Original Article

Effect of Solutol HS 15 and Cremophor RH 40 on Dissolution and Bioavailability of Nateglinide through Solid Dispersions

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ABSTRACT

Introduction: To improve the aqueous solubility and bioavailability of nateglinide, we have earlier used poloxamer 188 and 407. Since solutol HS 15 and cremophor RH 40 are compatible and scalable polymers for industrial applications. **Materials and Methods:** We developed solid dispersions using these polymers. All data including Fourier transform infrared spectroscopy, differential scanning calorimetry, thermogravimetry analysis, x-ray diffraction and scanning electron microscopy suggested loss of crystallinity and amorphization. The stability of these was demonstrated as per the International Council for Harmonisation norms. **Results and Discussion:** Cremophor RH 40 (melting method) and solutol HS 15 based (solvent evaporation method) solid dispersions showed the highest saturation solubility (~ 65 fold). The significant difference ($p < 0.05$) in dissolution efficiency, time taken to release 50 % of drug, mean dissolution time and similarity factor signifies the remarkable enhancement of dissolution in these solid dispersions. Following oral administration of solid dispersions to rabbits, an increase of ~ 2.4 and ~ 1.8 folds in peak plasma concentration, area under curve respectively and decrease in time to reach peak plasma concentration (1 hr) of nateglinide, suggested the effectiveness of solid dispersions to improve the bioavailability. A 170% and 179% increase in relative bioavailability was demonstrated compared to the marketed formulation (Natiz 60) for these solid dispersions. **Conclusion:** Cremophor RH 40 solid dispersion showed relatively late release but a higher *In vitro-in vivo* correlation. It may be suggested that cremophor RH 40 promotes better absorption as compared to solutol HS 15 based solid dispersion.
Key words: Amorphization, Bioavailability enhancement, *In vitro-in vivo* correlation, Solutol HS 15, Cremophor RH 40, Pharmacokinetic.

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INTRODUCTION

The oral antidiabetic agent nateglinide (meglitinides class) is an anionic compound with a pK_a value of 3.1 and poor water solubility (8.8 mg/ L).[1] Nonetheless, it has good permeability and is labelled as BCS (Biopharmaceutical Classification System) class II drug.[2,3] Since poor aqueous solubility is a major hurdle for its oral bioavailability, nateglinide has attracted research efforts to increase solubility. In recent years several attempts have been made to overcome solubility and enhance bioavailability (Table S1 and S2). For optimum bioavailability, it is desirable to have higher release (> 85 %) in a shorter period of time (15 min).[2,3] However, many of these attempts have failed to achieve this (Table S1). Since the interaction of polymer and drug cannot be accurately predicted, their respective compositions (drug: polymer) need to be optimized. With this background, microcrystalline cellulose (1:2) and crosslinked polyvinylpyrrolidone (1:4) based formulations have been shown to achieve a release of > 85 % of nateglinide in 15 min to qualify as immediate release formulations.[3,4] However, there is no *in vivo* data to support the increase in bioavailability (Table S2). The poloxamer 188A (1:2)

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Table S1: Comparision of solubility and dissolution profiles of the different formulations as reported in literature and developed formulation.

Techniques for the development of formulations	Solubility (mg/ml)	Drug loading (% W/W)	Q_{15} (approximate in %)	Q_{30} (approximate in %)	Q_{60} (approximate in %)	Time taken to achieve 85 % drug release (min)	References
Complexation	NA	33.33	NA	NA	NA	NA	R1
Ternary solid dispersion	1	31.25	80	93	100	20	9
Nanoparticle	NA	-	05	10	20	NA	6
Co-mixing	NA	20	55	75	90	> 40	6
Co-milling	NA	20	85	95	100	15	7
Co-amorphous	0.531	19.35	50	90	100	> 20	10
Liquisolid	NA	7.25	85	92	96	15	11
Co-crystallization	NA	33.33	90	95	97	05	12
Self-emulsifying Solid dispersion	91.82	16.67	83.95	98.27	99.5	20	13
Solid dispersion	52.57	25	85.16	99.25	100	15	14
Solid dispersion (Cremophor RH 40 based MM)	64.59	16.67	67.29	74.89	88.29	52	-
Solid dispersion (Solutol HS 15 based SM)	64.87	16.67	85.76	87.85	91.74	15	-

Q_{15}, Q_{30} and Q_{60}: Cumulative amount of nateglinide release within 15, 30 and 60 min of dissolution respectively.

Table S2: Comparision of pharmacokinetic parameters of the diffrent formulations as reported in litearture and developed formulation.

Techniques for the development of formulations	Animal Dose (mg/kg)	Pharmacokinetics								References
			T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng h/mL)	$AUC_{0-\infty}$ (ng h/mL)	K_e (L/h)	MRT (h)	$T_{1/2}$ (h)	
Complexation	15	Nateglinide	4.25	7004	36120	NA	0.44	NA	3.56	R1
		Best formulation	1.1	1980	54600	NA	350	NA	2.20	
Ternary solid dispersion	10	Nateglinide	0.50	332.58	318.06	372.31	0.36	NA	1.88	9
		Best formulation	0.25	1750.96	1367.12	1472.29	0.55	NA	1.22	
Self-emulsifying solid dispersions	10	Best formulation	1.00	927.70	6748.44	7827.34	NA	11.03	7.16	13
Solid dispersion	10	Formulation	1.00	746.37	6530.20	8234.93	NA	14.00	8.82	14
Co-crystallization	5	Formulation	0.25	NA	NA	NA	NA	NA	NA	12
Solid dispersion	10	Cremophor RH 40 based MM	1.00	750.29	6785.02	9285.47	NA	16.96	10.47	-
Solid dispersion	10	Solutol HS 15 based MM	1.00	787.70	7123.12	10026.80	NA	17.87	10.491	-
Nanoparticle	NA	NA								6
Co-mixing	NA	NA								6
Co-milling	NA	NA								7
Co-amorphous	NA	NA								10
Liquisolid	NA	NA								11

R1: Vinod M, Jitendra N, Komal P, Rahul C, Gokul K. Enhancement of solubility with formulation and *in-vitro* evaluation of oral nateglinide compacts by liquisolid technique. Advances in Diabetes and Metabolism. 2013;1:57-64.

