Solid Dispersion of Nateglinide in Polyoxy Ethylene-Polyoxy Propylene Block Copolymer: in vitro and in vivo Evaluation

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ABSTRACT

Objective: The study was aimed to improve solubility and bioavailability of nateglinide preparing stable solid dispersions with polyoxy ethylene-polyoxy propylene block copolymer (poloxamer 188). Methods: The solid dispersions were prepared by the melting and solvent technique at 1:1, 1:2, 1:3 (w/w) of drug to carrier ratios. The formulations were characterized by fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction, scanning electron microscopy, dissolution behaviour, stability and in vivo performance. Result and Discussion: The results showed an increase in solubility (52.57 fold) and an enhancement in dissolution of solid dispersions compared to pure nateglinide (P<0.05). FTIR showed retainment of individual peaks indicated few characteristics groups in the drug structure. The DSC thermograms and XRD pattern showed the significant change in crystallinity to amorphous of nateglinide. Pharmacokinetic study was performed in rabbits, showed improved bioavailability (1.71 fold, AUC) of nateglinide in solid dispersions (1:3 w/w). Similarly Cmax and Tmax of solid dispersions showed significant difference over the pure drug. Conclusion: The study indicated poloxamer 188 was suitable carrier and melting technique was suitable method for improvement of dissolution and bioavailability of nateglinide.

Key words: Nateglinide, Poloxamer 188, Bioavailability, Crystallinity, Solid dispersion.

INTRODUCTION

Diabetes mellitus is probably one of the oldest diseases known to man about 3000 years ago.1 It is estimated that 552 million people would have diabetes mellitus by the year 2030.2 Nateglinide (meglitinides class) is a non-sulphonylurea insulinotropic oral anti-diabetic agent.3 Chemically, it is [N-(trans-4-isopropylcyclohexylcarbonyl) - D-phenylalanine] & structure shown under Figure 1. It is an oral meal time glucose regulator, stimulating the release of insulin from the pancreas by closing ATP-dependent potassium channels in the membrane of the β cells.4 It is prescribed as 60-120 mg three times daily (tid) prior to each meal, may be increased to 180 mg tid if necessary. Nateglinide is classified as a class II drug based on the biopharmaceutical classification system (BCS), due to its low water solubility and high permeability.5 Nateglinide is an anionic compound with pKa value 3.1 and log value 4.2. Nateglinide is freely soluble in ethanol, but it is practically insoluble in water (8.8 mg/L).6 Several approaches can be followed for the enhancement of solubility hence dissolution rate of lipophilic drugs like size reduction, solid dispersion (SD), complexation, prodrug approach, formation of salts.7-10 Some techniques like, nanotechnology,5 co-mixing,3 co-milling,6 complexation,11 liquisolid12 have been studied to enhance solubility of nateglinide. These techniques were partially fulfil the requirements. SD is an efficient technological and manufacturing approach to enhance the solubility and dissolution rate of lipophilic...
drugs first described by Sekiguchi and Obi in 1961.\textsuperscript{13} Preparation of SDs is practicable and economic methods to improve wettability, reduction in particle size, increase surface area and conversion of crystalline to amorphous state.\textsuperscript{8}

Many carriers like poloxamer, gelucire, polyethylene glycols (PEGs), sodium carboxymethyl cellulose, povidone, crospovidone, microcrystalline cellulose, polymethacrylate, chitosan, polyvinyl pyrrolidones are used to obtain SDs.\textsuperscript{7,9,10} Poloxamers are non-ionic polyoxyethylene-polyoxypropylene copolymers available in different grades, differing in the relative amounts of propylene and ethylene oxides added during manufacturing. They have been widely used primarily in pharmaceutical formulations as emulsifying or solubilising, wetting agents and prevents the recrystallization. Generally two common poloxamer grades were used namely poloxamer 188 (Lutrol\textsuperscript{®} F68) and poloxamer 407 (Lutrol\textsuperscript{®} F127) because of their low melting point, surfactant properties and oral safety.\textsuperscript{14,15}

