SELECTION OF EXCIPIENTS FOR NANOPARTICLES FORMULATIONS OF NATEGLINIDE THROUGH DRUG-EXCIPIENTS COMPATIBILITY STUDY

GOPI GOVINDASAMY, KANNAN KRISHNAMOORTHY*, MANAVALAN RAJAPPAN

Department of Pharmacy, Faculty of Engineering & Technology, Annamalai University, Annamalai Nagar 608002, Tamil Nadu, India.

*Email: egkkannan@yahoo.co.in

ABSTRACT

Objectives: Stability of Pharmaceutical formulations was often challenged by compatibility between drug and excipients. The primary aim of the study is to assess the compatibility between Nateglinide and excipients used in the preparation of Nateglinide loaded polymeric Nanoparticles.

Methods: In the present study, the possible interactions between Nateglinide with selected excipients were assessed by using Thermal and Isothermal stress testing (IST) technique. Initially, Differential Scanning Colorimetry (DSC) was used to assess the compatibility of excipients mixture. The drug and each selected excipients (1:1 w/w) were stored at 40 ± 2°C and 75 ± 5 % RH for 1 month. The samples were then characterised using Fourier Transform Infrared Spectroscopy (FTIR) and the spectra of drug-excipients mixture was compared with pure drug and excipients alone.

Results: DSC results indicates that Ethyl Cellulose was found to exhibit interaction with Nateglinide while other excipients Chitosan, Sodium tripolyphosphate and Polyvinyl alcohol were found to be compatible with Nateglinide. However, the results of FTIR and IST studies showed that all the excipients were compatible with Nateglinide.

Conclusion: Overall, the results showed that Nateglinide was compatible with all the excipients and can be used for development of Nateglinide loaded polymeric nanoparticle formulation.

Keywords: Nateglinide, Excipients, DSC, FTIR, IST, Compatibility.

INTRODUCTION

Drug-excipients compatibility studies lay the foundation for designing a chemically stable and effective dosage form and helps in careful selection of the most appropriate excipients. A successful formulation of nanoparticles depends on the selection of appropriate polymers and surfactants [1, 2]. Diabetes mellitus is a metabolic disease characterized by high blood glucose level resulting from defects in insulin secretion, insulin action or both [3]. Nateglinide has been exploited as a new class of oral hypoglycemic drug and excipients (1:1 w/w) were stored

FTIR Spectroscopy

The drug and polymers were mixed in 1:1 w/w ratio and placed in glass vials. Each vial was sealed using a Teflon-lined screw cap and

Received: 09 Mar 2013, Revised and Accepted: 27 Apr 2013

International Journal of Pharmacy and Pharmaceutical Sciences
ISSN: 0975-1491
Vol 5, Suppl 2, 2013

Research Article
the mixture of drug and polymers were stored at 40 ± 2°C and 75 ± 5 % RH for 1 month. The dried potassium bromide was placed into a mortar, 1% w/w of the drug sample was accurately weighed and mixed with the potassium bromide powder, subsequently the mixtures was grounded for 3-5 minutes. Generally, the sample concentration of potassium bromide should be in the range between 0.1% and 1%. The procedure involves dispersing a sample (drug and excipients as well as physical mixtures of the drug and excipients) in potassium bromide pellet and compressing into discs by applying a pressure of 5 ton for 5 min in a hydraulic press. The pellet were scanned by using FTIR (Avatar Model 330 FT-IR) in the spectrum was recorded in the region of 4000-400 cm⁻¹ [18, 19, 20].

Differential scanning calorimetry

Compatibility study for the mixtures of drug and excipients were performed by using differential scanning calorimeter (DSC 60 Shimadzu). Excipients selected for the nanoparticles formulations of nateglinide were shown in Table 1 at an appropriate ratio. Approximately, 2-10 mg of individual sample of the drug and excipients as well as physical mixtures of the drug and excipients were accurately weighed directly into the DSC aluminium pan and was crimped and scanned in the temperature range of 50-300°C. The heating rate was 20°C min⁻¹ in nitrogen atmosphere (Flow rate: 20 ml/min) and interactions were observed from obtained thermograms [20, 21].