has been used to develop solid dispersion (SD) of nateglinide that achieved rapid bioavailability with a time to reach the peak plasma concentration (T_{max}) of about 0.25 hr. Unfortunately, this also resulted in a very short half life ($t_{1/2}$) (< 1.22 hr).[5] Similar rapid absorption and low $t_{1/2}$ were also demonstrated with a complex of nateglinide with hydroxypropyl-cyclodextrin.[6] Thus these formulations were not demonstrated to have optimum pharmacokinetic and the correlation between *in vitro* dissolution and *in vivo* bioavailability was not established. Interestingly, a SD with poloxamer 188 (1:5) was shown by us to achieve 85.16 % release in 15 min with good *in vivo* correlation. A T_{max} of 1 h and $t_{1/2}$ of 8.82 hr suggested its optimum pharmacokinetics.[7] Although this formulation achieved desirable release and optimum bioavailability, there are some concerns regarding the use of poloxamer 188 in this formulation. The cost of the polymer and complexity of the manufacturing process (melting point, 52°C) in industrial scale are the limitations associated with poloxamer 188.[7,8] Thus in continuation of our effort to improve solubility and bioavailability of nateglinide we thought it worthwhile to develop new formulations with alternative polymers.

The solutol HS 15 and cremophor RH 40 are hydrophilic and non-ionic polymers. Because of their amphiphilic nature they are expected to stabilise the dispersion system.[8] Since recrystallisation following amorphisation is a challenge to the stability of dispersion system, these polymers can be used judiciously to maintain amorphous states of the dispersion system. Methods like kneading (KM), melting (MM) and solvent evaporation (SM) are used popularly as scalable industrial technologies for the manufacture of dispersion systems. However, neither the method nor the polymer alone (any random combination) can ensure a stable amorphous state for the drug. Thus it is desirable to find optimised polymer ratio and method for the development of a novel dispersion system for nateglinide to achieve higher solubility and bioavailability.

With these considerations, amorphization of nateglinide was achieved through the formation of novel SDs by MM and SM using solutol HS 15 and cremophor RH 40. Its influence on solubility, dissolution and bioavailability was established through *in vitro-in vivo* correlation (IVIVC) of nateglinide. In the absence of availability of any commercial SD formulation as positive control, Natiz 60 tablet, the conventional commercial product from Intas Pharmaceuticals Ltd., containing 60 mg of nateglinide was used as the control in the study.

MATERIALS AND METHODS

Materials

Nateglinide was donated by Aurobindo Pharma Ltd., India. BASF, India supplied solutol HS 15 and cremophor RH 40. Other reagents in analytical grade were supplied by Lotus enterprises, Andhra Pradesh, India.

Methods

Solid dispersions preparation

In nateglinide SDs, solutol HS 15 and cremophor RH 40 were employed as hydrophilic polymers. Initially, weight ratios (1:1, 1:3, 1:5, 1:7 and 1:9) of drug and polymer were taken to prepare SDs by MM and aqueous solubility was determined for ratio optimization. After optimization, SDs of nateglinide was formulated with the individual polymer at 1:5 weight ratios by KM, MM and SM. In KM, drug and either of the polymers was taken in a glass mortar. The mixture was kneaded for a specific time (10 min) to obtain a thick paste. In SM, nateglinide and polymer was dissolved in 10 mL of ethanol at room temperature with continuous stirring by magnetic stirrer (Royal scientific, India, Model: RSW 127) for an hour. The solvent was removed using a rotary evaporator (Royal scientific, India, Model: 137B) and further dried in hot air oven (Accumax, India, Model: AI-114) for complete evaporation of ethanol at 35°C. In MM, drug was added to the molten polymer. The blend was heated at 10°C above the melting point of each polymer for 10 min with continuous stirring. The system was cooled rapidly in an ice bath containing sodium chloride for 3 h. The products were collected and stored in a desiccator in anhydrous condition until further analysis.[7,9-11]

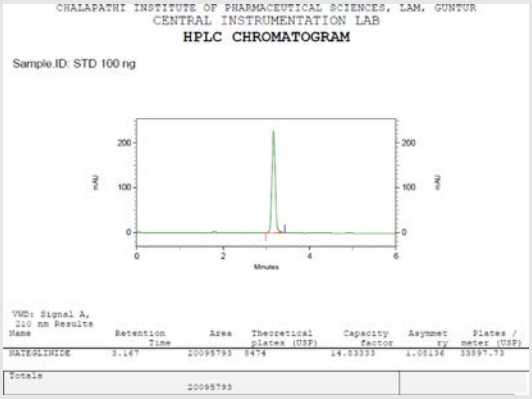
Determination of nateglinide

The established high performance liquid chromatography (HPLC) (Agilent 1220 infinity series, software: Ezichrome elite, Agilent Technologies) method for estimation of nateglinide was verified prior to its use for quantification *in vitro*. The same method was modified for *in vivo* analysis and verified for plasma matrix before quantification from plasma (Table S3).[7,9,12]

Determination of drug content and solubility

Drug content and solubility study were performed as reported earlier by our team.[7,9] Briefly, formulations equivalent to 50 mg of nateglinide was dissolve in 10 mL of ethanol and make up the volume (100 mL) with 0.5 w/v % of sodium lauryl sulphate (SLS) in 0.01N HCl. Solubility was determined by adding individually excess amount of samples in 10 mL of distilled water and shaken (water bath shaker, Remi lab world, RSB-12)

Table S3: Estimation of nateglinide in plasma samples by RP-HPLC.



Mobile phase:	10 mM phosphate buffer : acetonitrile (50 : 50; v/v)
Wavelength:	210 nm
Column:	Hyperchrom ODS-BP, (250 × 4.6 mm, 5µ)
Flow rate:	1.0 mL/min
Retention time Nateglinide:	3.16 min
Volume injected into HPLC:	10 µL
Range of Linearity:	100- 1000 ng/mL
Correlation:	1.00
LOD:	0.886492 ng/mL
LOQ:	2.686339 ng/mL

10 mg of nateglinide was dissolved in 10 mL of HPLC grade acetonitrile (1000 µg/mL). Suitable calibration standards were prepared in blank rabbit plasma with suitable dilution from stock solution to get final concentrations of 100, 200, 400, 600, 800, 1000 ng/mL.

for 48 h at 37°C. The samples were filtered, suitably diluted and examined by HPLC with little modifications. Studies were carried out in triplicate.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were recorded by using FTIR spectrophotometer (Jasco Inc, Japan, (Model: 6600). Samples (2-5 mg) were placed in sample holder and scanned over a wave number range of 500-4000 cm^{-1}.

