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Research Article

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

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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 drug-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 Poly vinyl 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. Designing 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 agent with the chemical name [*N*-(trans-4-isopropylcyclohexylcarbonyl)-*D*-phenylalanine] and the structure is shown in the Fig. 1 [4, 5]. Nateglinide is a D-phenylalanine derivative recently approved for the management of type II diabetes that can stimulate the release of insulin by inhibiting ATP- potassium channels present in pancreatic β-cells in the incidence of elevated blood glucose levels after oral administration [6, 7].

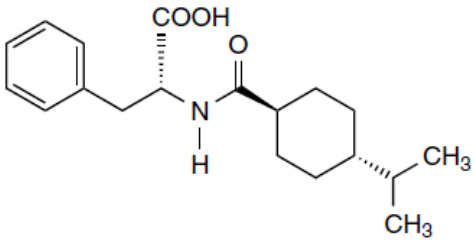

Fig. 1: Chemical Structure of Nateglinide

Nanoparticles represent an effective nanocarrier platform for the delivery of hydrophobic and hydrophilic drugs, since the drugs are protected from possible degradation by enzymes. The development of smart Nanoparticles can deliver drugs at a sustained rate providing better efficacy and lower toxicity for treatment of various diseases. Various polymers were used for the development of sustained release formulations, among them Ethyl cellulose, the biodegradable and biocompatible polymer has been reported to be advantageous due to its nature of solubilising a large number of hydrophobic drugs. Chemically, it is stable under storage and characterized by a good tolerability with lack of toxicity for patients. The biologically active drug is encapsulated within nanoparticles using this polymer with well-defined physical and chemical properties [8, 9]. Chitosan is a natural cationic polysaccharide derived by deacetylation of chitin, a copolymer consisting of combined units of glucosamine and N-acetyl glucosamine. It has shown promising results due to the polycation intrinsic properties including low toxicity, excellent biocompatibility, high loading and good delivery ability for hydrophilic molecules [10-12]. Sodium tripolyphosphate is non-toxic and has multivalent anions, used as a cross linking agent that can produce particles with good stability. The ionic interaction between the positively charged amino groups of chitosan and negatively charged counter ions of STPP results in the formation of gel. For pharmaceutical application, it can be used only by the second synthesis technique (Ionic Gelation) [13-15]. Polyvinyl alcohol is one of the most popular synthetic biodegradable, water-soluble polymers widely used in the pharmaceutical products as a surface active agent for decreasing the particle size of the formulations [16, 17].

In general, the incompatibility between drug and excipients can alter the bioavailability and stability which in turn affect their safety and efficacy [18]. The purpose of this present study was to evaluate the compatibility between Nateglinide with selected polymers and surfactant like ethyl cellulose, chitosan, sodium tripolyphosphate and polyvinyl alcohol by FTIR, DSC and IST.

MATERIALS AND METHODS

Nateglinide (NTG) was obtained as a gift sample from Glanmark Pharmaceutics Ltd Mumbai, India. Ethyl cellulose (EC) was procured from Himedia Laboratories Pvt Ltd, Mumbai, India. Chitosan and Sodium tripolyphosphate (STPP) were obtained from Ganesh Scientific Chemicals, India. Polyvinyl alcohol (PVA) was purchased from Fourts India Pvt Ltd, Chennai, India. All other chemicals and reagents used were of analytical grade.

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

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 4000-400cm^{-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

Sample	Ratio (drug-excipient)	T_{onset} (°C)	T_{peak} (°C)	ΔH_{fcorr} (J g^{-1} & kJ g^{-1})[a]
NTG	–	138.97	142.12	234.30 J g^{-1}
NTG + Ethyl cellulose	1:1	117.98	122.23	1.77 kJ g^{-1}
NTG + Chitosan	1:1	138.21	140.75	34.94 J g^{-1}
NTG + Sodium tripolyphosphate	1:1	139.98	142.39	76.52 J g^{-1}
NTG + Polyvinyl alcohol	1:1	140.23	143.23	75.80 J g^{-1}

[a] $\Delta H_{fcorr} = \Delta H_{fobs}$/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 analysed 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.

