APPLICATION OF SOLID DISPERSION TECHNIQUE IN SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF NATEGLINIDE

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INTRODUCTION

Diabetes is a chronic condition associated with abnormally high levels of sugar (glucose) in the blood. Diabetes was the 7th leading cause of death in the United States listed on death certificates in 2007. The two types of diabetes are referred to as type 1 (juvenile-onset or insulin-dependent diabetes) and type 2 (adult-onset or non-insulin-dependent diabetes mellitus [NIDDM]). The major complications of diabetes are both acute and chronic. The major goal in treating diabetes is to minimize any elevation of blood sugar (glucose) without causing abnormally low levels of blood sugar. Type 1 diabetes is treated with insulin, exercise, and diabetic diet. Type 2 diabetes is first treated with weight reduction, a diabetic diet, and exercise [1]. When these measures fail to control the elevated blood sugars, oral medications are used. If oral medications are still insufficient, insulin medications and other injectable medications are considered [2].

Insulin produced by the pancreas lowers blood glucose. The absence or insufficient production of insulin causes diabetes. The class of drugs known as meglitinides is relatively new, which act by binding selectively to pancreatic β-cells to stimulate insulin release. Unlike the sulfonylureas that bind to receptors on the insulin-producing cells, meglitinides work through separate potassium-based channel on the cell surface. Meglitinides may have a neutral effect on weight or cause a slight increase in weight [3]. The average weight gain caused by meglitinides appears to be lower than that caused by sulfonylureas and insulin appears to occur only in those native to oral antidiabetic drugs. Meglitinides are also relatively safe to use in people with impaired kidney function. Due to their mechanism of action, meglitinides may cause hypoglycemia, but the literature suggests that the risk is lower than that caused by sulfonylureas and insulin since their action is dependent on the presence of glucose [4]. Meglitinides appear to be more effective at lowering post-prandial blood glucose than metformin, sulfonylureas, and thiazolidinediones [5].

Nateglinide (NTG) is an oral antihyperglycemic agent used for the treatment of NIDDM. NTG is an amino acid derivative belongs to the meglitinides class of short-acting insulin secretagogues. It potentiates the effect of extracellular glucose on adenosine triphosphate-sensitive potassium channel and has little effect on insulin between meals and overnight [6]. As such, NTG is more effective at reducing post-prandial blood glucose levels and does not tend to lower fasting blood glucose levels to the same degree. Approximately one month of therapy is required before a decrease in fasting blood glucose is seen. The insulinnotropic effects of NTG are highest at intermediate glucose levels (3-10 mMol/l) and it does not increase insulin release already stimulated by high glucose concentrations (>15 mmol/l). Unlike the sulfonylureas which last longer in the body, NTG (Starlix) is very short-acting (half-life ~1.5 hr), with peak effects within one hour of oral administration [7,8]. For this reason, the immediate release (IR) tablets of NTG has been commercialized as an antidiabetic agent for the treatment of type 2 diabetics, and it is required to be administered at a dose of 60/120 mg twice or thrice a day just before meals. The major benefit of NTG is that the starting dose of 120 mg does not need to be adjusted upward, but rather remains constant. Therefore, to prolong its effect in the body and to decrease oscillations in concentration level in plasma. A modified drug delivery system is needed for NTG to improve solubility, dissolution rate, and patient compliance, and to decrease the side effects [9,10]. NTG is practically insoluble in water and has an absolute bioavailability of approximately 73%. Hence, it is desirable

Keywords: Controlled release, Diabetes mellitus, Dissolution, Meglitinides, Solid dispersion, Solubility.
to enhance the solubility and dissolution profile of NTG using various cyclodextrins (CD)/polyvinyl pyrrolidone (PVP) in combination with release retardant polymers such as ethyl cellulose (EC), hydroxy EC (HEC), hydroxypropyl methylcellulose (HPMC), Carbopol, Kollidon, and various natural gums [1,11,12].

NTG undergoes extensive first-pass metabolism by hydroxylation followed by glucuronide conjugation. The major metabolites possess less activity than the parent compound. One major metabolite, the isoprene, has the same potency as its parent compound. NTG is approximately 98% bound to proteins (primarily albumin and to a lesser extent to alpha-1 acid glycoprotein). Multipurcailtate drug delivery systems have considerable potential for the treatment of chronic diseases such as diabetes [13,14]. The important technological advantages of solid dispersions as used as drug carriers are high stability, high carrier capacity, feasibility of incorporation of both hydrophilic and hydrophobic substances, and feasibility of variable routes of administration including oral application and inhalation. These properties of solid dispersions enable improvement of drug solubility, dissolution rate, bioavailability, and may resolve the problem of patient noncompliance [15]. The proposed research studies were carried out on the enhancement of dissolution rate of NTG by solid dispersion technology employing various water dispersible carriers.