Thermogravimetry analysis (TGA) and Differential scanning calorimetry (DSC)

Thermograms were recorded (scan rate of 10°C/min) on Pyris Diamond Thermogravimetry /Differential thermal analysis instrument (PerkinElmer, Singapore). About 4-5 mg of samples were placed in an aluminium pan and hermetically sealed using a TA crimper. The resulting samples were pursed with 150 mL/min flow rate of nitrogen.

X-ray diffraction (XRD)

The crystallinity of samples was recorded on X-ray diffractometer (Ultima-III, Rigaku, Japan) at room temperature. The setting parameters of the diffractometer were: Cu Kα radiation (monochromatic, λ = 1.5418 Å), a voltage of 40 kV, current 30 mA. The scan speed 1sec/step, a step size of 0.02º and 2θ range of 5-70º was used.

Scanning electron microscopy (SEM)

Morphological characteristics of samples were analyzed on a JSM6360, Jeol SEM (UK) apparatus (45 nA probe current, 20 kV voltage and 60 sec counting time).

Dissolution studies

The USP II dissolution apparatus (Model no. TDT-08L, Electrolab, Mumbai) was used to carry out the *in vitro* dissolution. The studies were performed in triplicate while maintaining the sink condition with 1L of the medium (0.5 w/v % of SLS in 0.01N HCl). The temperature and stirring speed were maintained at 37 ± 0.5°C and 50 rpm respectively. Hard gelatin capsules (size 2) containing the equivalents to nateglinide 60 mg of binary SDs formulations were introduced using copper sinkers into dissolution medium. At a predetermined time (5, 10, 15, 30, 45, 60, 90 min) intervals, an aliquot of 5.0 mL of samples were withdrawn. The samples were filtered through a membrane filter (0.45 µm, Millipore) and suitably diluted with the mobile phase. Five mL of fresh buffer medium (37 ± 0.5°C) was replenished in each withdrawal. The amount of nateglinide release was analyzed using the HPLC method.

Stability test

Stability testing (40°C and 75 % relative humidity, RH) was performed in the stability chamber (Remi Instruments, India) as per the International Council for Harmonisation (ICH) guidelines.[13] Dissolution study and XRD were used to assess the alterations in the system periodically for 3 months.

Pharmacokinetic studies

Animal study

A comparative pharmacokinetic study was performed following approved protocols (02/IAEC/CIPS/2016-17). Twelve albino rabbits of 1.91 ± 0.7 kg (1-1.5 year's age) were divided into four equal groups of three rabbits per group. Rabbits were fasted for 24 hr prior to the experiments and given free access to the water. Nateglinide (10 mg/mL) as a suspension (0.5 % methylcellulose in water for injection) and its formulations equivalents were orally administered.[14] At different time points (0.15, 0.5, 0.75, 1, 2, 4, 8, 12 and 24 hr post dose) blood samples (one mL) were collected from marginal ear vein and transferred to

ethylenediaminetetraacetic acid (EDTA) - coated tubes for further treatment. The plasma was collected after centrifugation at 5000 rpm for 10 min and stored at -80°C until further analysis. The samples were prepared as reported earlier by us[9] and 10 µL was injected into HPLC for analysis.

Pharmacokinetic analysis

The pharmacokinetic parameters (C_{max}, maximum plasma concentration; T_{max}; AUC_{0-t}, area under the plasma concentration-time curve) were studied using the PKSolver[15] (open source software program) by non-compartmental analysis.

Statistical analysis

Data were presented in mean ± S.D. (standard deviation). The *t*-test at 0.05 levels considered as statistically significant.[16]

RESULTS

Optimization of drug/polymer ratio

Melting of polymers followed by stirring is known to facilitate permeation of molten polymers into the crystal lattice of drugs leading to amorphization.[17] Following this principle, polymer to drug ratio was optimised. There were 2.64 and 6.65 fold enhancements in solubility of nateglinide with increase in weight ratios of cremophor RH 40 from 1:1 to 1:3 and 1:5 respectively. With this ratio, the respective increase in solubility was 2.14 and 6.24 folds for solutol HS 15. Since further increase in polymer failed to increase the solubility, 1: 5 weight ratio of nateglinide to polymer ratio was considered optimum.

Effect of methods on the solubility of nateglinide and drug content studies

The SM depends on permeation of solubilised polymer into the crystal lattice for breaking the crystal structure to enhance solubility. Unlike this, the KM applies mechanical stress to break the crystal lattice and induce amorphisation aided by the polymer. Because of the variation in the inherent mechanisms, the degree of amorphisation or impact on solubility may differ. Thus to optimise the methods for achieving optimum SD with 1: 5 weight ratio of nateglinide to polymer, different SDs were prepared using MM, KM and SM. The water solubility of nateglinide at 37°C was 8.87 mg/L.[2] So enhancement in solubility was expressed in reference to this. With solutol HS 15, the solubility was increased by 37.20 fold in KM. Whereas, with same polymer, the increase was 66.30 fold and 64.87 fold in MM and SM respectively. Thus solubility was found to be more (approximately 1.75 time) with MM and SM as compared with KM. In the case of cremophor RH 40 based SDs, MM (64.60 fold) and SM (63.48 fold) showed significantly higher nateglinide solubility than KM (39.18 fold). With the incorporation of cremophor RH 40 in MM and SM, the solubility enhancement was approximately 1.70 times as compared with KM. Thus MM and SM were found to have similar but better impact on solubility as compared to that of KM. Analysis of the drug content revealed a range of 95.67- 97.50 % and 96.63 - 98.29 % for MM and SM SDs with cremophor RH 40 and solutol HS 15 respectively (Table 1).