### Table 1: Peak temperature and enthalpy values of Nateglinide in different drug-excipient mixtures

<table>
<thead>
<tr>
<th>Sample</th>
<th>Ratio (drug-excipient)</th>
<th>T_onset (°C)</th>
<th>T_peak (°C)</th>
<th>ΔH_fcorr (J g⁻¹ &amp; kJ g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTG</td>
<td>-</td>
<td>138.97</td>
<td>142.12</td>
<td>234.30 J g⁻¹</td>
</tr>
<tr>
<td>NTG + Ethyl cellulose</td>
<td>1:1</td>
<td>117.98</td>
<td>122.23</td>
<td>1.77 kJ g⁻¹</td>
</tr>
<tr>
<td>NTG + Chitosan</td>
<td>1:1</td>
<td>138.21</td>
<td>140.75</td>
<td>34.94 J g⁻¹</td>
</tr>
<tr>
<td>NTG + Sodium tripolyphosphate</td>
<td>1:1</td>
<td>139.98</td>
<td>142.39</td>
<td>76.52 J g⁻¹</td>
</tr>
<tr>
<td>NTG + Polyvinyl alcohol</td>
<td>1:1</td>
<td>140.23</td>
<td>143.23</td>
<td>75.80 J g⁻¹</td>
</tr>
</tbody>
</table>

\[ \Delta H_{	ext{fcorr}} = \Delta H_{	ext{obs}} / \text{drug conc. in sample (g/100 g)}. \]

Isothermal stress testing

Isothermal stress testing study involves storing the drug-excipient mixture with or without moisture at high temperature and determining the drug content. The drug with selected polymers and surfactant were weighed in 4 ml glass vials (n = 2) and mixed on a vortex mixer for 2 min. In each vials, 10 % distilled water was added and sealed using a Teflon-lined screw cap and stored at 50° C in hot air oven (Technico, India). These samples were regularly examined for any change of colour. After 4 weeks, these samples were analyzed quantitatively at 208.9 nm by using UV-visible spectrophotometer (Model UV-1650PC Shimadzu) [22, 23].

**RESULTS AND DISCUSSION**

Nateglinide and physical mixture of Nateglinide with excipients were stored at 40 ± 2°C and 75 ± 5 % RH for 1 month and FTIR studies were performed. Spectra obtained from a pure Nateglinide Fig. 2 showed a characteristic strong band at 1648.29 cm⁻¹ corresponds to the secondary amide while the band at 1714.57 cm⁻¹ are associated with carbonyl absorption (C=O). Conformation of C-O stretching OH bending of carboxylic acid spectra was given by the band at 1286.32 cm⁻¹ owing to hydrogen bonded O-H of COOH. The bands at 2927.83 cm⁻¹, 3306.14 cm⁻¹ is due to free alkenes group -CH3 (C-H cycloalkane) and secondary amide (-NH stretching). The sharp band at 754.32 cm⁻¹ & 699.46 cm⁻¹ (Between 770-700 cm⁻¹) indicates the Mano-Substituted Benzene.
Characteristic strong peaks at 1731 cm\(^{-1}\) in Ethyl cellulose is due to the \(\delta\)-lactones (6-membered ring). The strong peak present at 1114 cm\(^{-1}\) & 1063 cm\(^{-1}\) indicates the aliphatic ether. Mixture of Nateglinide and Ethyl cellulose showed no change in the position of the bands at 3305 cm\(^{-1}\) (N-H), 1648 & 1715 cm\(^{-1}\) [C=O], 1271 cm\(^{-1}\) C-O stretching OH bending (COOH) and 2920 cm\(^{-1}\) (Aliphatic C-H stretching) and Mano-Substituted Benzene in Nateglinide with Ethylcellulose.

