Enhancement of the solubility of the poorly water-soluble drug is one of the most challenging issues in the pharmaceutical industry. Limited drug dissolution and bioavailability depend on its solubility and permeability [1]. Amorphous solid dispersion has been proved as an effective method to enhance the solubility and dissolution behavior of many BCS II class drugs [2]. Nateglinide is an oral hypoglycemic agent used in the treatment of type II diabetes mellitus (non-insulin-dependent diabetes mellitus, NIDDM). Nateglinide is a non-sulfonylurea drug, belonging to BCS class II, low solubility, and high permeability [3].

Nateglinide solid dispersions were prepared by a common solvent evaporation method. Polymers like soluplus, kolliphor P188, sylloid 244FP, gelucire 48/16, astringent (HPMCAS), HPβCD, βCD were used in different combinations. The physicochemical characterization of the optimized ternary dispersion was studied by using FT-IR, DSC, and PXRD. Solubility and dissolution behavior of all dispersions were studied.

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Objective: Nateglinide is a commonly used oral hypoglycemic, biopharmaceutical classification system Class II drug, which shows relatively poor water solubility and variable bioavailability. The objective of the present investigation was to develop the binary and ternary solid dispersions of nateglinide for improved solubility and dissolution.

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soluplus, kolliphor P188, affinisol, sylloid 244 FP, gelucire 48/16, etc. In this drug and carrier were dissolved in a volatile solvent with homogeneous mixing. The volatile solvent was later evaporated at normal room temperature [13].

The present research work was aimed to study and explore new combinations of polymers for solubility enhancement. NTG binary and ternary dispersions were prepared by the common solvent evaporation method for solubility and dissolution enhancement. Finally, the optimized dispersions were formulated as tablets. In vitro drug release through in house formulations and marketed tablets were studied.

MATERIALS AND METHODS

Materials

The pharmaceutical grade of Nateglinide was obtained as a generous gift from Cipla Ltd. Goa, India. β-Cyclodextrin and Hydroxypropyl β-Cyclodextrin were purchased from Sigma Aldrich (Mumbai, India). Affinisol, soluplus, kolliphor P 188, gelucire 48/16, sylloid 244FP were provided as a gift sample by Lupin Ltd Aurangabad, India. Ethanol was purchased from Himedia Laboratories, Mumbai, India. All remaining ingredients were purchased from S. D Fine Chemicals (Mumbai, India).

Solubility determination of nateglinide

Nateglinide solubility was determined in different media like Phosphate buffer pH 6.8, Phosphate buffer pH 7.4, 0.1 N HCl, and reported dissolution media 0.5 % SLS in 0.01 N HCl. Binary and ternary complexes of NTG were formulated with polymers like soluplus, β-cyclodextrin and hydroxypropyl β-Cyclodextrin, and affinisol. The Solvent co-evaporation method was employed to prepare solid dispersions. The complexes were scraped and collected. Table 1. Shows the Composition of different binary and ternary SD.

Table 1: Composition of different binary and ternary SD

| Dispersion type | Combination                        | Code | Weight ratio |
|-----------------|------------------------------------|------|--------------|
| Binary dispersion | NTG and soluplus                   | F1   | 1:1          |
|                  | NTG and Soluplus                   | F2   | 1:2          |
|                  | NTG and HPβCD                      | F3   | 1:1          |
|                  | NTG and HPβCD                      | F4   | 1:2          |
|                  | NTG and BCD                        | F5   | 1:2          |
|                  | NTG and BCD                        | F6   | 1:3          |
|                  | NTG and Affinisol                  | F7   | 1:1          |
|                  | NTG and Affinisol                  | F8   | 1:2          |
|                  | NTG and Affinisol                  | F9   | 1:3          |
|                  | NTG and affinisol + kolliphor P188 | F10  | 1:2          |
| Ternary dispersion | NTG + Soluplus + Kolliphor P188   | F11  | 1:1:1        |
|                  | NTG + Soluplus + Affinisol         | F12  | 1:1:1        |
|                  | NTG + Soluplus + Gelucire 48/16    | F13  | 1:1:1        |
|                  | NTG + βCD + Na2CO3                 | F14  | 1:1:1        |
|                  | NTG + Soluplus + sylloid FP244     | F15  | 1:1:1        |