Table 1: Nateglinide solubility (µg/mL) and drug content (%) in KMs and SDs (1:5 weight ratio) prepared by using solutol HS 15 and cremophor RH 40 (mean ± S.D., *n* = 3).

Drug/Carriers	Preparation techniques	Solubility (µg/mL)	Drug content (%)
Nateglinide	-	8.87 ± 1.02	-
Solutol HS 15	KM	329.87 ± 2.93	97.66± 2.35
	MM	588.13± 3.17	97.50 ± 3.26
	SM	575.39 ± 2.81	98.29 ± 2.82
Cremophor RH 40	KM	347.46± 2.66	98.45 ± 2.18
	MM	572.99 ± 2.77	95.67± 2.52
	SM	563.03 ± 3.17	96.63 ± 2.50

Fourier transform infrared spectroscopy (FTIR) study

The drug-polymer interaction can be assessed from the IR spectrum and this can be used to ascertain the formation of dispersion system.[18] The characteristic peaks (Figure 1A) of nateglinide[19] were observed at 3307.92 cm^{-1} (N-H stretching), 3068.75 cm^{-1} (aromatic C-H stretching), 2964.59 cm^{-1} (C-H symmetric stretching), 2918.30 cm^{-1} (C-H asymmetric stretching) and 1687.71 cm^{-1} (C=O stretching). All the formulations exhibited the characteristic peaks of nateglinide without additional peaks. However, it showed shifting of carbonyl stretching vibration of nateglinide to 1684.30 cm^{-1} (cremophor RH 40 based MM) and 1685.27 cm^{-1} (Solutol HS 15 based SM). This can be attributed to hydrogen bond formations with polymeric groups which are not expected to alter the drug properties.[20] While the lack of covalent interaction suggest the formation of dispersion system, ability to form polar interaction hints at the possibility for enhancement in solubility of nateglinide in the SDs.[20]

Thermogravimetry analysis (TGA) study

The thermogravimetric analysis (Figure 1B) showed stability of nateglinide up to 250°C and those of solutol

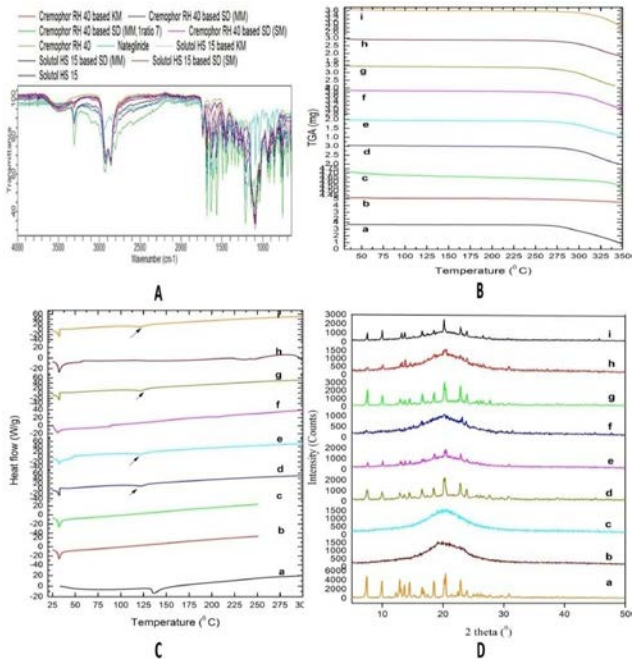


Figure 1: (A) FTIR spectra of nateglinide, solutol HS 15, cremophor RH 40 and its formulations developed by KM, MM, SM; (B) TGA curve; (C) DSC thermographs; (D) XRD plots of (a) nateglinide, (b) solutol HS 15, (c) cremophor RH 40, (d) solutol HS 15 based KM, (e) solutol HS 15 based SD (MM), (f) solutol HS 15 based SD (SM), (g) cremophor RH 40 based KM, (h) cremophor RH 40 based SD (MM), (i) cremophor RH 40 based SD (SM). Arrow in DSC: characteristic melting peak of nateglinide.

HS 15 and cremophor RH 40 upto 325°C (Figure 1Bb and Figure 1Bc). Since nateglinide with carriers exhibited stability at a higher temperature and the SD was processed at a much lower temperature (40°C), the formulation can be considered as thermally/chemically compatible

Differential scanning calorimetry (DSC) analysis

The DSC thermographs are shown in Figure 1C. An endothermic peak at 136.67°C with 89.83 J/g enthalpy of fusion (ΔH) (Figure 1Ca) and the characteristic glass transition (T_g) at 128.85°C (Figure S1A)[4] suggest the crystallinity of nateglinide. The solutol HS 15 (Figure 1Cb) and cremophor RH 40 (Figure 1Cc) were characterised by the endotherm at 32.2°C due to the melting point. Although the solutol HS 15 endothermic characteristics peak was retained in KM, the corresponding melting peak of the drug was slightly broadened and shifted towards the lower temperature (Figure 1Cd). The solutol HS 15 based SDs in MM exhibited a broad and lower endothermic peak with a decrease in enthalpy (ΔH = 13.47 J/g) for both drug and polymer (Figure 1Ce). The SM showed disappearance of melting point peak (Figure 1Cf) and appearance of Tg at 86.17°C (Figure S1B). The pattern of peaks for cremophor RH 40 based SD prepared by KM (Figure 1Cg) was similar to that of solutol HS 15 based SD. The DSC thermogram of cremophor RH 40 in MM and SM were almost unchanged while the melting peak of nateglinide in cremophor RH 40 based SDs in MM was relatively broad (Figure 1Ch) and showed a single Tg (111.46°C, Figure S1C). In the thermograms of SDs generated by cremophor RH 40 (SM), a less intense and board peak that shifted to lower temperature was observed (Figure 1Ci). This indicates the loss of crystallinity of the drug in the SDs.