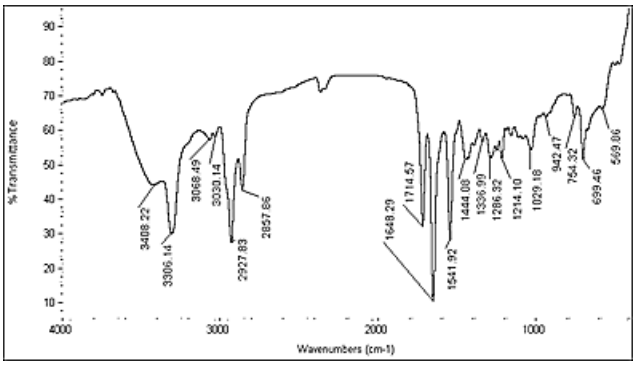

Fig. 2: FTIR spectrum of pure Nateglinide

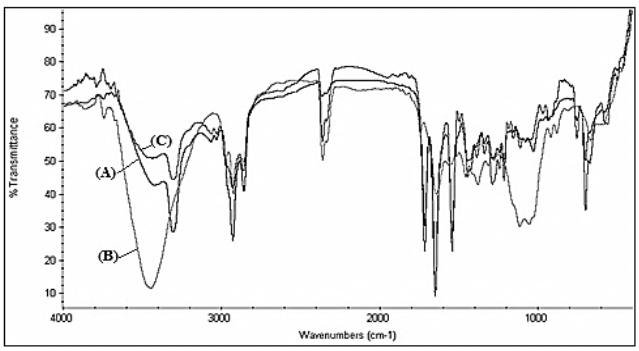

Fig. 3: FTIR spectrum of (A) Pure Nateglinide, (B) Ethyl cellulose and (C) Mixture of Nateglinide with Ethyl cellulose

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

S. No	F.G	Nateglinide (NTG)		F.G	Ethyl cellulose (EC)		F.G	NTG + EC (cm^{-1})
		Standard (cm^{-1})	NTG (cm^{-1})		Standard (cm^{-1})	EC (cm^{-1})		
1	2° N-H	3330-3060	3306	Lactones	1750-1775	1731	2° N-H	3305
2	C=O	1640 & 1700	1648, 1714	Ali Ether	1050-1150	1114, 1063	C=O/ Lactones	1648 & 1715
3	C-O	1320-1210	1286	-	-	-	C-O	1287
4	Ali C-H	2800-2900	2927	-	-	-	Ali C-H	2929

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 δ-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 & 1715cm^{-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 Ethyl cellulose.

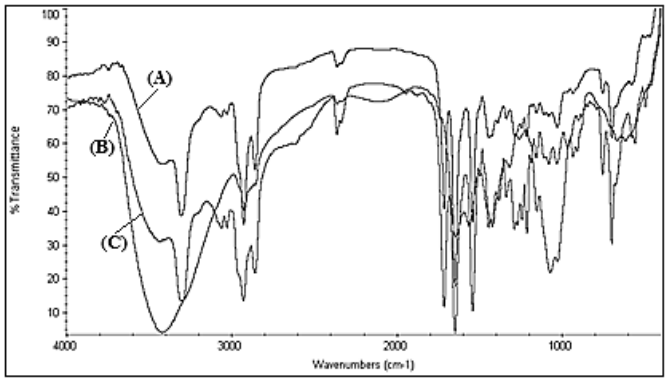

Fig. 4: FTIR spectrum of (A) Pure Nateglinide, (B) Chitosan and (C) Mixture of Nateglinide with Chitosan

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

S. No	F.G	Nateglinide (NTG)		F.G	Chitosan		F.G	NTG + Chitosan (cm^{-1})
		Standard (cm^{-1})	NTG (cm^{-1})		Standard (cm^{-1})	Chitosan (cm^{-1})		
1	2° N-H	3330-3060	3306	Ar C-H	2850-3000	2923	1°/2° NH	3302
2	C=O	1640 & 1700	1648 & 1714	1° NH	3400-3500	3425	C=O	1647 & 1714
3	C-O	1320-1210	1286	O-H	3200-3600	3425	C-O	1289
4	Ali C-H	2800-2900	2927	C-O	1100	1153	Ali C-H	2929

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.

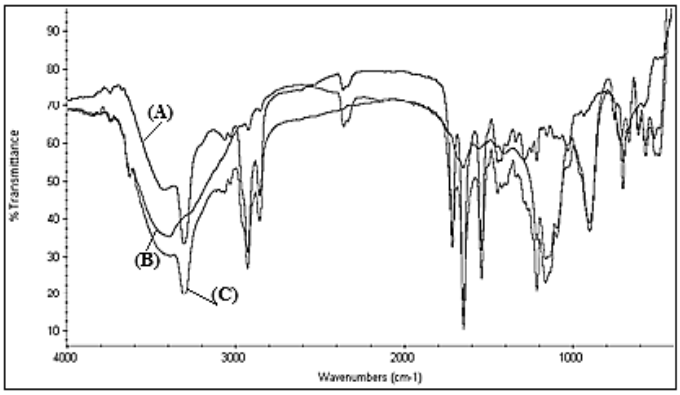

Fig. 5: FTIR spectrum of (A) Pure Nateglinide, (B) Sodium tripolyphosphate and (C) Mixture of Nateglinide with Sodium tripolyphosphate