For the improvement of compliance to patients, however, it is desired to develop an SR oral dosage form instead of IR tablet. NTG belongs to biopharmaceutical classification system Class II, that is, why we can develop a solubility/dissolution enhanced form of it using various techniques such as solid dispersion [16-21]. Because NTG is having low t<sub>1/2</sub> which is unable to reach the therapeutic concentration, CR formulations are designed. The release of NTG should be sustained as its therapeutic absorption window is in the intestine. The value of hydrophilic, polymer-based matrix system as carriers for controlled drug delivery is well recognized and increasingly demonstrated by the numerous patents, research papers, and the US food and drug administration approved matrix-based products [22]. In particular, water soluble cellulose ethers (e.g., HPMC, HPC, HEC, EC), PEO, Kollidon, Carbopol, and polycascharides such as locust bean gum (LBG) have been extensively used [23].

When we are combining both the technologies, we can enhance the efficacy of drug as well as we can maintain the drug concentration in plasma such that it maintains in therapeutic concentration for the desired time [24]. The present research endeavor was thus directed toward the development of safe and effective controlled-release dosage form of NTG to be taken once daily to maintain the optimum therapeutic concentration in therapeutic level in the intestine such that it maintains in therapeutic concentration for the desired time [24]. The present research endeavor was thus directed toward the development of safe and effective controlled-release dosage form of NTG to be taken once daily to maintain the optimum therapeutic concentration in therapeutic level in the intestine such that it maintains in therapeutic concentration for the desired time [24].

### MATERIALS AND METHODS

#### Materials

NTG was gift samples from Glenmark Pharmaceutical Ltd., Pune, EC, hydroxypropyl cellulose (HPC), hydroxy EC (HEC), β-CD, and HP β-CD (HP β-CD) were obtained from S.D. fine chemicals, Mumbai. HPMC K-100 was procured from Colorcon, Goa. Kollidon SR, polyvinylpyrrolidone (PVP) K-17, and polyvinylpyrrolidone K-30, microcrystalline cellulose (MCC), sodium starch glycolate (SSG) were obtained from S.D. fine chem. Ltd., Mumbai. LBG, Carbopol 971 P, Dicalcium phosphate (DCP), magnesium stearate, and colloidal silica were procured from Lubrol Pvt. Ltd., Mumbai. All other chemicals and solvents used were of analytical grade. The commercial brand of IR tablet: Starlix® containing 60 mg of NTG (batch No. A2O26SU, Novartis) was used for comparison of optimized solid dispersion in the present study.

#### Pre-formulation studies

**Standard plot of NTG**

NTG exhibits peak absorbance at 212 nm in 0.01 N hydrochloric acid (HCl) (pH 2) and pH 6.8 phosphate buffer containing 0.5% sodium lauryl sulphate (SLS). The concentration of NTG was found to be linear in range of 0-10 µg/ml with a correlation coefficient of r=0.999. The linear regression equation was found to be y=0.031x+0.002, which can be used for estimation of NTG drug concentration in 0.01 N HCl containing 0.5%.SLS. NTG has shown linear relationship in the range of 0-10 µg/ml in pH 6.8 phosphate buffer containing 0.5% SLS, and the regression equation was found to be y=0.024x-0.002 with a correlation coefficient (r) of 0.998, which can be used for the estimation of drug concentration.

#### Solubility studies

The solubility of NTG was determined by adding excess but measured amount (20 mg) of drug in 25 ml volumetric flask containing 0.01 N HCl with 0.5% SLS and kept in rotary shaker for 24 hrs at room temperature. The dispersions were filtered through Whatman filter paper (No.1) and analyzed for the quantity of drug dissolved by taking the absorbance and was determined from their respective standard plots.