X-ray diffraction (XRD) study

The XRD patterns of nateglinide, solutol HS 15, cremophor RH 40 and SDs are displayed in Figure 1D. For nateglinide, the diffractogram showed peak at 2θ° equivalent to 7.44°, 9.94°, 12.28°, 12.88°, 13.10°, 13.64°, 14.48°, 16.56°, 17.42°, 18.5°, 20.22°, 20.42°, 21.4°, 22.44°, 22.86°, 23.92°, 30.87° (Figure 1Da). These sharp and intense peak patterns support the crystallinity (89.25%) of nateglinide in agreement with the earlier reports.[2,3] Solutol HS 15 (Figure 1Db) and cremophor RH 40 (Figure 1Dc) exhibited no intense characteristics peaks.[20-22] The XRD diffractogram of nateglinide in solutol HS 15 (Figure 1Dd) and cremophor RH 40 (Figure 1Dg) prepared by KMs displayed characteristics diffraction peaks at 2θ equivalent to 7.74°, 9.94°, 12.88°, 14.48°, 16.56°, 18.5°, 20.22°, 20.42°, 22.86° and 30.87°. A loss of crystallinity of nateglinide from 89.25% to 57.89% (solutol HS 15 based KM) and 68.22% (cremophor RH 40 based KM) was observed. The XRD diffraction of nateglinide in solutol HS 15 based SDs in MM exhibited less intense peaks with the disappearance of peak at 16.56° (Figure 1De). These changes indicate the partial transition into the amorphous form (42.07% crystallinity). Relatively higher decrease of crystallinity (30.80%) was observed in the solutol HS 15 SM (Figure 1Df). XRD peaks of nateglinide at 2θ equivalent to 12.28°, 12.88°, 23.92°, 30.87° disappeared in cremophor RH 40 based SM. Whereas, peaks at 7.44°, 9.94° 13.64°, 14.48°, 16.56°, 17.42°, 18.5°, 20.22°, 20.42°, 21.4°, 22.44°, 22.86° became shorter implying partial conversion into amorphous form (Figure 1Di). It showed 41.03% of crystallinity. Further, characteristic peaks of nateglinide at 2θ equivalent to 12.28°, 12.88°, 16.56°, 17.42°, 18.5°, 20.42°, 21.4°, 22.44°, 22.86° disappeared in cremophor RH 40 based MM (Figure 1Dh). This suggested partial conversion (35.65%) to the amorphous state.

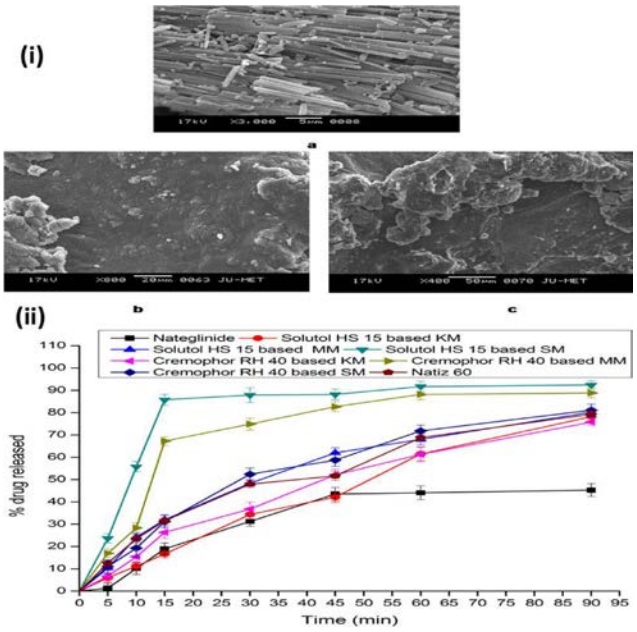


Figure 2: (i) SEM microphotographs of (A) pure drug nateglinide (B) solutol HS 15 based SD (SM) and (C) cremophor RH 40 based SD (MM). (ii) Dissolution profiles of nateglinide from different formulations and Natiz 60 (mean ± S.D., (*n* = 3).

Scanning electron microscopy (SEM) analysis

SEM photomicrographs of nateglinide and its selected SD formulations were shown in Figure 2i. Pure drug nateglinide was observed with irregular rod-shaped crystals.[9] However, the optimised SDs showed lack of these regular structures. The irregular morphology with porous surface suggests the disruption of crystal lattice and adsorption of polymers on to the drug surface.

Drug release study

The pure nateglinide exhibited release of 45.29 ± 2.91 % within 90 min (Figure 2ii). Solutol HS 15 and cremophor RH 40 based KM showed ~ 1.70 fold high dissolution rate with approximately 78 % release in a similar pattern within 90 min. Although solutol HS 15 based SD (MM) showed an incomplete drug release (80.2 ± 1.98 %), it enhanced dissolution rate by 1.8 fold. More than 85 % of the drug was released within 15 min when prepared in SM using solutol HS 15. This formulation showed ~ 92 % drug release within 90 min and the dissolution rate was ~ 4.50 fold higher than pure drug and KM within 15 min. The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) were significantly ($p < 0.05$) higher for solutol HS 15 based SD (SM) (Q_{15} - 85.76 ± 2.52 %; IDR- 5.72 %/min) as compared to that of pure drug (Q_{15} -18.96 ± 2.6 %; IDR - 1.26 %/min). The dissolution efficiency (DE) of this polymer based SD (SM, 42.47 %) was also higher than that of the drug (12.64 %). Consequently, the time taken to release 50 % ($T_{50\,\%}$) of drug was found to be much lower 9.04 min for solutol HS15 based SD (SM) in comparison to the drug (90 min). Accordingly, mean dissolution time (MDT) of this polymer based SD (1.13) was much less than the pure drug (2.29). Taken together these data suggest remarkable increase in dissolution rate in the solutol HS 15 based SD.

Cremophor RH 40 based SDs demonstrated an incomplete drug release within 90 min (Figure 2ii). Cremophor RH 40 MM and SM displayed more than 85 % and ~ 82 % drug release respectively within 60 min. Cremophor RH 40 based MM showed better drug release profile with 1.96 fold ($p < 0.05$) and 1.8 fold enhancement of dissolution rate than pure drug and its KM at 90 min. Also, the Q_{15} and IDR were significantly ($p < 0.05$) higher (Q_{15} – 67.29 ± 2.52 %; IDR- 4.48 %/min) as compared to that of pure drug (Q_{15} -18.96 ± 2.6 %; IDR - 1.26 %/min). Thus, its DE (36.68 %) was relatively higher and, the $T_{50\,\%}$ of drug was found to be much lower (12.87 min) in comparison to the drug (90 min). Consequently, its MDT (1.13) was much less than the pure drug (2.29). Comparison of the release profile of the SDs of both the polymers reveals significant difference ($p < 0.05$) in similarity factor (f_2). Thus the solutol HS 15 based SD (SM) showed higher the release rate. Taken together these data suggest remarkable increase in dissolution rate with the SDs. This was also better than that of the commercial product used in the study.

