DEVELOPMENT AND IN VITRO EVALUATION OF NANOSTRUCTURED LIPID CARRIERS (NLCs) OF GLICLAZIDE

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ABSTRACT

Gliclazide is a potential second generation oral hypoglycemic agent, which belongs to BCS class II drugs having low solubility and high permeability. It has log P value of 2.6, pKa of 5.8, molecular weight of 323.42, and has poor and variable oral bioavailability. The GI absorption rate of gliclazide is very slow and requires 2 to 8 hrs to reach peak serum levels. Therefore keeping these in mind, an attempt was made to prepare NLCs of Gliclazide which will provide controlled release, along with a concomitant improvement in solubility and dissolution profile of drug. Gliclazide loaded NLCs were produced by high shear homogenization coupled with ultrasonication technique using Precirol ATO 5 as solid lipid, Capryol 90 as liquid lipid, Tween 20 as surfactant and Transcutol HP as a cosurfactant. The NLCs were characterized for entrapment efficiency, particle size and in vitro drug release. The optimized batch was subjected to freeze drying using trehalose as cryoprotectant and the freeze dried powder was filled into hard gelatin capsule of suitable size. In vitro release studies of NLC capsules showed that Gliclazide exhibited an initial burst release followed by a sustained release of 88.46% compared to the marketed S.R. tablet which showed a slow and sustained release of 86.34% at the end of 24 hours.

KEYWORDS: Nanostructured lipid carrier, Gliclazide, Sustained release.

INTRODUCTION

Recently, innovative solid lipid carriers, such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have gained much interest to achieve controlled drug...
delivery. SLN and NLC are alternative colloidal drug carrier systems to emulsions, liposomes, and polymeric nanoparticles and consist of a matrix of lipid, which are solid at both room and body temperatures having a mean particle size between 50 and 1000 nm.[1] The primary difference between SLN and NLC is that the latter are prepared by mixing solid lipids with liquid lipids rather than highly purified lipids with a relatively similar molecular structure, as that used in SLN formulation. Consequently, NLC matrices consist of a less-ordered lipid matrix with imperfections, which may lead to an increase in drug-loading capacity and prevent drug expulsion during prolonged storage periods.[2,3]

Some advantages offered by NLCs are good physical stability, high drug payload, controlled drug release, specific targeting, scalability and feasibility of delivering both lipophilic and hydrophilic drugs. The protective effect of NLCs, coupled with their sustained/controlled release properties, prevents drugs/macromolecules from premature degradation and improves their stability in the gastrointestinal tract. These colloidal carriers have shown to improve bioavailability of poorly water soluble drugs.[4]

Gliclazide is a potential second generation oral hypoglycemic agent widely used for the treatment of noninsulin-dependent diabetes mellitus (NIDDM). Being a BCS class II drug, gliclazide is practically insoluble in water. It is extensively metabolized by the liver and has a half-life of around 10.4 hours.[5,6] In general, rapid gastrointestinal (GI) absorption is required for oral hypoglycemic drugs, in order to prevent a sudden increase in blood glucose level after food intake in patients with diabetes mellitus. However, the GI absorption rate of gliclazide, in conventional dosage form (i.e., tablets), appears to be rather slow. Several studies using healthy volunteers or patients revealed that the time to reach peak serum gliclazide concentration ranged from 2 to 8 hours following oral administration of the gliclazide tablet. It has been suggested that the slower absorption is due to either its poor dissolution owing to its hydrophobic nature or poor permeability across the gastrointestinal membrane.[7,8]

The objective of the present study was to increase the solubility and dissolution rate of gliclazide by formulating it into NLCs which will lead to controlled release of drug as well. NLC formulations were prepared by using Precirol ATO 5, Capryol 90, Tween 20 and Transcutol HP by high shear homogenization coupled with ultrasonication technique. The prepared systems were characterized for particle size, entrapment efficiency and in vitro drug
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release. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies were also performed to investigate the status of the lipid and the drug.

MATERIALS AND METHODS

Materials

Gliclazide was kindly provided by Cipla Pharmaceuticals Ltd., Mumbai, India. Solid lipids such as Compritol ATO 888, Precirol ATO 5, liquid lipids and surfactants such as Capryol 90 and Transcutol HP were obtained as gift samples from Gattefosse India Pvt. Ltd. Imwitor 900K, Imwitor 491 and Dynasan 114 were obtained as gift samples from Sasol GmbH, Germany. Trehalose and Tween 80 were purchased from Sigma-Aldrich, Mumbai, India. Dialysis bag (molecular weight cut off 12-14 kDa; pore size 2.4 nm) was supplied by Hi Media, Mumbai, India. All solvents and reagents used were of analytical reagent grade.