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

S. No	F.G	Nateglinide (NTG)		F.G	Sodium tripolyphosphate (STTP)		F.G	NTG + STTP (cm^{-1})
		Standard (cm^{-1})	NTG (cm^{-1})		Standard (cm^{-1})	STTP (cm^{-1})		
1	2° N-H	3330-3060	3306	Ali P=O	1150	1160	2° NH	3306
2	C=O	1640 & 1700	1648 & 1714	P-O-P	870-1000	901	C=O	1647 & 1714
3	C-O	1320-1210	1286	-	-	-	C-O	1213
4	Ali C-H	2800-2900	2927	-	-	-	Ali C-H	2929

F.G: Functional Groups

The Sodium tripolyphosphate FTIR spectrum was characterized by a sharp peak at 1160 cm^{-1} and a strong peaks at 901 cm^{-1} owing to Aliphatic P=O stretching and P-O-P stretching. Nateglinide-Sodium tripolyphosphate mixture showed the characteristics peaks at 3306 cm^{-1}, 1647 & 1714 cm^{-1}, 2929 cm^{-1} and 1213 cm^{-1} as shown in Fig. 5 and Table 4. The results confirm that there is no change in the position of the bands peaks in the mixture of Nateglinide with Sodium tripolyphosphate.

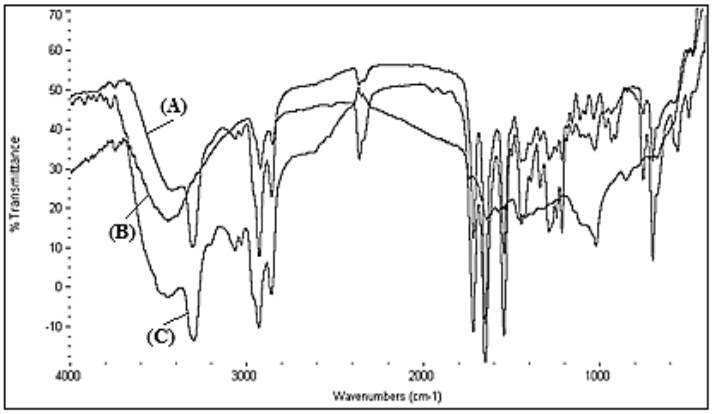

Fig. 6: FTIR spectrum of (A) Pure Nateglinide, (B) Polyvinyl alcohol and (C) Mixture of Nateglinide with Polyvinyl alcohol

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

S. No	F.G	Nateglinide (NTG)		F.G	Polyvinyl alcohol (PVA)		F.G	NTG + PVA (cm^{-1})
		Standard (cm^{-1})	NTG (cm^{-1})		Standard (cm^{-1})	PVA (cm^{-1})		
1	2° N-H	3330-3060	3306	C-H	2800-2990	2921	2° NH	3299
2	C=O	1640 & 1700	1648 & 1714	O-H	1330-1420	1375, 1454	C=O	1648 & 1715
3	C-O	1320-1210	1286	C-O	1180-1260	1150	C-O	1214
4	Ali C-H	2800-2900	2927	-	-	-	Ali C-H	2930

F.G: Functional Groups

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, 2852 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 (T_{onset}) (138.97°C), peak transition temperature (T_{peak}) (142.12°C) and heat of mingle or enthalpy (ΔH_f) (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 (T_{onset} and T_{peak}) 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.