Formulation of binary and ternary solid dispersions

A weighed amount of nateglinide and polymer were mixed, dissolved in common solvent ethanol; the mixture was then sonicated for 10-20 min using ultra-probe sonicator Model Frontline Sonicator FS-250 (Ahmedabad, India) to prepare the homogenous solution later the solvent evaporated at room temperature. Nateglinide and polymers were dissolved in ethanol in different ratios (1:1,1:2, 1:3,1:4) to prepare SD by the solvent evaporation technique until we find the best proportion of drug and polymer. The prepared complexes were studied for solubility. In this same way, complexes were prepared with Soluplus, βCD, HPβCD, and Affinisol. Solubility for all prepared complexes was determined and the best ratios of the drug: polymer was decided. To formulate a ternary complex, a binary complex with the best solubility was selected and formulated. The combinations of polymers given in the following table 1. In the given ratio, the drug and polymers were dissolved in ethanol with continuous stirring and the solvent was evaporated at room temperature. Prepared complexes were then scraped and studied [14, 15]. The graphical abstract of the formulation is shown in fig. 1.

Determination of saturated solubility of NTG and prepared solid dispersions

To determine the solubility of the Nateglinide pure drug and dispersions, an excess quantity of the drug or its dispersions equivalent to 50 mg nateglinide were added to a 10 ml Volumetric flask containing 5 ml of the 0.5% SLS in 0.01 N HCl (Dissolution media of Nateglinide), the vials were stirred at 100 RPM with a magnetic stirrer for 24 h, the aliquots were filtered through 0.45-micron filter paper. The aliquots were diluted and assayed spectrophotometrically at 210 nm using a UV-Vis spectrophotometer (UV-1700 PharmSpec, Shimadzu, Kyoto, Japan). The calibration curve in different media was previously prepared for Nateglinide at 210 nm [16]. Similarly, Solubility of pure nateglinide is also determined in phosphate buffers pH 6.8, pH 7.4 and pH 1.2.

Fourier transform infrared spectroscopy

IR spectra of the pure NTG, all the formulated dispersion, were recorded on the FTIR spectrophotometer (Shimadzu 8400S, Japan) with KBr as the reference standard. FTIR study was conducted to study the alteration in the structure of pure NTG after the
formulation of ternary dispersions. FTIR determines drug-polymer compatibility. 2–3 mg samples were mixed with about 4 mg of potassium bromide, compressed through the manual press to form a thin disc. The IR spectra were recorded at a scanning range from 4000–400 cm\(^{-1}\).

**Powder X-ray diffraction**

The PXRD patterns of the pure nateglinide and the optimized NTG-ternary dispersion were obtained using an X-ray diffractometer, Miniflex II (Regaku, USA). The samples were scanned in the range of 5 ° to 50 ° (diffraction angle 2θ), Cu K α line as the source of radiation with nickel filter, at the 40-kV voltage and 25-mA current.

**Differential scanning calorimetry**

DSC thermograms of pure NTG and the optimized NTG dispersion were obtained by scanning from 10–400 °C at 10 °C/min with a differential scanning calorimeter (Mettler toledo, Japan). Each sample (approximately 5 mg) was weighed in a standard open aluminum pan using an empty pan as a reference.