Physical stability test

Amorphous states can be thermodynamically unstable. So the solutol HS 15 SM and cremophor RH 40 MM based SDs were studied for stability. The XRD and dissolution analysis was used to assess stability of the formulations following ICH guidelines.[13] The stability of the SD was assessed at prescribed intervals (0, 1, 2, 3 months). After a storage period of 3 months, the XRD pattern (Figure 3Ai and 3Bi) of both polymer based SDs did not show any additional peak also there was no variation in the intensity of the peaks of the nateglinide. The cremophor RH 40 (MM) and solutol HS15 (SM) formulations showed 35.95 % and 31.73 % of crystallinity respectively. This suggested the maintenance of its initial states in both the polymer based SDs. In agreement with this, their dissolution profiles exhibited similarities to their initial formulations ($p > 0.05$). The f_2 values for the solutol HS 15 and cremophor RH 40 based SDs were 90.32 and 85.66 respectively. These results indicated cremophor RH 40 and solutol HS 15 are equally capable to prevent the recrystallization.

In vivo studies

Pharmacokinetic studies were carried out for nateglinide, solutol HS 15 based SD (SM) and cremophor RH 40 based SD (MM) and Natiz 60 in rabbits, to assess the correlation between *in vitro* dissolution and *in vivo* bioavailability. Since these two formulations showed a higher rate of dissolution and stability they were chosen for the *in vivo* bioavailability study.

Remarkable differences were observed in the plasma profile (Figure 4i) of nateglinide and those of the SDs (Table 2). The relative bioavailability of nateglinide from cremophor RH 40 based SD (MM) and solutol based SD (SM) was enhanced by 170.71 % and 179.22 % respectively compared to Natiz 60 (Table 2). With a T_{max} of 1 hr for nateglinide, the SDs suggested significantly ($p < 0.05$) faster absorption compared to the pure drug. This can be correlated to higher solubility and release of nateglinide. There was 2.36 fold and 2.48 fold enhancement of C_{max} of SDs prepared by cremophor RH 40 and solutol HS 15 respectively than pure nateglinide. The $t_{1/2}$ of the formulations were 10.91 h and 10.47 hr respectively. This is very close to the $t_{1/2}$ of the pure drug nateglinide (Table 2). This suggests that the SDs didn't adversely affect the drug disposition. The mean residence time (MRT) was significantly higher ($p < 0.05$) in cremophor RH 40 and solutol HS 15 formulations than crystalline nateglinide (Table 2).

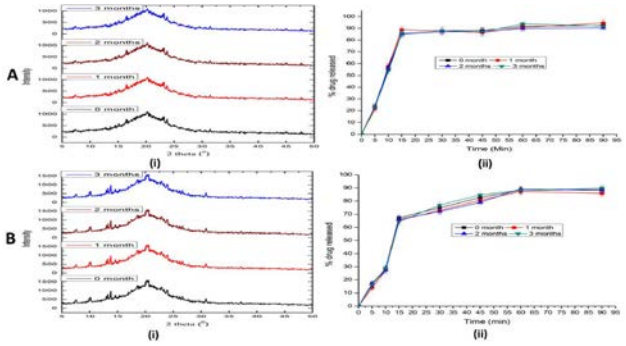


Figure 3: Stability study of (A) solutol HS 15 based SD (SM), (B) cremophor RH 40 based SD (MM) (i) XRD plots, (ii) Dissolution profile (mean ± S. D., *n*=3).

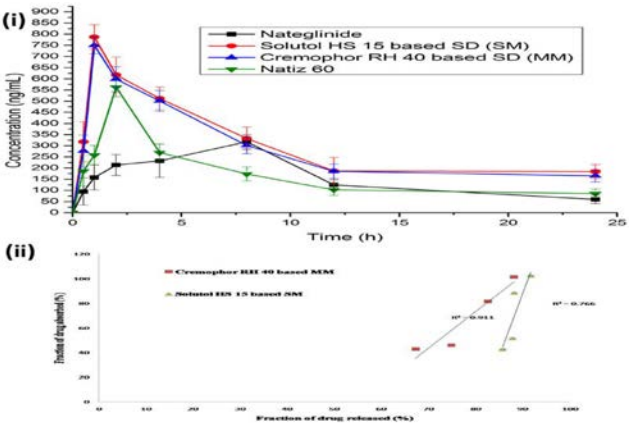


Figure 4: (i) Plasma profiles of pure drug nateglinide, solutol HS 15 based SD (SM), cremophor RH 40 based SD (MM) and Natiz 60 (mean ± S. D., *n* = 3). (ii) *IVIVC* of cremophor RH 40 based SD (MM) and solutol HS 15 based SM formulation of nateglinide.

In vitro-in vivo correlation (IVIVC)

The fraction of nateglinide released *in vitro* (F_r) was correlated to the fraction available *in vivo*. The fraction of drug available over a time period (F_a) was calculated by Wagner-Nelson method[23] as shown below.

$$F_a = \left[\left(\frac{C_t + k_e AUC_{o-t}}{k_e AUC_{o-\infty}}\right)\right] \times 100 \qquad \text{Eq.1}$$

Where C_t is the observed plasma concentrations and k_e is the elimination rate constant.

This was plotted against fraction of drug release (F_r) during the same period in the dissolution study. For IVIVC the cumulative amount of drug release over 1 hr was correlated to the absorption phase of AUC (T_{max} = 1 hr). Although the solutol HS 15 based SD (SM) showed higher solubility, relatively low correlation (0.766) was observed with bioavailability. Compared

Table 2: Pharmacokinetic parameters of pure drug nateglinide, solutol based SD (SM), cremophor RH 40 based SDs (MM) and Natiz 60 in rabbits (mean ± S.D., *n* = 6).