Melting (Fusion) (MM), solvent evaporation/solvent method (SM), melting-solvent, spray drying, closed melting, microwave treated or microwave generated, fusion-cooling, fusion evaporation, hot melt extrusion, supercritical fluid precipitation, melt agglomeration are some of the techniques reported by different researcher for the preparation of SDs.\textsuperscript{8,9,10} The MM is a mixture of drug and polymer that has been melted and rapidly cooled to obtain the supersaturation of the drug. There is no use of solvents and need high temperature is the advantage and disadvantage of this method respectively, so the use of thermolabile drugs is a limitation. The SM consists of the solubilization of the drug and carrier in a common volatile solvent or mixture of solvents that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented, since the evaporation of organic solvent occurs at low temperature.\textsuperscript{16-18}

So, an attempt was made to investigate the possibility of enhancing the dissolution and bioavailability of nateglinide SDs prepared by MM and SM with polyoxyethylene-polyoxypropylene copolymer (poloxamer 188). SDs are characterize using flourier transfer infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffractometry (PXRD) scanning electron microscopy (SEM), stability studies, dissolution and pharmacokinetic evaluation.

**MATERIALS AND METHODS**

**Materials**

Nateglinide was obtained as gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Poloxamer 188 was purchased from Yarrow Chem Pvt Ltd, Mumbai, India. All the other chemicals and reagents were of HPLC grade and purchased from lotus enterprises, Visakhapatnam.

**Preparation of binary SD**

Binary SDs at various weight ratios 1: 1, 1: 2 and 1: 3 (drug:carrier) were prepared by MM and SM. In MM, nateglinide was added to the molten base comprising poloxamer 188. The blend was heated 10°C above the melting point of carrier for 10 minutes with continuous stirring. The system was cooled rapidly in an ice bath containing sodium chloride for 3 h. In SM, minimal quantity of ethanol was used to dissolve the nateglinide and carrier (poloxamer 188) by continuous stirring with a magnetic stirrer for at room temperature. Solvent was removed under reduced pressure using a rotary evaporator (Model R-215, Buchi, Switzerland) kept at 40°C until all the solvents were evaporated. The obtained mass was further dried at 40°C in hot air oven for 12 h. The resulting SDs were scraped, pulverised in a mortar and pestle and passed through 40 mesh sieve. The samples were stored in screw cap glass vials and kept in a desiccator until further uses. Physical mixtures (PMs) were also prepared mixing in a motor and pestle for 10 min in order to obtain a homogenous mixture.

**Determination of nateglinide**

A valid reversed phase high pressure liquid chromatography (HPLC, Agilent 1220 infinity series, software: Ezichrome elite, Agilent Technologies, USA) method was used with slight modification for quantification of nateglinide for *in vitro and in vivo* studies.\textsuperscript{19} A revered phase hyperchrom ODS-BP, (250 X 4.6 mm, 5µ) column used for separation. The mobile phase was 10 mM phosphate buffer: acetonitrile (50:50; v/v). The effluent was observed at 210 nm after a retention time of 3.16 min with a flow rate of 1.0 mL/min. The assay was linear for nateglinide in the concentration range of 100-1000 ng/mL.

**Determination of drug content**

An accurately weight of SDs or PMs, equivalent to 50 mg of nateglinide was taken in a 100 mL of volumetric flask. Each mixture was dissolved in few mL of ethanol and made up to the volume with 0.01 N HCl with 0.5% w/v sodium lauryl sulphate (SLS). The solution was filtered through a 0.45 µm membrane filter paper and quantified by HPLC after doing appropriate dilution.

**Solubility determination**

An excess amount of the sample was placed in water individually in stoppered glass vial. The samples were shaken for 48 h at 37°C in a horizontal shaker. The resulting supernatant was filtered through a Millipore
filter (pore size 0.45 µm). The filtrate (1mL) was diluted immediately and assayed. 20

**In vitro dissolution studies**

In vitro dissolution studies were performed in triplicate using the USP II dissolution test apparatus (Electrolab, Mumbai, Model no. TDT-08L) maintained at temperature of 37 ± 0.5°C at 50 rpm speed in 1000 mL of 0.01N HCl with 0.5 w/v % of SLS. The dissolution studies were performed for pure drug and formulations containing an equivalent to 60 mg of the nateglinide. At the predetermined sampling intervals (5, 10, 15, 30, 45, 60, 90 min), 5 mL samples were withdrawn, filtered through membrane filter (0.45 µm, Millipore). Fresh medium (37°C) was added after each sampling to maintain its constant volume throughout the test. The filtrate sample (1 mL) was suitably diluted with the mobile phase and was subsequently quantified using HPLC. Experiments were performed in triplicate.