METHODS

Screening of lipids, oils and surfactants

For studying the solubility in solid lipids, accurately weighed 10 mg of Gliclazide was taken in a series of test tubes, the solid lipids were added in increments, and the test tubes were heated in a controlled temperature water bath kept at 10°C above the melting point of the respective lipid. The test tubes were intermittently vortexed using cyclone mixer and observed for any drug residue. The amount of lipid required to completely solubilize the drug in the molten state was estimated.\(^9\)

For determining the solubility in different oils, an excess amount of drug was added to 2 ml of oil in a vial. After tightly capping, these vials were kept on mechanical shaker for the period of 72 hours at room temperature. If the entire drug in vial was dissolved in respective oil then more amount of drug was added during the period of 48 hours. After that, it was centrifuged at 10,000 rpm for 30 minutes to separate the undissolved drug. The supernatant thus obtained was then filtered through membrane filter (0.45 μ). The filtrate was diluted appropriately with methanol and absorbance was recorded by UV spectroscopy at the wavelength of 228 nm.\(^10\) The concentration of Gliclazide dissolved in oil was determined.

The solubility of Gliclazide in various surfactants was determined by adding excess amount of drug to a 3% w/v surfactant solution in each respective vial. Vials containing this mixture were mixed using cyclone mixer and agitated on mechanical shaker for 72 hours at room temperature to attain equilibrium. The vials containing drug in surfactant solutions were centrifuged at 10,000 rpm for 30 minutes to separate the undissolved drug. The supernatant
thus obtained was then filtered through membrane filter (0.45 μ). The filtrate was diluted appropriately with methanol and absorbance was recorded by UV spectroscopy at the wavelength of 228 nm. The solubility of Gliclazide (mg/ml) in surfactants and solubilizers was determined by back calculation.[11]

**Selection of solid lipid to liquid lipid ratio**

The solid and liquid lipid with the best-solubilizing potential for Gliclazide i.e., Precirol ATO 5 and Capryol 90 were mixed in different ratios viz., 95:5, 90:10, 85:15, 80:20, 70:30, and 60:40 in order to establish the miscibility of the two lipids. The total amount of lipid selected for use was 500 mg. The lipid mixtures were kept at 85ºC for 1 hour in water bath shaker. After that the samples were allowed to cool at room temperature. The miscibility between the two components was investigated by smearing a cooled sample of the solid mixture onto hydrophilic filter paper, followed by visual observation to determine the presence of any liquid oil droplets on the filter paper. A binary mixture exhibiting a melting point above 40ºC and which did not reveal the presence of oil droplets on the filter paper was selected for use in the development of Gliclazide-loaded NLCs.[12] Further optimization of solid lipid to liquid lipid ratio was done by taking batches.

**Need and Selection of a Cosurfactant**

It was observed that the batches produced with Tween 20 alone were not completely stable after 24 hours and also variation in particle size was seen. Hence, there was a need of inclusion of a cosurfactant or coemulsifier. It has been reported in literature that use of surfactant and co-surfactant of hydrophilic and lipophilic natures yield better stabilization of the dispersed system. Therefore Transcutol HP which is an amphiphilic cosurfactant was included in the formulation.[13] Three formulations having different tween 20 to transcutol HP ratio i.e. 3:1, 4:1, 5:1 were designed. The formulation having highest % EE and optimum particle size was selected.

**Preparation of NLCs**

The preparation of NLCs dispersion was based on the principle of ‘High shear homogenization coupled with Ultrasonication’ technique. Accurately weighed solid lipid (Precirol ATO 5), liquid lipid (Capryol 90) and cosurfactant (Transcutol HP) were heated at about 75ºC and drug (Gliclazide) was added to obtain a clear melting solution. An aqueous phase was prepared by dissolving surfactant (Tween 20) in distilled water and heated to same temperature as that of oil phase. Then this hot aqueous surfactant solution was added to the
oil phase and homogenization was carried out (at 9,000 rpm and temperature 75°C) for 12 minutes by using Ultra Turrax T25 digital (IKA, Germany). This step produced coarse oil in water emulsion, which was further sonicated at ultrasonication power of 30 Watt (W) using a SONAPROS PR-250M ultrasonicator (Oscar Ultrasonics, Mumbai) for 10 minutes. Gliclazide-NLCs were obtained by allowing hot nanoemulsion to cool at 4-8°C under magnetic stirring for 10 to 15 minutes.