#### Drug-excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy analysis was performed to pure drug (NTG), physical mixtures of drug with β-CD (1:1), HP β-CD (1:1), PVP K-17 (1:1), PVP K-30 (1:1) PM, HP β-CD (1:1) kneading method (KM), PVP K-30 (1:1) KM, and final optimized formulation. The IR absorption spectra of the pure drug with different excipients were taken in the range of 4000-450 cm⁻¹ using KBr disc method. Around 1-2 mg of the substance to be examined was triturated with 300-400 mg of finely powdered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15 mm diameter and pellet of suitable intensity by a hydraulic press. Each spectrum was derived from 16 single average scans collected under identical conditions at a spectral resolution of 2cm⁻¹.

#### Preparation of solid dispersions

**Solubility determination**

Solubility studies were performed in triplicate according to the Higuchi and Connors method. To improve solubility and dissolution rate of NTG, complexation with β-CD, HP β-CD, PVP K-17, and PVP K-30 were prepared at different concentrations [27]. Sixteen formulations of NTG solid dispersions were prepared by two different methods, namely, PM and KM.

#### Analysis of prepared solid dispersions

The formulations prepared were subjected to pre-compression parameters and physicochemical properties evaluation. In vitro dissolution studies were performed for two hours using USP dissolution test apparatus II in 0.01 N HCl containing 0.5% SLS at 50 rpm and 37±0.5°C [28]. The amount of NTG released from the SR tablet formulations was estimated at 212 nm using a UV spectrophotometer.

#### Preparation of IR layer

Formulation of IR layer was done by taking pure drug NTG 60 mg (loading dose) labeled as formulation I of total weight 400 mg. Formulations 12, 13, 14, and 15 were prepared by employing drug: excipient complexes in the ratio 1:2 β-CD and HP β-CD by PM and KM with SSG and MCC as a super disintegrant and diluent, respectively. All the formulated IR tablets employing solid dispersions exhibited rapid and higher drug dissolution when compared to tablets formulated with pure drug (F1) and also commercial tablets of NTG (Starlix®).

#### Preparation of SR layer

Formulation trials were done using the six-stated polymers by wet granulation method. The SR tablet of 470 mg containing 270 mg (maintenance dose) of NTG was prepared using various controlled-release polymers, namely, cellulose derivatives such as EC, HEC, HPMC,
Kollidon to enhance the aqueous solubility of the drug; saccharide derivatives such as LBG; and acrylic acid derivatives such as Carbopol. In the present SR matrix formulation, DCP was used as filler to impart physical stability to the drug. Colloidal silica and magnesium stearate were used as glidant and lubricant, respectively, to improve the flow properties; povidone was used as a binder and purified water as a solvent for the binder.

Twelve formulations were prepared by varying the concentration of six polymers at two levels of 15% and 30%. The formulations prepared were subjected to evaluation of pre-compression parameters and physicochemical properties. In vitro dissolution studies were conducted for 12 hrs using USP dissolution rate test apparatus II in 0.01 N HCl containing 0.5% SLS for 2 hrs followed by pH 6.8 phosphate buffer at 50 rpm and 37±0.5°C. The amount of NTG released from the SR tablet formulations was estimated at 212 nm using a UV spectrophotometer.

Preparation of bilayer tablet
All the ingredients were passed through 100 mesh sieve separately. Weighed quantity of NTG and all other excipients except lubricant and glidant were taken in mortar and prepared the wet mass using PVP K-30 binder solution in ethanol. This wet mass was passed through 60 mesh sieve and dried in hot air oven at 50°C up to optimum drying. Dried granules were passed through 100 mesh sieve. Magnesium stearate and AEROSIL were added to these dried granules. Later, these were subjected for punching using RIMEK multi station tablet punching machine using round flat surface punches of 12 mm diameter. After compression of the SR layer, the upper punch was lifted, and the optimized blend of powder for IR layer (containing 60 mg NTG) was poured into the die cavity, containing initially compressed SR matrix tablet (containing 270 mg NTG). This bilayer tablet compression was performed by RIMEK multi station punching machine using flat punches. The details of the composition of the IR (11-15) and SR (S1-S12) layer of bilayer tablet are given in Table I.

Analysis of IR and SR formulations of bilayer tablet
Evaluation of pre-compression parameters of prepared formulations
The blend of all the prepared formulations was evaluated for their flow properties before compression by characterization of bulk density, tapped density, compressibility index, Hausner’s ratio, and angle of repose.