**Fourier transform infrared spectroscopy**

FTIR spectroscopy was used to investigate the probability of chemical interaction between ingredients. Sample (2 mg) and potassium bromide (10 mg) were weighed and homogenized using a mortar. The mixtures were compressed using a hydraulic press to obtain a translucent pellet. The pellet was placed in an infrared spectrophotometer (Shimadzu IR-Prestige -21, Kyoto, Japan). The samples were analysed over a scanning range of 4,500-500 cm⁻¹.

**Differential scanning calorimetry**

DSC was performed for the pure nateglinide, poloxamer 188 and the formulations using a DSC apparatus (Pyris Diamond Thermo gravimetry (TG) /Differential thermal analysis (DTA), PerkinElmer, Singapore). The powdered sample (3-5 mg) was hermetically sealed in aluminium pans and lids were crimped using a TA crimper and heated at a constant rate of 10°C/min over a temperature range of 20-350°C, using nitrogen as purge gas at a flow rate of 150 mL/min. Platinum crucible used with alpha alumina powder as reference.

**Powder X-ray diffraction**

Powder XRD was performed at room temperature with an X-ray diffractometer (Ultima-III, Rigaku, Japan). Monochromatic Cu Kα radiation (λ = 1.5418Å) was obtained with a Ni-filtration and a system of diverging and receiving slides of 0.5° and 0.1 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and current of 30 mA over a 20 range of 3-40° using a step size of 0.02° at a scan speed of 1sec/step.

**Scanning electron microscopy**

The morphology of the samples was examined by a SEM apparatus (Model- JSM6360, Jeol, UK) equipped with an energy dispersive X-ray (EDX) Oxford ISIS 300 micro-analytical system. The samples were covered with carbon coating in order to increase conductivity of the electron beam. Operating conditions were accelerating voltage 20 kV, probe current 45 nA, and counting time 60 sec.

**Stability test**

Long term stability testing of poloxamer 188 based SDs (SM) were performed as per the ICH guidelines in the stability chamber (25°C and 60% RH) (Remi Instruments, India). 21 Samples were analysed periodically for 6 months. The samples were subjected to DSC and PXRD to explore the changes in the system.

**Pharmacokinetic studies**

**Animal study**

The objective of this study was to characterize the bioavailability of nateglinide from SDs as compared with the pure drug. The procedure for the in vivo study was approved by the institutional animal ethical committee and appropriate guidelines for the use of animals were followed during the study. Twelve male New Zealand rabbits (body weight 1.75 ± 0.08 kg) divided randomly into two groups (n=6), were fasted for 24 h prior to the experiments and given free access to the water. Pure drug nateglinide (10 mg/mL suspended in 0.5% methyl-cellulose prepared in water for injection) and poloxamer 188 based SDs (MM) at a dose equivalent to 10 mg/kg of nateglinide were administered orally. Blood samples (1 mL) were collected from marginal ear vein at time points of 0.5, 1, 2, 4, 8, 12 and 24 h post dose and transferred to ethylenediaminetetraacetic acid (EDTA) - coated tubes to prevent coagulation. Then blood samples were centrifuged at 5000 rpm for 10 min and the obtained plasma samples were stored at – 80°C until analysis.

**Preparation of sample**

Frozen plasma samples were thawed at ambient temperature prior to extraction. In polypropylene tubes (5 mL capacity), 0.1 mL of plasma was transferred with 2 mL of diethyl ether was added for extraction. Then, the mixture was vortexed for 15 min and centrifuged up to 20 min. The supernatant layer was separated to a clean centrifuge tube and the obtained plasma samples were stored at – 80°C until analysis.
**Pharmacokinetic analysis**

The software program PKSolver was used to analyze pharmacokinetic parameters by non-compartmental analysis. Maximum plasma concentration ($C_{max}$), time to reach the peak plasma concentration ($T_{max}$) and area under the plasma concentration-time curve ($AUC_{0-t}$) were obtained from plasma data.²²

**RESULTS AND DISCUSSION**

Amorphous SDs were formulated with polyoxyethylene-polyoxypropylene copolymer (poloxamer 188). The SDs were prepared in MM and SM at 1:1, 1:2, 1:3 drug to carrier weight ratios.