### Dissolution study of ternary dispersions

In vitro drug release through ternary solid dispersions and the pure drug (equivalent to 60 mg) was carried out in different dissolution media, including 0.5% SLS in 0.01 N HCl, 0.1 N HCl phosphate buffer having pH 6.8 and 7.4. Dissolution studies were carried out using the Electrolab USP II paddle apparatus at 37±0.5 °C in 1000 ml dissolution media; paddle speed was 50rpm, sampling was done at the time interval of 10, 20, 30 and 45 min. Aliquots were collected at different time intervals and filtered through a 0.45 μm filter. The fresh dissolution media was replaced again. The aliquots were subsequently diluted and the concentration of the drug was determined using a UV spectrophotometer at 210 nm.

### Tablet formulation

After the solubility and dissolution study, the best ternary complexes were selected. For the best ternary complexes, tablets were formulated. For the formulation of a tablet karnavati tablet punching machine was used. For the prepared tablet dissolution, Disintegration, Hardness, Friability, Weight variation test was performed [17]. Table 2 shows the composition of formulated tablets.

### Dissolution study of formulations

For optimized formulations and marketed formulation dissolution study was performed in different dissolution media. All the parameters were kept similar to the dissolution study. The percentage of drug release from the optimized formulation and marketed formulation was calculated and compared. Sampling was done at the time interval of 10, 20, 30 and 45 min. The speed of the paddle was kept at 50 RPM.

### RESULTS AND DISCUSSION

#### Saturation solubility of NTG

Saturation solubility of NTG was determined in various media like reported dissolution media 0.5% SLS in 0.01 N HCl, Phosphate buffer pH 6.8 and pH 7.4 and 0.1 N HCl. Values of Saturation solubility of NTG in various Dissolution media are given in the following table 3. Preliminary studies revealed that NTG is a poorly water-soluble drug and shows pH-dependent solubility at different physiological pH ranges. It was found that Solubility of NTG gradually increased from acidic pH to alkaline pH.

#### Saturation solubility study of the prepared solid dispersions

All the batches of the above Binary mixtures, ternary mixtures, and pure drugs were subjected to saturation solubility studies at room temperature in 0.5% SLS in 0.01 N HCl, which is reported dissolution media for nateglinide. The amount of drug dissolved was analyzed by the UV-Vis spectroscopy at 210 nm. Nateglinide forms a very transparent solid solution after solvent evaporation with Soluplus and Affinosil. Saturation solubility study of NTG and all prepared dispersion was found as follows. Fold enhancement in solubility was calculated. Ternary solid dispersion of NTG with soluplus and kolliphor P188 shows the highest fold enhancement solubility. Table 4. Shows saturation solubility data of nateglinide in various ternary dispersion.

### FTIR

FT-IR is an important technique to predict a possible interaction of the drug with polymers in the solid-state. FT-IR spectroscopy was used to detect the presence of possible interactions between NTG, soluplus, affinosil, sylloid 244 FP, kolliphor P 188 that, if it should result in shifting of the absorption bands characteristic for functional groups, which is involved in the interaction.

### Table 2: Formulation of NTG tablets

| S. No. | Ingredient         | N1 Quantity (mg) | N2 Quantity (mg) | N3 Quantity (mg) |
|--------|--------------------|------------------|------------------|------------------|
| 1.     | Nateglinide        | 60               | 60               | 60               |
| 2.     | Soluplus          | 60               | 60               | 60               |
| 3.     | Affinosil          | 60               | -                | -                |
| 4.     | Kolliphor P188     | -                | 60               | -                |
| 5.     | Sylloid 244 FP     | 36               | -                | 60               |
| 6.     | Avicel 102         | 36               | 36               | 36               |
| 7.     | Croscarmellose sodium | 2          | -                | -                |
| 8.     | Lactose            | -                | 20               | -                |
| 9.     | Magnesium Stearate | -                | 2                | 2                |
| 10.    | Talc               | 2                | 2                | 2                |
|       | The total weight (mg) | 220           | 240              | 220              |