The optimized NLC dispersions were freeze dried with the selected cryoprotectant (Trehalose) to convert the nanoparticles in the form of dry powder and was directly filled in hard gelatin capsules of suitable size.

**Evaluation and characterization of Gliclazide NLCs**

**Entrapment efficiency**

Nanoparticle dispersion was centrifuged at 10,000 rpm for 30 min to separate the nanoparticles. NLCs dispersion was aggregated by addition of electrolyte such as NaCl to facilitate the separation of the nanoparticles. After centrifugation the supernatant was analyzed for amount of free drug by using UV-spectrophotometric method after suitable dilution with methanol at λ\text{max} of 228 nm.[14] The EE was calculated by the following formula:

\[
\% \text{ Entrapment efficiency (EE)} = \frac{\text{Amount of drug added} - \text{Unentrapped drug}}{\text{Amount of drug added}} \times 100
\]

**Particle size analysis**

The Particle size analysis was done by using NANOPHOX particle size analyzer (Sympatec GmbH, Germany). The principle behind the particle size measurement is cross correlation laser diffraction. Dispersions were diluted with doubled distilled water to ensure that the light scattering intensity was within the instrument’s sensitivity range. Measurements were carried out at a scattering angle of 90° at 25°C to the incident light and data were collected over a period of 2 minutes. The PDI measured the size distribution of the nanoparticles population.

**DSC study**

DSC analysis was performed to check the drug-lipid interaction in nanoparticulate formulations and crystallinity of drug. Samples were analyzed on SII Nanotechnology EXSTAR DSC 6220 in scanning range of 30-300°C at a heating rate of 10°C/min. DSC scans of plain drug, Drug-lipid physical mixture, Drug-trehalose and NLC formulation were recorded and compared.
X-ray diffraction study
X-ray scattering measurements were carried out with Pan-analytical Xpert PRO MPD X-ray diffractometer. Anode material used was copper having K$_{\alpha 1}$ and K$_{\alpha 2}$ radiation wavelength of 1.5405 and 1.5444 respectively with generator voltage of 45 KV and tube current of 40 mA and detected using Xcelerator diffracted beam monochromator. X-ray diffraction was carried out on pure Gliclazide, Lmix (Precirol ATO 5 and Capryol 90), blank freeze dried NLC and drug loaded freeze dried NLC.

Comparison of in vitro release profiles of Gliclazide NLC capsule and marketed SR tablet.
The marketed sustained release tablet of Gliclazide (Diamicron MR 30 mg) was used for the study. Drug release from both the formulations were studied in pH 7.4 phosphate buffer (900 ml) using USP XXIII dissolution testing apparatus type I with rotating basket at 100 rpm and temperature was maintained at 37 ± 0.5°C. 5 ml samples were withdrawn at different time intervals of 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours from dissolution medium and replaced with 5 ml of fresh buffer maintained at same temperature.$^{[15]}$ The withdrawn samples were filtered through syringe filter. The filtrate was injected into the column and assayed for Gliclazide content at the $\lambda_{max}$ of 228 nm using validated HPLC method. The % cumulative release versus time graphs were plotted and compared.

The HPLC analysis was carried out using an Agilent Technologies 1200 series system, based on quaternary pump plus autosampler, UV detector and EZ-Chrome software. The column Hemochrom Intsil, C-18 (250 x 4.6 mm, 5 mm i.d. and 5 µm particle size) was maintained at 25°C. An isocratic mobile phase used was ACN: 50 mM Potassium dihydrogen phosphate buffer (pH 3.6 adjusted by orthophosphoric acid) (70:30 %v/v) with the flow rate of 0.9 ml/min and detection was carried out at $\lambda_{max}$ of 228 nm.