**Drug content and solubility studies**

The drug content of the PMs and SDs of the poloxamer 188 ranged between 97.12 to 99.56 and 98.55 to 102.39% respectively (Figure 2). This indicated these techniques were suitable for formulation with high recovery, reliable and reproducible with uniform drug distribution. The aqueous solubility of nateglinide was found to be 8.27 mg/L, at 25ºC and similar result was also reported by Maggi et al. Solubility of nateglinide was increased as the concentration of carrier increased. PMs showed less drug solubility than SDs (MM and SM). In PM, hydrophilic nature of the poloxamer 188 may help to solubilise the drug that enhanced the solubility. Solubility of nateglinide in poloxamer 188 showed 52.57 fold and 39.10 fold increased solubility in MM and SM at 1:3 weight ratio (Figure 2). The significant improvement in solubility of nateglinide in poloxamer 188 may due to the polymeric surface active nature of carrier and swelling, upon contact with water. Conversion of crystalline nateglinide into amorphous state also might be another reason for enhancement of solubility.²³

**Drug release study**

The luminal dissolution rate is most likely the limiting step in the intestinal absorption for poorly water soluble drugs. The dissolution rate enhancement is of paramount importance to increase the bioavailability of nateglinide after oral administration. The cumulative release of nateglinide at various time intervals from the PMs and SDs made by using various concentration of poloxamer 188 are depicted in Figure 3. The pure drug nateglinide exhibited an incomplete dissolution (~ 45%) after 90 minutes of assay. PMs of nateglinide with polaxamer 188 in all ratios showed higher drug release than that of pure nateglinide due to the presence of highly hydrophilic carrier. Dissolution rates for SDs were greater than those for PMs and nateglinide alone. SDs (MM, 1:3 ratio) showed faster and complete drug release within 30 min. In 30 minutes, SDs of polaxamer 188 MM showed 85-100% drug release and SM displayed 79-83% drug release. SD (MM, 1:3 w/w) demonstrated better drug release than other ratios of same method, used for the further study.

Dissolution was remarkably improved in both systems compared to pure nateglinide (P < 0.05). Statistical analysis showed that there was no significant difference in the percentage nateglinide release from SDs prepared by MM and SM (P > 0.05) at 1:1 and 1:2 but there was significant difference of drug release at 1:3 weight ratio in 30 min. The enhanced dissolution rate of SDs may be due to hydrophilic, surfactant nature at 30 minutes of carrier and
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drug conversion to amorphous state, reduction of particle size.\textsuperscript{24} Hence, poloxamer 188 was suitable carrier for better drug release, thus bioavailability enhancement.

The $Q_{15\text{min}}$ and $Q_{90\text{min}}$ values (percent drug dissolved within 30 and 90 minute) and relative dissolution rate in 30 minute (RDR\textsubscript{30min}) of nateglinide, physical mixture and its SDs in poloxamer 188 prepared at different drug: carrier ratios were illustrated in Table 1. In order to compare the effect of carrier on drug dissolution behaviour, $Q_{15\text{min}}$, $Q_{90\text{min}}$, RDR\textsubscript{30min} values are calculated. From the Table 1, it is evident that as the concentration of poloxamer 188 was increased, $Q_{15\text{min}}$ and $Q_{90\text{min}}$ of SDs prepared by the techniques of melting was increased. The ratio RDR\textsubscript{30min} values were increased in physical and melting except SM (decreased at 1:3 ratio).

From this discussion it was illustrated that carrier poloxamer at 1:3 w/w ratio was sufficient to enhance the nateglinide dissolution.

### FTIR Analysis

Infrared spectroscopy was used to evaluate the possible interaction between drug and carriers used in various prepared SDs. The FTIR spectra of nateglinide, poloxamer 188, PMs and their SDs prepared by MM and SM are presented in Figure 4. The IR spectrum of pure nateglinide showed a characteristic peak of aromatic C-H stretching vibration at 3068 cm\textsuperscript{-1}. An asymmetric stretching peak at 2918 cm\textsuperscript{-1} and symmetric stretching peak at 2864 cm\textsuperscript{-1} were detected for C-H group. A peak at 3307 cm\textsuperscript{-1} evidenced the N-H stretching vibration. The characteristic peak for C=O stretching for ketone showed at 1687 cm\textsuperscript{-1}.