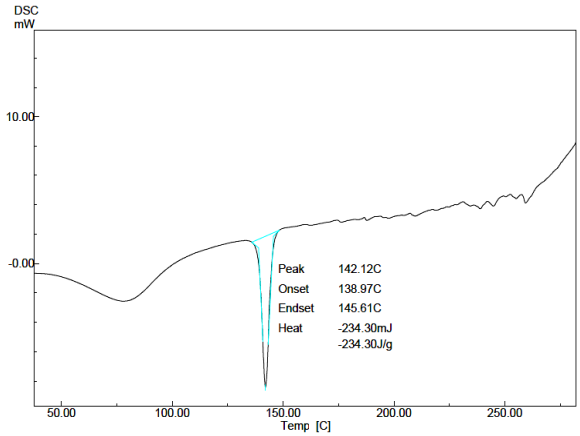

Fig. 7: DSC thermogram of Nateglinide

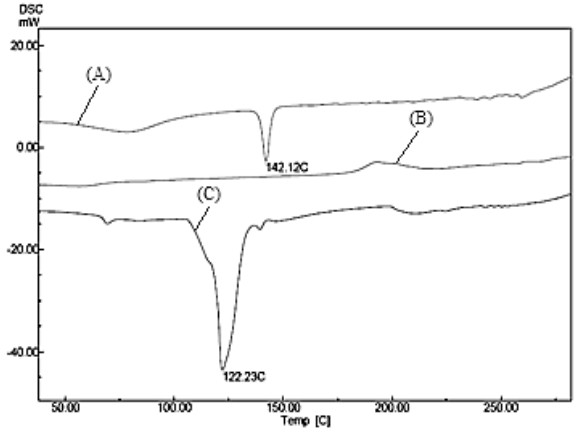

Fig. 8: DSC thermograms of (A) Nateglinide, (B) Ethyl cellulose and (C) Nateglinide with Ethyl cellulose mixture

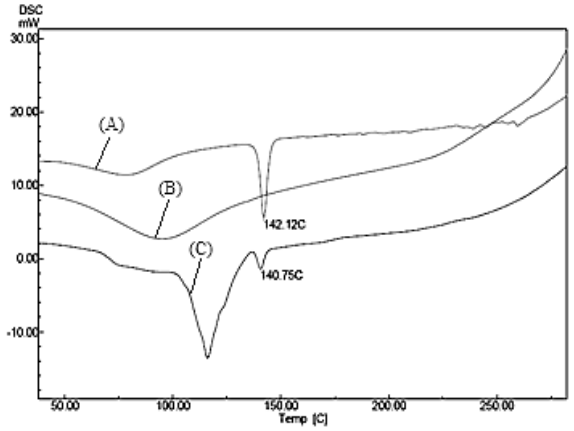

Fig. 9: DSC thermograms of (A) Nateglinide, (B) Chitosan and (C) Nateglinide with Chitosan mixture

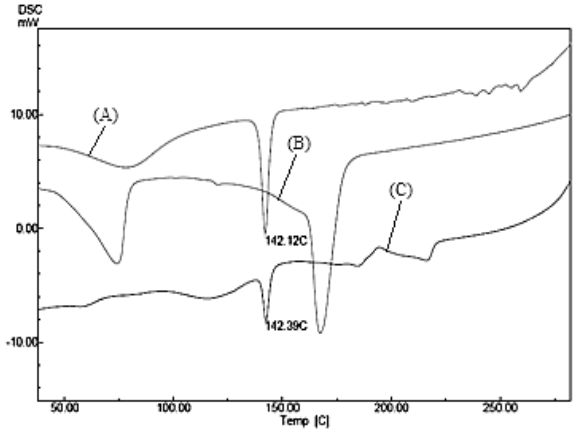

Fig. 10: DSC thermograms of (A) Nateglinide, (B) STPP and (C) Nateglinide with STPP mixture

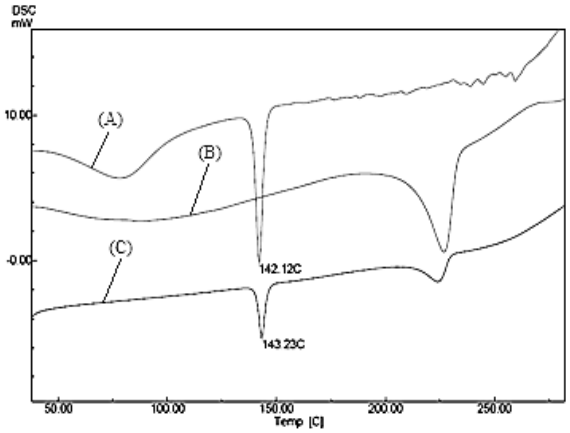

Fig. 11: DSC thermograms of (A) Nateglinide, (B) PVA and (C) Nateglinide with PVA mixture

Table 6: Results of UV analysis of the samples under Isothermal stress testing after 4 weeks

Sample	Ratio (Drug-excipient)	% Drug remaining[a]		Changes in physical appearance
		Control Sample[b]	Stress Sample[c]	
Nateglinide (NTG)	–	100.34 ± 1.10	99.07 ± 1.56	No
NTG + Ethyl cellulose	1:1	98.52 ± 0.71	100.72 ± 0.65	No
NTG + Chitosan	1:1	99.34 ± 1.52	97.34 ± 1.82	No
NTG + Sodium tripolyphosphate	1:1	100.14 ± 1.78	99.44 ± 0.85	No
NTG + Polyvinyl alcohol	1:1	97.34 ± 0.81	100.64 ± 1.45	No

[a]Mean ± standard deviation (n=2)

[b]Drug-excipients blends without added water and stored in refrigerator (2° to 8°C)

[c]Drug-excipients blends with 10% added water and stored at 50°C for 4 weeks

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 Poly vinyl 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.

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