RESULTS AND DISCUSSION
Screening of lipids, oils and surfactants
The lipid, itself, is the main ingredient of lipid nanoparticles that influence their drug loading capacity, their stability and the sustained release behavior of the formulations. Selection of appropriate lipids is essential prior to their use in preparation of lipid nanoparticle dispersions. The lipid which gave stable dispersion, solubilized maximum amount of drug and compatible was selected. Among the various solid lipids screened, Precirol ATO 5
showed highest solubility for Gliclazide (480mg lipid for 10mg drug) as shown in table 1. Hence, it was selected as model lipid for formulation and development studies.

Table 1: Amount of solid lipid required to solubilize 10 mg of Gliclazide

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Lipid</th>
<th>Amount of lipid (mg) required to solubilize Gliclazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compritol 888 ATO</td>
<td>535 ± 1.84</td>
</tr>
<tr>
<td>2</td>
<td>Precirol ATO 5</td>
<td>480 ± 1.46</td>
</tr>
<tr>
<td>3</td>
<td>Imwitor 900 K</td>
<td>668 ± 2.51</td>
</tr>
<tr>
<td>4</td>
<td>Imwitor 491</td>
<td>720 ± 1.67</td>
</tr>
<tr>
<td>5</td>
<td>Dynasan 114</td>
<td>570 ± 2.68</td>
</tr>
<tr>
<td>6</td>
<td>Glyceryl tripalmitate</td>
<td>794 ± 3.21</td>
</tr>
<tr>
<td>7</td>
<td>Glyceryl tristearate</td>
<td>More than 1000 mg</td>
</tr>
<tr>
<td>8</td>
<td>Geleol</td>
<td>More than 1000 mg</td>
</tr>
</tbody>
</table>

Among the various liquid lipids screened, Capryol 90 showed highest solubility for Gliclazide (29.656 mg/ml of oil) as shown in table 2. Main role of Capryol 90 in NLCs formation is to disorganize the structure of lipid matrix and improve drug incorporation ability and drug loading. Hence Capryol 90 was considered as the best choice for the preparation of NLCs to maximize the entrapment of drug.

Table 2: Solubility of Gliclazide in different oils

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Oil</th>
<th>Saturation solubility (mg of drug/ml of oil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isopropyl myristate</td>
<td>4.728</td>
</tr>
<tr>
<td>2</td>
<td>Isopropyl palmitate</td>
<td>4.184</td>
</tr>
<tr>
<td>3</td>
<td>Miglyol 812</td>
<td>9.138</td>
</tr>
<tr>
<td>4</td>
<td>Capryol 90</td>
<td>29.656</td>
</tr>
<tr>
<td>5</td>
<td>Oleic acid</td>
<td>22.309</td>
</tr>
<tr>
<td>6</td>
<td>Ethyl oleate</td>
<td>17.493</td>
</tr>
<tr>
<td>7</td>
<td>Labrafil M1944</td>
<td>11.305</td>
</tr>
</tbody>
</table>

Generally surfactants exhibiting poor drug solubility materialize the drug moieties in the lipid core and impart firm association of drug with the lipid matrix. So, surfactants exhibiting least solubility for Gliclazide were to be selected. Gliclazide exhibited least solubility in Poloxamer 407, Tween 20, Cremophor RH 40, Solutol HS 15 and Lutrol 400. The selected surfactants were screened by taking batches and evaluated for parameters like stability and particle size (Table 3). From the observations, it was concluded that Tween 20 as a surfactant produces stable batches with desired particle size. Hence, Tween 20 was chosen as surfactant for the formulation.
Table 3: Composition of batches for surfactant selection

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Drug (mg)</th>
<th>Total Lipid (mg)</th>
<th>Surfactant</th>
<th>Surfactant concentration (%)</th>
<th>Stability</th>
<th>Particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>500</td>
<td>Poloxamer 407</td>
<td>2</td>
<td>Aggregation of particles seen</td>
<td>756.12</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>500</td>
<td>Tween 20</td>
<td>2</td>
<td>Stable</td>
<td>266.62</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>500</td>
<td>Cremophor RH 40</td>
<td>2</td>
<td>Unstable</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>500</td>
<td>Solutol HS 15</td>
<td>2</td>
<td>Unstable</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>500</td>
<td>Lutrol 400</td>
<td>2</td>
<td>Gelling observed</td>
<td>--</td>
</tr>
</tbody>
</table>

Selection of solid lipid to liquid lipid ratio

In terms of visual assessment, for the binary mixtures of ratios 95: 5 to 70: 30, no oil droplets were seen on samples smeared on filter paper. Only in the binary mixture of ratio 60: 40, droplets of oil were observed on the filter paper. It may well be desirable to have relatively high liquid lipid content in a binary mixture of Precirol ATO 5 and Capryol 90 in order to enhance the solubility of Gliclazide in the lipid medium as the drug exhibits a marginally better solubility profile in the liquid lipid than in solid lipids. However, the results suggest that a liquid lipid content of 30% w/w or less was optimal and concentrations higher than 30% w/w are likely to result in the production of immiscible mixtures.