**Table 2:** FTIR spectroscopy data of Nateglinide and Ethyl cellulose in (40 ± 2°C and 75 ± 5 % RH) storage condition

<table>
<thead>
<tr>
<th>S. No</th>
<th>F.G</th>
<th>Nateglinide (NTG)</th>
<th>Ethyl cellulose (EC)</th>
<th>NTG + EC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard (cm(^{-1}))</td>
<td>NTG (cm(^{-1}))</td>
<td>F.G</td>
</tr>
<tr>
<td>1</td>
<td>2(^{\circ})N-H</td>
<td>3330-3060</td>
<td>3306</td>
<td>Lactones</td>
</tr>
<tr>
<td>2</td>
<td>C=O</td>
<td>1640 &amp; 1700</td>
<td>1648,</td>
<td>Ali Ether</td>
</tr>
<tr>
<td>3</td>
<td>C-O</td>
<td>1320-1210</td>
<td>1286</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>All C-H</td>
<td>2800-2900</td>
<td>2927</td>
<td>-</td>
</tr>
</tbody>
</table>

**F.G: Functional Groups**

Fig. 3 and Table 2 show the FTIR spectra of Nateglinide, Ethyl cellulose and mixture of Nateglinide with Ethyl cellulose. The characteristic strong peaks at 1731 cm\(^{-1}\) in Ethyl cellulose is due to the \(\delta\)-lactones (6-membered ring). The strong peak present at 1114 cm\(^{-1}\) & 1063 cm\(^{-1}\) indicates the aliphatic ether. Mixture of Nateglinide and Ethyl cellulose showed no change in the position of the bands at 3305 cm\(^{-1}\) (N-H), 1648 & 1715 cm\(^{-1}\) [C=O], 1271 cm\(^{-1}\) C-O stretching OH bending (COOH) and 2920 cm\(^{-1}\) (Aliphatic C-H stretching) and Mano-Substituted Benzene in Nateglinide with Ethylcellulose.

**Table 3:** FTIR spectroscopy data of Nateglinide and Chitosan in (40 ± 2°C and 75 ± 5 % RH) storage condition

<table>
<thead>
<tr>
<th>S. No</th>
<th>F.G</th>
<th>Nateglinide (NTG)</th>
<th>Chitosan</th>
<th>NTG + Chitosan</th>
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<tr>
<td></td>
<td></td>
<td>Standard (cm(^{-1}))</td>
<td>Standard (cm(^{-1}))</td>
<td>(cm(^{-1}))</td>
</tr>
<tr>
<td>1</td>
<td>2(^{\circ})N-H</td>
<td>3330-3060</td>
<td>2850-3000</td>
<td>2923</td>
</tr>
<tr>
<td>2</td>
<td>C=O</td>
<td>1640 &amp; 1700</td>
<td>1648 &amp; 1714</td>
<td>1(^{\circ})NH</td>
</tr>
<tr>
<td>3</td>
<td>C-O</td>
<td>1320-1210</td>
<td>1286</td>
<td>O-H</td>
</tr>
<tr>
<td>4</td>
<td>All C-H</td>
<td>2800-2900</td>
<td>2927</td>
<td>C-O</td>
</tr>
</tbody>
</table>

**F.G: Functional Groups**

FTIR spectra of pure Nateglinide, Chitosan and mixture of Nateglinide with Chitosan were shown in Fig. 4 and Table 3. Chitosan exhibits a peak at 3425 cm\(^{-1}\) corresponds to the combine peaks of NH\(_2\) and OH group. A characteristic broad peak at 1153 cm\(^{-1}\) indicates the the stretching of C-O. The peak at 2923 cm\(^{-1}\) is attributed to the aromatic C-H stretching. The mixture of Nateglinide with Chitosan shows no significant changes in the peaks of secondary amide [N-H], carbonyl absorption [C=O], C-O stretching OH bending (COOH), Aliphatic C-H stretching and Mano-Substituted Benzene in observed value of Nateglinide and Chitosan.

**Fig. 5:** FTIR spectrum of (A) Pure Nateglinide, (B) Sodium tripolyphosphate and (C) Mixture of Nateglinide with Sodium tripolyphosphate
The results confirm that there is no change in the position of the bands peaks in the mixture of Nateglinide with Sodium tripolyphosphate.