The characteristic peaks at 2883.58 cm\textsuperscript{-1} and 1109 cm\textsuperscript{-1} are assigned to stretching vibrations of the O-H and C-O groups of poloxamer 188. The spectra of PM and SDs are largely similar to the addition spectra of individual components. The characteristic peak nateglinide at 1687 cm\textsuperscript{-1} was shifted to 1682.54 cm\textsuperscript{-1} indicated formation of hydrogen bonding between nateglinide-poloxamer 188. The SDs spectrum did not show any additional peak indicating the absence of any significant chemical reaction between nateglinide and carriers.

### DSC Study

The thermograms of drug, poloxamer 188, their PMs and SDs demonstrated in Figure 5. The DSC thermogram

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**Table 1: The $Q_{15}$, $Q_{90}$ and RDR after 30 min of nateglinide, PMs and its SDs in poloxamer 188 prepared at different drug: polymer ratios**

<table>
<thead>
<tr>
<th>Carrier</th>
<th>Ratio</th>
<th>PM</th>
<th>SDs</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$Q_{15}$</td>
<td>$Q_{90}$</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td>18.96</td>
<td>45.29</td>
</tr>
<tr>
<td>Poloxamer 188</td>
<td>1:1</td>
<td>29.4</td>
<td>53.3</td>
</tr>
<tr>
<td></td>
<td>1:2</td>
<td>30.52</td>
<td>54.85</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>34.8</td>
<td>59.25</td>
</tr>
</tbody>
</table>

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**Figure 4: FTIR spectra of pure drug nateglinide, carrier, PM and its SDs (1:3 w/w).**

**Figure 5: DSC thermograms of pure drug nateglinide, carrier, PM and its SDs (1:3 w/w).**
of nateglinide exhibited a well defined endothermic peak at 136.67 °C with enthalpy of fusion (ΔH) 89.83 J/g corresponding to its melting point indicating its crystallinity.\textsuperscript{25} The endotherm of poloxamer 188 displayed a characteristic melting peak at 60.80°C with heat of fusion 182.81 J/g. Thermal behaviour of PM of drug and poloxamer 188 showed that the melting peak of nateglinide was shifted to a lower temperature (130.05°C). In the DSC curve of SDs (MM) the melting peaks of poloxamer 188 was almost unchanged but the melting endotherms of nateglinide showed intense changes. The decreased in melting peak of nateglinide indicated transition to amorphous form. In SDs (SM) showed both drug and carrier melting peak indicated partial conversion to amorphous form. The above result indicated that during preparation of SDs, the drug partially exist in amorphous state. As the concentration (weight ratio) of poloxamer 188 was increased from 1: 1 ratio to 1: 2 and 1:3 ratios, indicating the melting peaks of drug become shorter and broader with decrease in heat of fusion (ΔH= 6.10 J/g) (thermogram not shown). This indicates that most of the drug exist in the amorphous state and the amount of poloxamer 188 used was sufficient to solubilise nateglinide.

**PXRD study**

The PXRD patterns of nateglinide, poloxamer 188, their PM and SDs are shown in Figure 6. The X-ray diffractogram of nateglinide exhibited sharp and intense peak at 2θº equivalent to 10º, 13º, 14.25º, 19º, 20º, 23º indicated crystalline in nature. Similar crystalline pattern was also observed by Maggi \textit{et al.} in 2013.\textsuperscript{5} Poloxamer 188 showed two prominent peaks at 19º and 23º indicated semicrystalline in nature. A comparison of XRD of pure drug with that of PMs and SDs showed reduction in peak intensity but drug still retained some of its crystallinity. PXRD pattern of PMs did not exhibit significant change of crystallinity of the drug but SDs showed change of crystallinity in poloxamer 188 formulations. There was no sharp and intense peak in SD of poloxamer 188 prepared by MM, indicates crystallinity of the drug was disappeared, indicates amorphous state, which supports the DSC and dissolution data.

**SEM study**

The photomicrographs of nateglinide shown in Figure 7 (A) illustrated irregular size and morphology of drug crystals. Poloxamer 188 appeared as smooth surfaced spherical particles shown in the Figure 7 (B). In PM, drugs were deposited in poloxamer 188. The photomicrographs indicating the drug was incorporated in the polymers revealed that the larger crystals of nateglinide were transferred to less crystalline structures in their SDs. The wrinkled surface of the SDs indicated increase in surface area that may playing a major role to increase in solubility. Physical transformation to amorphous of nateglinide in the SDs, which was further confirmed by DSC and XRPD studies.