The % entrapment efficiency (EE) of different batches of NLCs having the ratio of solid lipid: liquid lipid from 80: 20 to 60: 40 is shown in table 4. It is clear from the data obtained that as the ratio was increased from 80: 20 to 70: 30, the % EE was increased from 74.43 to 78.62. However, when the formulation contains more than 30% w/w of Capryol 90, the % EE was decreased to 75.06.

This is because at higher contents of the liquid lipid, a part of the liquid lipid was expelled from the crystal lattice of the solid fat, which can lead to partitioning of drug in the aqueous phase, thereby decreasing the entrapment efficiency. Based on these observations, Precirol ATO 5 and Capryol 90 in the ratio of 7: 3 was selected as final working ratio of solid lipid: liquid lipid since at this ratio it exhibited good solubility for Gliclazide, had higher entrapment efficiency and at the same time formed a solid matrix on cooling, which is a prerequisite for NLC fabrication.
Table 4: % EE of different solid lipid: liquid lipid ratio

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Precirol ATO 5: Capryol 90</th>
<th>% Entrapment efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80:20</td>
<td>74.43</td>
</tr>
<tr>
<td>2</td>
<td>70:30</td>
<td>78.62</td>
</tr>
<tr>
<td>3</td>
<td>60:40</td>
<td>75.06</td>
</tr>
</tbody>
</table>

Selection of a Cosurfactant

Transcutol HP is an amphiphilic liquid, well accepted for peroral and dermal route and can effectively partition into aqueous and lipid phase offering better stability to the system. It has an HLB value of 4 which enhanced the solubility of Gliclazide into the lipid matrix and resulted in the formation of stable NLCs. The % EE, particle size and polydispersity index (PDI) of different batches of NLCs having the ratio of tween 20: transcutol HP from 3:1 to 5:1 is shown in table 5. From the data, it was evident that higher amounts of transcutol HP relative to tween 20 produced NLC dispersions with low entrapment efficiency and larger particle size. The aim was to select the ratio which gives maximum % EE and lower particle size with stable NLCs dispersion. Hence, ratio of 5:1 was chosen for tween 20: transcutol HP which produced stable NLCs with desired % EE, particle size and PDI.

Table 5: % EE, particle size and PDI of different Tween 20: Transcutol HP ratio

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Drug (mg)</th>
<th>Total lipid (mg)</th>
<th>Tween 20: Transcutol HP (250 mg)</th>
<th>% EE</th>
<th>Particle size (nm)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>500</td>
<td>3:1</td>
<td>72.55</td>
<td>228.21</td>
<td>34.24</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>500</td>
<td>4:1</td>
<td>73.48</td>
<td>202.47</td>
<td>31.08</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>500</td>
<td>5:1</td>
<td>75.76</td>
<td>187.99</td>
<td>24.54</td>
</tr>
</tbody>
</table>

Evaluation and characterization of Gliclazide NLCs

Entrapment efficiency and Particle size

The lipid and surfactant concentration affects %EE and particle size. The % EE increased with increase in concentration of total lipid content of formulations. The % EE increased when the concentration of total lipid was increased from 3 to 7% due to the increase in solubility of Gliclazide in Precirol ATO 5 and Capryol 90. However it significantly decreased on increasing the concentration of total surfactant from 1.5 to 3.5%.

Particle size distribution is one of the most important characteristics for the evaluation of the stability of colloidal systems. The PDI gives information about the homogeneity of particle size distribution in the system. As the concentration of lipid increases, particle size increases since at high lipid concentration, there is a tendency of lipid to coalesce. As the concentration
of surfactant increases, the particle size decreases which may be due to the surfactant-induced reduction in surface tension between aqueous phase and lipid phase, thus preventing particle aggregation. Hence Batch 3 (Table 5) having total lipid concentration of 500mg and surfactant: co-surfactant concentration in the ratio of 5:1 was selected as final batch which showed maximum entrapment of 75.76% and minimum particle size of 187.99 nm with good stability.