Table 1: Formulation details of immediate and SR layer of bilayer tablet

| Ingredients (mg/tab) | I1 | I2 | I3 | I4 | I5 | S1 | S2 | S3 | S4 | S5 | S6 | S7 | S8 | S9 | S10 | S11 | S12 |
|----------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| NTG                  | 60 | -  | -  | -  | -  | 270| 270| 270| 270| 270| 270| 270| 270| 270| 270| 270|
| Drug: β-CD 1:2 (KM)  | 172| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Drug: HP β-CD 1:2 (KM)| -  | 200| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Drug: β-CD 1:2 (PM)  | -  | -  | 180| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Drug: HP β-CD 1:2 (PM)| -  | -  | -  | 180| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| SSG                  | -  | 20 | 20 | 20 | 20 | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| MCC                  | 312| 200| 172| 192| 192| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Kollidon SR          | -  | -  | -  | -  | -  | 67.5| 135| -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Carbopil 971P        | 67.5| -  | -  | -  | -  | 135| -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| EC                   | -  | -  | -  | -  | -  | -  | -  | -  | 67.5| 135| -  | -  | -  | -  | -  | -  |
| HEC                  | -  | -  | -  | -  | -  | -  | -  | -  | -  | 67.5| 135| -  | -  | -  | -  | -  |
| LGP                  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| HPMC K-100           | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| DCP                  | 86.5| -  | -  | -  | -  | 86.5| 86.5| 86.5| 86.5| 86.5| 86.5| 86.5| 86.5| 86.5| 86.5| 86.5|
| PVP K-30             | 86.5| -  | -  | -  | -  | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| Colloidal silica     | 22  | -  | -  | -  | -  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| Magnesium stearate   | 2  | 2  | 2  | 2  | 2  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| Total amount         | 400| 400| 400| 400| 400| 450| 450| 450| 450| 450| 450| 450| 450| 450| 450| 450|


Evaluation of post-compression parameters of prepared formulations
The weight variation, hardness, thickness, and friability of the tablets were measured in electronic balance (Shimadzu, Mumbai), hardness tester (Pfizer, Mumbai), digital caliper (Vernier, Mumbai) and friabilator (Electrolab, Mumbai), respectively.

Estimation of drug content in tablets
An accurately weighed quantity (10 mg and 45 mg) of powdered IR and SR tablet was transferred separately to a 100 ml volumetric flask, and the NTG was extracted into 50 ml of methanol. The volume is made up to 100 ml with 0.01 N HCl containing 0.05% SLS for IR and pH 6.8 phosphate buffer for SR formulation [29]. The stock solutions were filtered and suitably diluted with the corresponding solvent. The drug content was assayed using double-beam UV-Visible spectrophotometer (model SL210, Elico, Hyderabad), in a 1 cm quartz cell, at 212 nm in both IR and SR formulations. Each drug content estimation procedure was replicated six times.

In vitro dissolution rate studies
In vitro dissolution studies of IR formulations
Dissolution of the tablets was carried out on USP XXIII dissolution type I apparatus (Model No. TDT-08L, Electrolab, Mumbai). The tablet was fixed to the paddle by hydration mechanism. The dissolution vessel was filled with 900 ml of 0.01 N HCl containing 0.5% SLS (pH 2.0) and the temperature of the dissolution medium was maintained at 37±0.5°C. The rotational speed of the paddle was set at 50 rpm. At suitable intervals, 5 ml of sample was withdrawn and same volume of fresh medium was replaced. The withdrawn samples were filtered, diluted when necessary with the dissolution medium, and analyzed spectrophotometrically at 212 nm using 0.01 N HCl containing 0.5% SLS as blank. The mean cumulative percentage drug release was calculated and plotted against time.

In vitro dissolution studies of bilayer tablets
Dissolution of the tablets was carried out on USP XXII dissolution type I apparatus (Model No. TDT-08L, Electrolab, Mumbai). The tablet was fixed to the paddle by hydration mechanism. The dissolution vessel was filled with 900 ml of 0.01 N HCl containing 0.5% SLS (pH 2.0) for first two hours and thereafter replaced with pH 6.8 phosphate buffer for the remaining 10 hrs. The temperature of the dissolution medium was maintained at 37±0.5°C with paddle rotational speed of 50 rpm. At suitable intervals, 5 ml of sample was withdrawn, and the same
volume of fresh medium was replaced. The withdrawn samples were filtered, diluted when necessary with the dissolution medium, and analyzed spectrophotometrically at 212 nm for NTG content. The mean cumulative percentage drug release was calculated and plotted against time. During the drug release studies, all the formulations were checked at intervals for their physical integrity.

