregating, so there was no significant change in particle size before and after lyophilization. SLN was re-dispersed in aqueous media.

**Stability Testing Studies**

The intermediate stability testing studies for SLN-3 was performed for 6 months according to the ICH Guidelines. The SLN-3 of Ibuprofen was kept at 30 °C ± 2 °C and 65% ± 5 % Relative Humidity in stability chamber. Particle size measurement, Drug entrapment and Drug release were fixed as physical parameters for stability testing. The results are given in Table 2.

After performing the stability study it was observed that at intermediate stability testing conditions there was no change in the particle size distribution, drug entrapment and drug release of the optimized formulation. At zero days the cumulative % drug release was found to be 75.58% and after three months it was 74.78% and after six months the release comes to 74.31%. This change in drug release is very negligible. The particle size which generally increases with the age of formulation is also observed with very little change. So from this study we can conclude that the prepared SLN of ibuprofen will be stable during storage.

**CONCLUSION**

Solid Lipid Nanoparticles of Ibuprofen, a poorly water soluble model drug is prepared by hot homogenization technique using stearic acid (lipid) Phospholipion 80 H (surfactant) and Tween-80 as stabilizer. The preformulation study shows the compatiblity (FTIR study) of Ibuprofen with the other formulation ingredients and the drug is molecularly dispersed (DSC study) into the lipid. The particle size determinations confirm the particle size distribution in the nanoparticulate range. In-vitro drug release through the dialysis membrane from the prepared SLNs is much higher than the pure drug. The stability study indicates the stability of the formulations without changing its performance on storage. Hence formulation of Ibuprofen in SLN enhances the dissolution rate as well as it will enhance the bioavailability of the drug which could be stabilized during storage.

**ACKNOWLEDGMENT:**

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**REFERENCES**


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