### Table 3: Saturation solubility data of nateglinide in various dissolution media: (mean±SD, n = 3)

| S. No. | Nateglinide saturation solubility different media | Solubility (mg/ml) |
|--------|--------------------------------------------------|--------------------|
| 1.     | In 0.1 N HCl                                     | 0.52±0.027         |
| 2.     | In Phosphate buffer Ph 6.8                       | 2.13±0.123         |
| 3.     | In Phosphate buffer Ph 7.4                       | 6.86±0.145         |
| 4.     | In 0.5% SLS in 0.01 N HCl                         | 2.85±0.032         |

### Table 4: Saturation solubility data of nateglinide in various ternary dispersion

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| 4.     | In 0.5% SLS in 0.01 N HCl            | 2.85±0.032         |
ternary formulations. On the spectrum of formulation F 11 (NTG: soluplus: kolliphor P 188), the sharp absorption peak of NTG, positioned at 2927 cm⁻¹, changed to a broad absorption band positioned around 2883 cm⁻¹, while the absorption band positioned at 1741 cm⁻¹ shifted to 1743 cm⁻¹. In pure drug IR, N-H Stretching is observed at 3300 cm⁻¹, in the optimized ternary complexes showing the best solubility, almost disappearance of characteristic N-H stretching peak of NTG at 3300 cm⁻¹, this indicated the hydrogen bond interaction between NTG and Polymer complexes. In this case, –OH groups present in the NTG may be interacting with the terminal–OH and ether oxygen groups present in soluplus and form hydrogen bonds.

Soluplus shows a characteristic peak at 1750 cm⁻¹ and 1650 cm⁻¹ corresponding to the carbonyl–C = O group, 2747 and 2890 cm⁻¹ for C-H, and broadband in the range 3200-3400 cm⁻¹ representing the terminal–OH groups. The spectrum of Kolliphor P 188 is characterized by strong absorption peaks at 2880 cm⁻¹ signifying the aliphatic–C-H stretch, 1339 cm⁻¹ (in-plane O-H bend), and 1098 cm⁻¹ (C -O-stretch) Other absorption bands of NTG became indistinguishable. Formulation F 12 (NTG-soluplus-affinisol), and formulation F 15 (NTG-soluplus-sylloid 244), showed very similar IR spectra. Comparative graphs of some ternary dispersion are shown in the following fig. 2.

Table 4: Saturation solubility data of nateglinide in 0.75% SLS (Reported dissolution media) (mean±SD, n = 3)

| Formulation code | Combination                      | Saturation solubility (mg/ml) | Fold enhancement in solubility |
|------------------|----------------------------------|-----------------------------|-----------------------------|
| F1               | NTG and Soluplus (1:1)           | 59.96±0.263                 | 20.96                       |
| F2               | NTG and Soluplus (1:2)           | 57.26±0.127                 | 20.02                       |
| F3               | NTG and HPBCD (1:1)              | 28.02±0.243                 | 9.79                        |
| F4               | NTG and HPBCD (1:2)              | 30.18±0.115                 | 10.55                       |
| F5               | NTG and BCD (1:2)                | 32.88±0.247                 | 11.49                       |
| F6               | NTG and BCD (1:3)                | 35.90±0.562                 | 12.55                       |
| F7               | NTG and Affinosil (1:1)          | 45.84±0.316                 | 16.02                       |
| F8               | NTG and Affinosil (1:2)          | 42.24±0.261                 | 14.76                       |
| F9               | NTG and Affinosil (1:3)          | 32.11±0.344                 | 11.22                       |
| F10              | NTG and Kolliphor P188 (1:1)     | 43.69±0.245                 | 15.27                       |
| F11              | NTG+Soluplus+Kolliphor P188      | 68.38±0.453                 | 23.90                       |
| F12              | NTG+Soluplus+Affinosil           | 49.89±0.123                 | 17.44                       |
| F13              | NTG+Soluplus+Gelucire 48/16      | 72.82±0.595                 | 25.46                       |
| F14              | NTG+BCD+Na2CO3                   | 38.57±0.183                 | 13.48                       |
| F15              | NTG+Soluplus+Sylloid 244FP       | 48.86±0.496                 | 17.08                       |