Drug release kinetics
The release rate kinetics and mechanism of drug release from the IR and SR formulations were analyzed by fitting the data obtained into zero- and first-order models using PCPDISSO v2 software [30]. Based on the correlation coefficient (r) value, the best-fit model was selected.

RESULTS AND DISCUSSION
Pre-formulation studies
Solubility studies
The drug NTG has shown highest solubility in pH 6.8 phosphate buffer (1.61 mg/ml), followed by 0.01 N HC1 containing 0.5% SLS (0.61 mg/ml) and the least in distilled water (0.36 mg/ml) [33]. NTG is an acidic drug with one ionizable group (pKa=3.1) [34]. Hence, it requires enhancement of solubility to increase the bioavailability of the drug in the management of type 2 diabetes mellitus.

Drug-excipient interaction studies
From the FTIR data observed in Fig. 1, it was concluded that there were no considerable changes even after the development of tablet with reference to the respective spectrums. The FTIR spectrum of NTG shown a characteristic peak at 3424.41 cm⁻¹ due to COOH–O–H stretching, peak at 3315.91 cm⁻¹ was observed due to N–H stretching of the secondary amide. The peaks at wave numbers 2924.74 and 2854.45 cm⁻¹ were correspondence to CH₃–C–H stretching, respectively. The COOH–C=O stretch at 1713.72 cm⁻¹ and the secondary amide C=O stretching at 1649.45 cm⁻¹ were observed. All characteristic peaks obtained in the pure drug spectra were observed in physical mixture with minor shifts indicating there is no significant interaction between the drug (NTG) and the excipients which were employed in the present study.

![Fig. 1: Fourier transform infrared spectras of (a) NTG, (b) NTG: β-CD, (c) NTG: HP β-CD, (d) NTG: PVP K-17, (e) NTG: PVP K-30, and (f) optimized formulation (F12), NTG: Nateglinide, CD: Cyclodextrin, HP: Hydroxypropyl, PVP: Polyvinylpyrrolidone](image-url)
Solid dispersions
Solubility determination
The effect of four different carriers, that is, β-CD, HP β-CD, PVP K-17, and PVP K-30 on the solubility and dissolution rate of NTG was studied at different concentrations [35]. At 1% w/v of HP β-CD, NTG had shown the highest solubility of 97.5% as shown in Fig. 2.

The solubility of NTG was increased as the concentration of carrier was increased in the solid dispersions due to the formation of inclusion complexes. The solubility of NTG was 40% at zero percent carrier concentration and increases to around 90% at one percent concentration of β-CD, PVP K-17, and PVP K-30. The solubility of NTG was increased up to 98% at one percent concentration of HP β-CD, indicating the formation of soluble inclusion complex between NTG and carrier.

Analysis of prepared solid dispersions
All the solid dispersions prepared were found to be fine free-flowing powders. The drug content was uniform in all the solid dispersion batches. The dissolution of NTG from all the solid dispersions was rapid and several times higher than the dissolution of the corresponding pure drug as shown in Table 2.

Drug dissolution from all solid dispersions followed first-order kinetics. All the dissolution parameters estimated, that is, $T_{90}$, $T_{50}$, DE30%, and $K_d$ values indicated rapid and higher dissolution of the drug (NTG) from solid dispersions than that of corresponding pure drug. The dissolution rate of nateglinide with various carriers is in the order of: HP β-CD > β-CD > PVP K-30 > PVP K-17. In each case, the dissolution rate ($K_d$) and DE30% were increased as the concentration of carriers in the solid dispersions was increased.

For solid dispersions prepared with β-CD, a 1.9- and 2.3-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of physical mixture. A 2.85- and 3.36-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of KM. A 2.38- and 2.51-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:2 ratio of KM. A 2.53- and 2.89-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:2 ratio of physical mixture. A 4.28- and 4.76-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of KM. A 4.66- and 3.49-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:2 ratio of KM.

Whereas for solid dispersions prepared with PVP K-17, a 2.38- and 2.35-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of physical mixture. A 2.85- and 2.82-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of KM. A 2.53- and 2.51-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:2 ratio of KM. A 2.85- and 3.23-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:1 ratio of KM. A 4.28- and 3.90-fold increase in dissolution rate ($K_d$) and DE30%, respectively, was observed with 1:2 ratio of KM.