Parameter	Nateglinide	Solutol HS 15 Based SD (SM)	Cremophor RH 40 based SD (MM)	Natiz 60
T_{max} (h)	8.00 ± 0.001	1.00 ± 0.01*	1.00 ± 0. 001*	2.00 ± 0.00
C_{max} (ng/mL)	317.78 ± 31.78	787.70 ± 54.72*#	750.29 ± 48.52*#	562.77 ± 42.87
AUC_{0-t} (ng h/mL)	3810.79 ± 789.33	7123.12 ± 1232.95*#	6785.02 ± 1064.25*#	3974.39 ± 702.18
$AUC_{0-\infty}$ (ng h/mL)	4442.78 ± 1062.61	10026.80 ± 2263.78*#	9285.47 ± 1617.94*#	5584.38 ± 1213.62
MRT (h)	12.64 ± 0.87	17.87 ± 2.21*	16.96 ± 1.78*	18.21 ± 1.69
$t_{1/2}$ (h)	7.33 ± 0.96	10.91 ± 2.01	10.47 ± 2.05	12.99 ± 1.07

*$p < 0.05$ (t-test), compared to pure nateglinide; # $p < 0.05$ (t-test), compared to the Natiz 60

to this, a good correlation ($r2$ = 0.911) was observed (Figure 4ii) between F_r and F_a for the cremophor RH 40 based SD (MM). Point to point correlation was also observed between F_r and F_a. Thus, The IVIVC can be categorised as level A.[23]

DISCUSSION

Formulation of SD is a suitable approach to increase drug solubility. Optimisation of drug to polymer ratio as well as the method of processing is critical to the formation and stabilisation of amorphised SDs.[24] Permeation of molten polymer into the drug lattice is known to promote amorphization.[17] Thus the MM was selected for optimisation of the polymer ratio. Cremophor RH 40 and solutol HS 15 are amphiphilic in nature. The amphiphilic polymers entrap the drug with the lipophilic tail while increasing wettability with the hydrophilic head. Thus an increase in concentration of both cremophor RH 40 and solutol HS 15 enhanced the solubility of nateglinide due to increase in the polymeric surface activity that is known to aid wettability.[25] However, beyond the weight ratio of 1:5 there was insignificant increase in solubility. This may be because of the fact that higher proportion of polymer in SD forms gel layer in contact with water that acts as a diffusion barrier and retards further solubilisation.[26] Thus, 1:5 weight ratio was selected for further studies.

MM and SM were found to be more suitable methods for enhancing the solubility of nateglinide with a drug to polymer weight ratio of 1:5. This can be partly explained by the fact that unlike KM, both SM and MM rely on permeation of polymer in solution or liquid state to break the crystal structure leading to higher solubility. Both cremophor RH 40 and solutol HS 15 displayed similar solubility enhancement pattern in MM and SM. Further, these methods are known to induce some degree of amorphisation that is promoted and stabilised by these polymers. These SDs also showed high (> 95 %) drug content. Taken together, the cremophor RH 40 and solutol HS 15 based SDs showed promising solubility with high drug content. Loss of crystallinity is one of the primary reasons for higher solubility of the SDs. To evaluate this and its implication on solubility, the formulations were further investigated.

The optimised SDs were characterised by FTIR spectra. The peaks assigned to nateglinide were also found in those of SDs. While this suggested lack of any chemical interaction with the polymer, slight shift in the peaks of carbonyl groups indicated possible polar hydrogen bonding with the polymers. This is characteristic of a dispersion system[18] and the FTIR data indicates the formation of SDs.

The polymers in amorphous SDs can modulate the thermal stability of the drug.[27] The disappearance of endothermic peak assigned to nateglinide (Figure 1Cf) and appearance of T_g at 86.17°C (Figure S1B) in solutol HS 15 based SDs (SM) suggested formation of the amorphous state of the drug. Although the melting point peak of nateglinide in cremophor RH 40 based MM did not disappear in the DSC curves (Figure 1Ch), it was found to be broadened along with appearance of a single T_g at 111.46°C (Figure S1C). This indicates some degree of amorphization.

To further evaluate this, the diffraction pattern and crystallinity of the SDs were studied. SDs developed by KM showed relatively higher degree of crystallinity irrespective of the polymers (Figure 1Dd and Figure 1Dg). However SDs developed by MM and SM displayed relatively less crystallinity. While Solutol HS 15 based SM displayed lowest crystallinity (Figure 1Df), disappearance of the major diffraction peaks and decrease of the intensity of drug peaks in cremophor RH 40 based MM indicated higher degree of conversion to amorphous state (Figure 1Dh).

To further validate these findings, the SEM data were analysed. As expected, regular shape was visible for the crystalline nateglinide (Figure 2ia),[9] whereas it was found to be disrupted in the optimised SDs with appearance of homogeneous but irregular surface.

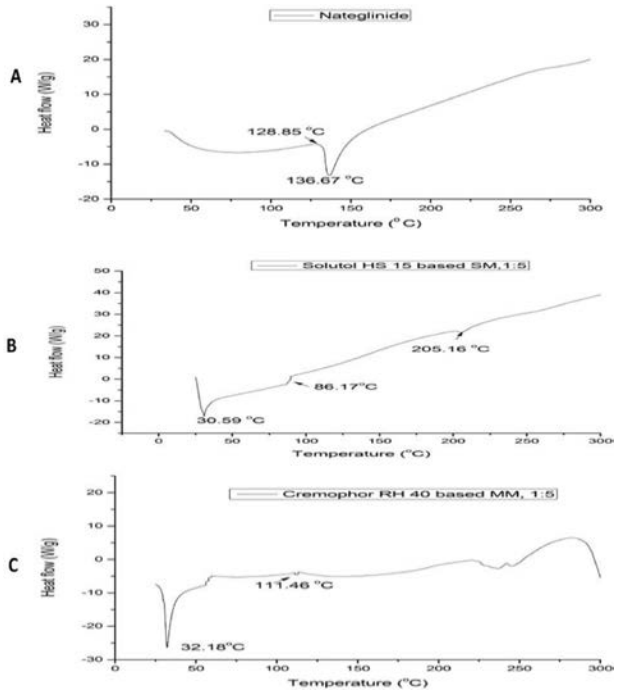


Figure S1: Tg of the (A) nateglinide, (B) solutol HS 15 based SM, (C) cremophor RH 40 based MM (1:5).