**Table 4: FTIR spectroscopy data of Nateglinide and Sodium tripolyphosphate in (40 ± 2°C and 75 ± 5% RH) storage condition**

<table>
<thead>
<tr>
<th>S. No</th>
<th>F.G.</th>
<th>Nateglinide (NTG) Standard (cm⁻¹)</th>
<th>FTG (cm⁻¹)</th>
<th>Sodium tripolyphosphate (STTP) Standard (cm⁻¹)</th>
<th>FTG (cm⁻¹)</th>
<th>NTG + STTP (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z=</td>
<td>3330-3060</td>
<td>3306</td>
<td>1150</td>
<td>1160</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>2</td>
<td>N-H</td>
<td>1640 &amp; 1700</td>
<td>1648 &amp; 1714</td>
<td>870-1000</td>
<td>901</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>3</td>
<td>C=O</td>
<td>1320-1210</td>
<td>1286</td>
<td>1330-1420</td>
<td>1375, 1454</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>4</td>
<td>All C-H</td>
<td>2800-2900</td>
<td>2927</td>
<td>1180-1260</td>
<td>1150</td>
<td>2⁻-NH</td>
</tr>
</tbody>
</table>

**Table 5: FTIR spectroscopy data of Nateglinide and Polyvinyl alcohol in (40 ± 2°C and 75 ± 5% RH) storage condition**

<table>
<thead>
<tr>
<th>S. No</th>
<th>F.G.</th>
<th>Nateglinide (NTG) Standard (cm⁻¹)</th>
<th>FTG (cm⁻¹)</th>
<th>Polyvinyl alcohol (PVA) Standard (cm⁻¹)</th>
<th>FTG (cm⁻¹)</th>
<th>NTG + PVA (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z=</td>
<td>3330-3060</td>
<td>3306</td>
<td>2800-2990</td>
<td>2921</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>2</td>
<td>N-H</td>
<td>1640 &amp; 1700</td>
<td>1648 &amp; 1714</td>
<td>1330-1420</td>
<td>1375, 1454</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>3</td>
<td>C=O</td>
<td>1320-1210</td>
<td>1286</td>
<td>1180-1260</td>
<td>1150</td>
<td>2⁻-NH</td>
</tr>
<tr>
<td>4</td>
<td>All C-H</td>
<td>2800-2900</td>
<td>2927</td>
<td>-</td>
<td>-</td>
<td>2⁻-NH</td>
</tr>
</tbody>
</table>

**Fig. 6: FTIR spectrum of (A) Pure Nateglinide, (B) Polyvinyl alcohol and (C) Mixture of Nateglinide with Polyvinyl alcohol**

The data obtained from the FTIR spectrum of Nateglinide, Polyvinyl alcohol and mixture of Nateglinide-Polyvinyl alcohol were shown in Fig. 6 and Table 5. The spectrum of PVA shown peaks at 2921, 2952 and 1150 cm⁻¹ and indicates the stretching of OH, aliphatic CH and CO, respectively. Also, there is a band at 1454 cm⁻¹ due to CH bending vibration. The spectrum of both the Nateglinide-Polyvinyl alcohol physical mixture shows peaks at 3299 cm⁻¹ (secondary amide), 1648 & 1715 cm⁻¹ (C=O stretching), 2930 cm⁻¹ (Aliphatic C-H stretching) and 1214 cm⁻¹ (C-O stretching OH bending [COOH]). The results signify that the mixture of Nateglinide with Polyvinyl alcohol is compatible.

DSC thermoanalytical curves of drug and drug-excipients mixtures are illustrated in Figure 7-11. DSC scans were performed for the drug and drug-excipient mixtures at the temperature range of 30-350°C. Thermal analysis of the pure drug and excipient were compared with the mixture of drug with excipient. The onset temperature of peak (Temax) (138.97°C), peak transition temperature (Temax) (142.12°C) and heat of mingling enthalpy (ΔHf) (234.30 J g⁻¹) of Nateglinide with various excipient mixtures were summarized in Table 1.