From Fig. 3, it is clear that when compared to pure drug NTG, drug inclusion complexes prepared with different CDs (β-CD, HP β-CD) by PM and KM gave the maximum solubility and dissolution rate of drug from prepared solid dispersions. Hence, inclusion complexes of NTG with β-CD and HP β-CD in the ratio of 1:2 (drug:polymer) were further optimized by preparing IR layer of NTG.

IR formulation
Analysis of prepared IR formulations
All the pre-compression parameters such as angle of repose (<25°), compressibility index (15.05-20.02%), and Hausner’s ratio (<1.25) were within the limits of official standards displaying good flow properties of the prepared granules (I1-I5).

All post-compression parameters such as weight variation, hardness, thickness, friability, disintegration time, and drug content were found to be within the limits of official standards. The weight variation for a tablet weighing around 400 mg was found to be within official limits of NMT 5%. The measured hardness of the tablets of each batch of all formulations, that is, I1-I5 was between 3 and 3.5 kg/cm² and optimum for an IR formulation. The percent friability of formulated tablets was found to be <1% ensuring that IR layer was mechanically stable. The thickness of the tablets was found to be almost uniform in all formulations I1-I5 in the range of 2.0-2.2 mm with less % RSD. The drug content of each batch formulations (I1-I5) was evaluated as per the standard protocol, and the percentage of drug content was found to be 98.2-99.4%. The disintegration time of all the prepared IR formulations was <30 seconds, with a least disintegration time of 24 sec from formulation I3 prepared with HP β-CD drug complex (1:2) by KM.

Table 2: Estimated dissolution parameters of NTG solid dispersions

<table>
<thead>
<tr>
<th>S. No.</th>
<th>$T_{90}$ (minutes)</th>
<th>$T_{50}$ (minutes)</th>
<th>DE 30%</th>
<th>$K_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-CD 1:1 (PM)</td>
<td>30</td>
<td>&gt;120</td>
<td>53.73</td>
<td>0.008</td>
</tr>
<tr>
<td>β-CD 1:1 (KM)</td>
<td>13</td>
<td>&gt;120</td>
<td>59.05</td>
<td>0.012</td>
</tr>
<tr>
<td>β-CD 1:2 (PM)</td>
<td>16</td>
<td>&gt;120</td>
<td>78.55</td>
<td>0.010</td>
</tr>
<tr>
<td>β-CD 1:2 (KM)</td>
<td>10</td>
<td>90</td>
<td>81.51</td>
<td>0.016</td>
</tr>
<tr>
<td>HP β-CD 1:1 (PM)</td>
<td>15</td>
<td>&gt;120</td>
<td>61.11</td>
<td>0.010</td>
</tr>
<tr>
<td>HP β-CD 1:1 (KM)</td>
<td>11</td>
<td>95</td>
<td>64.86</td>
<td>0.020</td>
</tr>
<tr>
<td>HP β-CD 1:2 (PM)</td>
<td>12</td>
<td>110</td>
<td>60.10</td>
<td>0.014</td>
</tr>
<tr>
<td>HP β-CD 1:2 (KM)</td>
<td>6</td>
<td>55</td>
<td>83.11</td>
<td>0.028</td>
</tr>
<tr>
<td>PVP K-17 1:1 (PM)</td>
<td>35</td>
<td>&gt;120</td>
<td>55.20</td>
<td>0.010</td>
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<tr>
<td>PVP K-17 1:1 (KM)</td>
<td>22</td>
<td>&gt;120</td>
<td>56.81</td>
<td>0.012</td>
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<tr>
<td>PVP K-17 1:2 (PM)</td>
<td>27</td>
<td>&gt;120</td>
<td>65.87</td>
<td>0.012</td>
</tr>
<tr>
<td>PVP K-17 1:2 (KM)</td>
<td>18</td>
<td>98</td>
<td>67.71</td>
<td>0.018</td>
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<tr>
<td>PVP K-30 1:1 (PM)</td>
<td>45</td>
<td>&gt;120</td>
<td>58.88</td>
<td>0.008</td>
</tr>
<tr>
<td>PVP K-30 1:1 (KM)</td>
<td>38</td>
<td>&gt;120</td>
<td>62.23</td>
<td>0.010</td>
</tr>
<tr>
<td>PVP K-30 1:2 (PM)</td>
<td>40</td>
<td>&gt;120</td>
<td>59.10</td>
<td>0.008</td>
</tr>
<tr>
<td>PVP K-30 1:2 (KM)</td>
<td>30</td>
<td>&gt;120</td>
<td>57.73</td>
<td>0.012</td>
</tr>
</tbody>
</table>