Fig. 2: Overlay diagram of FTIR of pure nateglinide, NTG-soluplus-kolliphor, NTG-soluplus-gelucire, NTG-soluplus-sylloid ternary solid dispersions

Powder X-ray diffraction

The PXRD diffractograms of NTG and the optimized NTG-ternary dispersion are presented in fig. 3. As can be seen from the PXRD spectra of pure NTG, showed sharp characteristic diffraction peaks at 2θ diffraction angles of 5, 10.5, 12, 15 and 19 confirming the crystalline nature of the pure drug. In the PXRD spectra of optimized ternary solid dispersions, no characteristic peaks were observed. Broad hallows were observed, indicating the amorphous nature of NTG in ternary dispersions.

Differential scanning calorimetry

DSC thermograms of pure NTG and the optimized NTG-ternary dispersion are shown in fig. 4. The DSC curve of pure NTG exhibited a single endothermic peak at 130 °C, which indicates its melting point. Thus NTG exhibited in crystalline Form. The characteristic peak of the pure drug disappeared in the thermogram of ternary dispersions. This indicates a molecular dispersion of NTG in ternary dispersions. The total disappearance of the drug melting peak indicates the occurrence of the amorphous nature of NTG in ternary dispersions. The exothermic peak for the NTG-ternary dispersion was observed at 345.29 °C.

Dissolution Study of dispersions

Ternary dispersions with the highest solubility were selected and drug dissolution was studied through the selected combinations. The percentage of NTG release was calculated through all selected dispersion. The study was performed in different dissolution media. Table 5. Shows dissolution study of nateglinide ternary solid dispersions in different dissolution media (Percentage drug release) after 10 min of dissolution.
Fig. 3: PXRD thermogram of pure NTG and optimized ternary dispersion

Fig. 4: DSC thermogram of pure NTG and optimized ternary dispersion

Table 5: Dissolution study of nateglinide ternary solid dispersions in different dissolution media (Percentage drug release) after 10 min of dissolution

| Complexes                  | Dissolution media |
|----------------------------|-------------------|
|                            | 0.5% SLS in 0.01 N HCl | 0.1 N HCl | Ph. 6.8 buffer | Ph. 7.4 buffer |
| Pure NTG                   | 29.87             | 10.07     | 26.67          | 28.56          |
| NTG+Solvuplus+KolliphorP188| 100.89            | 100.54    | 89.54          | 94.67          |
| NTG+Solvuplus+Affinisol    | 100.38            | 72.87     | 100.03         | 100.18         |
| NTG+Solvuplus+Sylloid      | 98.89             | 100.35    | 93.53          | 95.67          |
| NTG+Solvuplus+Gelucire 48/16| 100.13           | 98.92     | 94.36          | 96.55          |
| NTG+BCD+Na2CO3             | 89.34             | 97.67     | 80.72          | 83.96s         |
NTG dissolution from solid dispersions

The complexes showing more fold enhancement in solubility were selected and their dissolution study was performed in all selected media. Dissolution profiles of NTG from the pure drug were studied in dissolution media and percentage drug release through prepared formulations in all dissolution media, are shown in table 5. From the presented dissolution profiles, it can be observed that pure NTG dissolves slowly and incompletely, with less than 30% of NTG dissolved after 45 min of testing. Dissolution of all prepared ternary dispersions in 0.5% SLS in 0.01 N HCl, was faster relative to pure NTG. The fastest NTG dissolution rate was achieved from the formulation from complex ternary F13 (NTG+Soluplus+Gelucire 48/16) 100.13% of the drug was released within 10 min of dissolution while from F11 (NTG+Soluplus+KolliphorP188), with 100.89% of NTG dissolved after 20 min of Dissolution. F12 (NTG+Soluplus+Affinisol) dissolves 100.13% after 45 min. As all the prepared ternary dispersions were in powdered form, many were dissolved 100% within 10 min of dissolution. The percentage of drug release of all SD was very slow in 0.1 N HCl. All ternary dispersions prepared with soluplus were dissolved completely at all the dissolution media. Formulated combinations successfully enhanced the dissolution of NTG.