The DSC thermogram of Nateglinide showed a sharp endothermic peak at 142.12°C and peak onset at 138.97°C (Fig. 7). In majority cases, the melting endothermic of the drug (Temax and Temax) was well treated with slight broadening or shifting towards the lower temperature range. It has been reported that the shape of the peaks of the DSC thermogram and enthalpy may change due to the presence of impurity in the materials used for analysis. Thus, changes in the melting endotherm of the drug from 142.12 to 138.97°C could be due to the mixing of the drug and excipients, which lower the purity of each component in the mixture, indicate potential incompatibility [18, 24].
The DSC thermogram of Ethyl cellulose showed no peaks, indicating the complete amorphous nature of ethyl cellulose [25]. However, the DSC thermogram of the Nateglinide-Ethyl cellulose mixture shows a disappearance of the Nateglinide peak at 122.23°C (Fig. 8). The result shows that there was some physical incompatibility between Nateglinide and Ethyl cellulose.

The DSC thermogram of Chitosan showed a broad peak at 95.15°C over a large temperature range is attributed to water loss due to evaporation of absorbed water and this represents the energy required to vapourise water present in the samples [26]. Melting endothermic peak of Nateglinide lay at 140.75°C in the Nateglinide-Chitosan mixture indicating that there was no interaction between Chitosan and Nateglinide as shown in Fig. 9.

The DSC thermogram of Sodium tripolyphosphate showed a single broad endothermic peak and a sharp endothermic peak at 74.13 and 167.38°C respectively. The thermogram of Nateglinide-Sodium tripolyphosphate mixture (Fig. 10) showed an endothermic peak of Nateglinide at 142.39°C, indicating that Nateglinide was compatible with Sodium tripolyphosphate.

The DSC thermogram of Polyvinyl alcohol, a broad endotherm was observed at 226.83°C. The thermogram of the Nateglinide-Polyvinyl alcohol mixture showed (Fig. 11) broadening and shifting of the Nateglinide peak to a lower temperature (143.23°C). This result shows that Nateglinide and Polyvinyl alcohol are compatible.

Fig. 7: DSC thermogram of Nateglinide

Fig. 8: DSC thermograms of (A) Nateglinide, (B) Ethyl cellulose and (C) Nateglinide with Ethyl cellulose mixture

Fig. 9: DSC thermograms of (A) Nateglinide, (B) Chitosan and (C) Nateglinide with Chitosan mixture
In Isothermal stress testing, results obtained from drug and mixtures of drug-excipients confirmed that there is no change in physical appearance at ambient temperature. The mixture was also predominantly examined for physical stable, liquefaction or gas formation and drug degradation with all the excipients. The percentage of drug remaining at the end of the study at 50°C was shown in the Table 6.

**CONCLUSION**

The compatibility studies of Nateglinide with various selected polymers and surfactant were performed using different analytical methods. DSC and FTIR were used to evaluate possible incompatibilities of drug and excipients. DSC results indicates that Ethyl cellulose was found to exhibit interaction with Nateglinide while other excipients Chitosan, Sodium tripolyphosphate and Polyvinyl alcohol were found to be compatible with Nateglinide.

However, the results of FTIR studies showed that all the excipients were compatible with Nateglinide and the possibility of incompatibility between Nateglinide and Ethyl cellulose was ruled out.

The results of Isothermal stress testing (IST) showed that there is no change in colour and drug content after 4 weeks under storage condition. Therefore, no definite evidence of interaction was observed between Nateglinide with excipients. The present study concludes that Nateglinide and the selected excipients (Ethyl cellulose, Chitosan, Sodium tripolyphosphate and Polyvinyl alcohol) can be used in the development of drug-loaded polymeric nanoparticles formulations.

**ACKNOWLEDGMENT**

The authors are grateful to Department of Pharmacy, Annamalai University and UGC-BSR, New Delhi for providing financial assistance.
REFERENCE