**Physical stability test**

The amorphous state of the drug in SD was thermodynamically unstable. It reverts back to its stable crystalline form. So, stability study was performed for the SDs according to ICH guidelines. DSC thermograms of the formulation showed single peak without any additional peaks confirm formulation was stable under the storage conditions (Figure 8). PXRD pattern did not show any sharp and intense peaks indicated there was no recrystallization. This results confirmed good physical stability.

![Figure 6: X-ray diffraction pattern of pure drug nateglinide, carrier, PM and its SDs (1:3 ratio w/w).](image)

![Figure 7: SEM microphotographs of (A) pure drug nateglinide, (B) poloxamer188, (C) PM, (D) MM, (E) SM.](image)
of the formulation during storage and poloxamer 188 may played a leading role to prevent recrystallization.

**In vivo studies**

The SDs (MM, 1:3 ratio) was stable and higher rate of dissolution rate was selected for *in vivo* study and compare with pure drug nateglinide. Pharmacokinetic study was performed in rabbits, to assess the *in vivo* bioavailability. The plasma concentration-time curves after oral administration of pure drug and formulation were depicted in Figure 9 and the essential pharmacokinetics parameters were summarized in the Table 2. The AUC of the formulation was significantly higher (1.71 fold) than the pure drug that indicates improvement of oral bioavailability of formulation. C<sub>max</sub> and T<sub>max</sub> were increased by 2.35 and 8 fold respectively which revealed rapid absorption of drug from SD as compared to pure drug, which may be attributed to higher solubility of amorphous nateglinide in SD. Mean residence time (MRT) and t<sub>1/2</sub> of nateglinide SD were 12.63 h and 14.00 h respectively.

**CONCLUSION**

The obtained results demonstrated, SDs formulated using poloxamer 188 as suitable carrier and MM was suitable method for the enhancement of dissolution rate and bioavailability of nateglinide. The poloxamer 188 has the greater capacity to prevent the recrystallization during the storage condition, which produced a stable product. These findings could be explained by conversion of crystalline into amorphous form (a more soluble form), increase wettability, decrease in particle size, decrease in agglomeration of particles were supported by the FTIR, DSC, XRD, SEM analysis.

**CONFLICT OF INTEREST**

No conflict of interest

**ACKNOWLEDGEMENT**

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**ABBREVIATION USED**


**Table 2: Pharmacokinetic parameters of pure drug nateglinide and poloxamer 188 based SDs (MM) in rabbits (mean ± S.D., n = 6)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nateglinide</th>
<th>SD-MM (1:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>8.00 ± 0.05*</td>
<td>1.00 ± 0.05*</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>317.79 ± 28.96</td>
<td>746.37 ± 41.27</td>
</tr>
<tr>
<td>AUC₀₋₅ (ng h/mL)</td>
<td>3814.01 ± 145.91</td>
<td>6530.20 ± 79.43</td>
</tr>
<tr>
<td>AUC₀₋∞ (ng h/mL)</td>
<td>4446.02 ± 113.39</td>
<td>8234.93 ± 127.68</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>12.63 ± 0.09</td>
<td>14.00 ± 0.44</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>7.30 ± 1.16</td>
<td>8.82 ± 1.55</td>
</tr>
</tbody>
</table>

*p < 0.05 (t-test)
REFERENCES


PICTORIAL ABSTRACT

SUMMARY

• Solid dispersions of nateglinide (a poorly water soluble drug) was prepared using block copolymer poloxamer 188 using melting and solvent method at different ratios in order to improve its dissolution rate and its bioavailability.
• Nateglinide showed greater solubility (~ 52 fold) in melting method and ~ 39 fold in solvent method at 1:3 weight ratio.
• Solid state characterization and stability study of solid dispersions revealed amorphization of nateglinide and stable solid dispersions respectively.
• Solid dispersion showed marked improvement of dissolution rate and bioavailability (1.71 fold) than pure drug.
• The melting method and novel carrier was found to be suitable for improvement of dissolution and bioavailability of nateglinide.
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