Thus the DSC, XRD and SEM data are in agreement and suggest amorphisation of nateglinide in the SDs. This justifies the observed enhancement in solubility, as the amorphous states are known to allow solvent permeation and solubilisation by increasing wettability and decreasing molecular aggregation.[21,22,28]

Dissolution is key to achieve higher oral bioavailability.[29] The incomplete release of nateglinide suggests dissolution until attainment of thermodynamic solubility, as beyond this the concentration remained constant. Compared to this, solutol HS 15 and cremophor RH 40 based SDs exhibited higher dissolution. These SDs showed rapid dissolution in the initial stages and reached higher concentration, forming highly supersaturated solutions. Although solubility of SDs prepared by KMs was significantly higher than that of pure nateglinide, it was relatively less than those of SDs prepared by SM and MM. The higher dissolution in solutol HS 15 based SM is in agreement with their higher degree of amorphization. The significant difference in DE, $T_{50\ \%}$, MDT and f_2 signifies the remarkable enhancement of dissolution in the solutol HS 15 based SD (SM) and cremophor RH 40 based SD (MM). Also the dissolution rate was faster than that of the commercial product. Along with the solutol HS 15 SD (SM), the cremophor RH 40 SD (MM) showed more than 85 % of the drug release in 60 min of time. Thus the dissolution profile is suggestive of the increased solubility that is an outcome of the higher degree of amorphisation.

Since the SDs are not completely amorphized, maintaining the supersaturation in aqueous system or *in vivo* can be a challenge. This is because the formulation has to maintain this state for adequate time to ensure higher bioavailability. The crystallization/amorphization kinetics under dissolution environment was not studied under in this work to quantitatively express the stability of this supersaturation state. Nevertheless, the stability study was carried out while intermittently evaluating the degree of crystallinity in order to evaluate amorphous stability of the SDs. The XRD study after storage period signifies the maintenance of its initial states in cremophor RH 40 and solutol HS15 based SDs. Thus, there was no recrystallization during storage that indicated the physical stability of SDs. The f_2 values of the dissolution after storage period suggest that cremophor RH 40 and solutol HS 15 are equally capable to prevent the recrystallization. This may be attributed to the ability of solutol HS 15 and cremophor RH 40 to reduce the nucleation rate by stabilizing the drug surface and minimizing the molecular mobility.[13]

The plasma profile in Figure 4 and pharmacokinetic parameters in Table 2 of the cremophor RH 40 and solutol based SDs showed remarkable differences as compared with pure drug and commercial product. These results suggest significant improvement in oral bioavailability of nateglinide. Compared to the prior arts in this area (Table S2), it shows better optimisation of absorption and elimination as evident from a T_{max} of 1 hr and $t_{1/2}$ of more than 8 hr. This may be due to higher solubility that promotes absorption and tissues distribution. Unlike some previous formulations which displayed immediate release but very short $t_{1/2}$, (Table S2) these SDs displayed longer $t_{1/2}$ for nateglinide. The higher bioavailability may be linked to the higher dissolution. To investigate this, IVIVC analysis was carried out.

For IVIVC the cumulative amount of drug release over 1 hr was correlated to the absorption phase of AUC (T_{max} = 1 hr). The cremophor RH 40 based SD (MM) showed a level A correlation. Accordingly, the *in vitro* dissolution data can be used to predict the bioavailability of nateglinide. Unlike this, the solutol HS 15 based SD showed relatively poor correlation. Although the solutol HS15 based SD showed quick release, a proportionate increase in bioavailability (absorption) was not observed. Interestingly cremophor RH 40 SD showed relatively late release but a higher IVIVC correlation. Thus it may be suggested that cremophor RH 40 promotes better absorption as compared to solutol HS15 based SD.

CONCLUSION

With an optimized drug to polymer weight ratio of 1:5 the SDs were demonstrated to achieve higher rates of dissolution. This was attributed to the amorphization as evident from the loss of crystallinity of nateglinide in the SDs. The solutol HS 15 was found to facilitate quicker release as compared to the cremophor RH 40. Although both polymers ensured similar bioavailability, the IVIVC was better with cremophor RH 40 based SD. The effect of cremophor RH 40 on solubility and bioavailability was found to be comparable to those of polymers (poloxamer 188 and poloxamer 407) earlier reported by our group.[12,13] Thus the cremophor RH 40 based SD can be investigated further, to develop a suitable formulation for nateglinide.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

APIs: Active pharmaceutical ingredients; **BCS:** Biopharmaceutical classification system; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transform infrared spectroscopy; **IVIVC:** *In vitro in vivo* correlation; **KM:** kneading method; **SDs:** Solid dispersions; **SEM:** Scanning electron microscopy; **SM:** Solvent evaporation method; **TGA:** Thermogravimetry analysis; **XRD:** X-ray diffraction analysis; **PVPC:** crosslinked polyvinylpyrrolidone.

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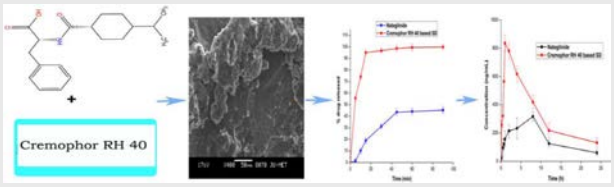
PICTORIAL ABSTRACT



SUMMARY

The study was aimed to improve dissolution and bioavailability of the developed stable amorphous solid dispersions (SDs) of nateglinide and establish IVIVC. Cremophor RH 40 and solutol HS 15 based SD showed ~ 65 fold aqueous solubility enhancement. SDs were characterised by FTIR, DSC, TGA, XRD and SEM. It revealed the higher transformation of nateglinide in the SD from crystalline to amorphous state. Relatively higher decrease of crystallinity (30.80%) was observed in the solutol HS 15 SM. Pharmacokinetic study signified the effectiveness of SDs to improve bioavailability. Poor aqueous solubility of nategilinide was overcome by design of SDs. Level A correlation demonstrated between in vitro release and bioavailability of nateglinide.

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