In vitro dissolution studies
All the formulated IR tablets employing solid dispersions exhibited rapid and higher drug dissolution when compared to formulation prepared with pure drug (I1) and commercial tablets of NTG (Starlix®). The dissolution rate of the five formulations were in the order of F3>F5>F2>F4>F1 as shown in Fig. 4. Among all the carriers tested, HP β-CD in the ratio of 1:2 prepared by KM gave the highest enhancement of dissolution rate and dissolution efficiency of NTG. The prepared formulations I1-I5 followed first-order kinetics with a T90, respectively. 

The prepared formulations I1-I5 followed first-order kinetics with a higher correlation coefficient (r) values for Higuchi plot indicating the drug release occurs through diffusion mechanism. This was further confirmed by Korsmeyer-Peppas “n” values lying within 0.66-0.80, exhibiting non-Fickian diffusion mechanism of drug release.

Comparison of optimized IR formulation with marketed product
The dissolution rate and dissolution efficiency DE30% of I3 were greater than marketed formulation of NTG (Starlix®) as shown in Fig. 4. In the case of F2 formulation, a 12.09- and 1.51-fold increase in dissolution rate (K) and DE30%, respectively, was observed. For F3 formulation, a 17.2- and 1.67-fold increase in dissolution rate (K) and DE30%, respectively, was observed. For F4 formulation, a 5.51- and 1.35-fold increase in dissolution rate (K) and DE30%, respectively, was observed. For F5 formulation, a 9.31- and 1.45-fold increase in dissolution rate (K) and DE30%, respectively, was observed.

In the case of marketed formulation (Starlix®), an 11.7- and 1.45-fold increase in dissolution rate (K) and DE30%, respectively, was observed. The observed responses for the NTG-marketed IR tablets (Starlix®) were found to be 5 minutes, 92% drug release and 48 minutes for T30, DR60, and T90, respectively. Similarity factor (f1) and dissimilarity factor (f2) values of the matrix tablet were below 15 (10.5) and above 50 (51.0), respectively, indicated similarities between the optimized formulation (I3) and theoretical release profiles.

SR formulation
As NTG is having low t1/2, which is unable to reach the therapeutic concentration, CR formulations are designed. The release of NTG should be sustained as its therapeutic absorption window is in the intestine.

Evaluation of pre-compression parameters
The prepared granules were evaluated for pre-compression parameters such as bulk density, tapped density, compressibility index, and Hausner’s ratio before being punched into tablets. The angle of repose of the formulations S1-S12 was found to be below 35° indicating excellent flow properties of the formulation. The compressibility index of formulations S1, S8, S11, and S12 were found to be in the range of 12.00-14.60%, indicating the free flow, while the formulations S2, S3, S4, S5, S6, S7, S9, and S10 compressibility index was in the range of 18.00-28%, indicating poor flow properties. The Hausner’s ratio of the formulations S1-S12, except S2 and S4 was <1.25 indicating good flowability.

Evaluation of post-compression parameters
The formulated tablets were evaluated for post-compression parameters such as weight variation, thickness, hardness, diameter, friability, and content uniformity. The weight variation for a tablet weighing around 450 mg was found to be within官方 limits of NMT 5%. The measured hardness of the tablets of each batch of all formulations, that is, S1-S12 was between 5 and 6.5 kg/cm², optimum for an SR formulation. The percent friability of formulated tablets was found to be <1% ensuring that SR layer was mechanically stable. The thickness of the tablets was found to be almost uniform in all formulations S1-S12 in the range of 3.1-3.3 mm with less percentage RSD. The drug content of each batch formulations (S1-S12) was evaluated as per the standard protocol, and the percentage of drug content was found to be 97.00-99.33%.

In vitro dissolution studies
From the results of the in vitro dissolution profiles of the SR matrix formulations (Fig. 5), it can be observed that the rate of release retardant power of the six polymers taken was in the order of Carbopol 971P>EC>Kollidon SR>LBG-HPMC>HEC. The formulations S7, S9, and S12 prepared with HEC (1:1), LBG (1:1), and HPMC K-100 (1:2) as release controlling polymer has shown a drug release of 88%, 83%, and 80%, respectively, at the end of 12 hrs. Among all formulations, S7, S9, and S12 exhibited the desired...
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