Dissolution study of formulations

Ternary dispersions showing improved drug release were formulated as NTG tablets. Dissolution study of optimized NTG tablets and marketed formulation, Glinate-60 was performed in different dissolution media. The comparative drug release was observed as follows. Table 6 shows comparative Percentage drug release from in house and marketed tablets in 0.5% SLS in 0.01% HCl dissolution media. Fig. 5 shows a Comparative percentage drug release from NTG marketed tablet and prepared tablets.

Table 6: Percentage drug release of tablets in 0.5% SLS in 0.01% HCl dissolution media

| Time in min | N1  | N2  | N3  | Marketed brand Glinate 60 |
|------------|-----|-----|-----|---------------------------|
| 0          | 0.7 | 0.1 | 0.4 | 0.4                       |
| 10         | 59.57 | 33.67 | 49.28 | 63.79                   |
| 20         | 89.54 | 50.45 | 61.33 | 82.42                   |
| 30         | 100.17 | 78.34 | 77.86 | 100.32                  |
| 45         | 92.28 | 100.89 | 100.65 | 88.39                   |

Fig. 5: Comparative percentage drug release from NTG marketed tablet and prepared tablets

DISCUSSION

After solubility and dissolution determination of binary solid dispersions, we found that with all selected polymers, the solubility of the drug increases up to a certain limit beyond that it remains the same. Soluplus forms a solid solution with drugs that allows the drug in a dissolved state and shows superior performance to enhance solubility. NTG with soluplus shows more solubility at 1:1 ratio and solubility decreases with increasing concentration of soluplus. This might be due to higher concentration may result in a cloudy or turbid aqueous solution. This is due to the formation of colloidal soluplus micelles. Molecular dispersion might be the reason behind the enhanced solubility of drugs with soluplus. By considering the size of the dosage form, we have considered 1:1 as a good ratio to make formulation.

In ternary dispersions, NTG-Soluplus-KolliphorP188 combination enhanced solubility dramatically. Ternary dispersion with kolliphor P188 and soluplus, enhanced solubility of NTG Synergistically [18]. Another mechanism involved may be that, soluplus being hydrophilic makes a wet layer around the drug molecule which allows the transfer of solvent to the surface of the drug molecule which makes the drug molecule solubilize [19].

NTG-Soluplus-Gelucire 48/16 ternary combination was proved best. This combination enhanced the solubility of NTG by 25.46 fold. Gelucire 48/16 is a non-ionic surfactant proved as a solubilizer as well as a bioavailability enhancer. This polymer forms micelle solution with aqueous media, it enhances the wettability of the drug thereby improves solubility.

CONCLUSION

In the present investigation, there was a significant improvement in the solubility and dissolution profile of NTG by formulating ternary solid dispersions. Ternary solid dispersions prepared by the common solvent evaporation method proved a successful method to enhance the solubility of NTG. Solubility and dissolution were enhanced significantly with soluplus and kolliphor P188. Soluplus and gelucire 48/16 with NTG enhanced solubility dramatically. F11 and F13 ternary dispersions were having the best solubility. Prepared tablets show very good dissolution. All formulations N1, N2, N3 showed the complete drug release after 45 min. Among all prepared formulations N1 was found best. 100 % Drug was released from the marketed tablet and N1 after 30 min. Formulating ternary solid dispersions of NTG with Soluplus and Kolliphor could be a potential strategy to improve the solubility of NTG.

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Authors declare that the work done by the names mentioned in the article and all the liabilities and claims related to the content of the article will be borne by the authors.

CONFLICT OF INTERESTS
The authors declare that no conflict of interest associated with this work.

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