**DSC study**

DSC studies were performed to investigate the physical state of the drug in the NLC, because this aspect could influence the *in vitro* and *in vivo* release of the drug from the system. DSC thermograph of Gliclazide exhibited a sharp endothermic peak at 174.93°C as seen from Fig 1A. From the peak of physical mixture of Gliclazide with Lipid mix, it was confirmed that the drug was melted in the lipid mixture, as there was no melting event of Gliclazide seen (Fig 1B).

Also a decrease of enthalpy was recorded after blending drug and Lmix, indicating presence of more unstable polymorphic forms and predicting high drug loading capacity. The thermograph of physical mixture of Gliclazide with cryoprotectant i.e. Trehalose exhibited endothermic peak for Trehalose at 214.32°C and a sharp endothermic peak of Gliclazide at the same place (Fig 1C). The melting peak of pure drug was totally disappeared in the thermogram of freeze dried NLC (Fig 1D), evidencing the absence of crystalline drug in the NLC powder. The endothermic peak at 60.29°C indicated melting point of the Lmix and the peak at 214.32°C is endothermic peak of Trehalose in the NLC formulation.

**X-ray diffraction study**

Fig 2 shows the characteristic XRD peaks of Gliclazide, Lmix, blank and drug loaded freeze dried NLC respectively. In this study, the characteristic peaks for Gliclazide and Lmix were not seen in the diffraction pattern of the optimized NLC freeze dried product. From this we can conclude that Gliclazide was completely incorporated into NLC freeze dried powder and remains in the amorphous form.
Fig 1: DSC thermograms of A. Gliclazide, B. Drug lipid physical mixture, C. Drug and trehalose, D. Freeze dried NLC formulation.
Fig 2: X-ray diffraction pattern of A. Gliclazide, B. Lipid mix, C. Blank freeze dried NLC and D. Drug loaded freeze dried NLC
Comparison of in vitro release profiles of Gliclazide NLC capsule and marketed SR tablet

Figure 3, shows the comparative release of Gliclazide from NLC capsule and marketed sustained release tablet. The drug release from NLC capsule and marketed sustained release tablet at the end of 24 hrs was found to be 88.46 and 86.34 % respectively. It was also clear that in case of NLC capsule, a biphasic release pattern was observed i.e. a burst release in initial stage followed by a sustained release. About 40 % of loaded Gliclazide was released from the capsule within the first 2 hrs. The occurrence of burst release clearly indicates the location of certain amount of Gliclazide onto the surface of NLCs, whereas the sustain release profile suggests the release of Gliclazide from the core of lipid matrix to the release medium. While in case of Marketed SR formulation, the drug was released in a sustained manner right from initially. The initial fast release of drug from the NLC capsule could be desirable for oral hypoglycemic agents in order to prevent postprandial plasma glucose levels in diabetic patients.[16]

CONCLUSION
Nanostructured lipid carriers have been used as one of the carrier systems for increasing solubility and oral bioavailability of poorly water soluble drugs. In the present work stable gliclazide NLCs were prepared by high shear homogenization coupled with ultrasonication technique which was converted into dry powder by lyophilization. Formulation developed using Precirol ATO 5, Capryol 90, Tween 20 and Transcutol HP showed high EE and satisfactory particle size distribution. DSC and XRD studies proved the favorable crystalline
behavior of NLCs for protection and entrapment of Gliclazide. *In vitro* release studies of Gliclazide NLCs was comparable to the marketed S.R. tablet with NLC formulation showing better release characteristics. Thus the Gliclazide NLCs can be proposed as a promising drug delivery system for improving the solubility and release kinetics of drug. Further studies are needed to investigate these formulations for its performance *in vivo*, which might aid in dose reduction by avoiding presystemic metabolism and untoward effect due to direct absorption of the drug at the desired site of action.

**ACKNOWLEDGMENTS**

The authors are thankful to Cipla Pharmaceuticals Ltd., Mumbai, India, Gattefosse India Pvt. Ltd and Sasol GmbH, Germany for providing gift samples of drug and excipients respectively. The authors are grateful to Tata Institute of Fundamental Research (TIFR), Mumbai, India, for providing facility and assistance during XRD studies.

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