ORIGINAL ARTICLE

Design, Development, and Evaluation of Controlled Release Tablets of Nateglinide Solid Dispersions

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Abstract

Objective: The current study deals with formulation and evaluation of nateglinide solid dispersion (SD) incorporate into tablet formulation for controlled release of the drug. **Methods:** The nateglinide SD prepared using crospovidone and evaluated for drug content and drug dissolution. The optimized SD formulation incorporated into tablet using HPMC K100 and Cederela gum. All the tablet formulations evaluated for pre-compression, post-compression, drug dissolution, and excipient compatibility study. **Results:** The formulation SD15 comprising of drug, crospovidone, and sodium lauryl sulfate in 1:3:2 ratio displayed 48-fold enhancement in drug solubility when compared to pure drug. The formulation SD15 displayed maximum yield of 98.96% and maximum drug content of 99.68% chosen optimal for tablet formulation. Fourier transforms infrared studies revealed that there is no incompatibility between drug and polymers found. X-Ray diffractometer studies revealed that the optimized SD formulation was found to be in amorphous state. Total 15 formulations of controlled release tablet blends evaluated for micrometric properties show that all the formulations possess good flow properties F12 formulation with maximum drug content of 99.93% and drug release of 99.98% over 16 h was chosen for further characterized. The release kinetics suggest that drug release followed zero order and release from tablets was anomalous non-Fickian diffusion super Case II transport. **Conclusion:** The combination of SD and application of hydrophilic and hydrophobic polymers in matrix formation facilitated superior dissolution and absorption profile with greater patient compliance.

Key words: Antihyperglycemic agent, controlled release tablet, crospovidone, HPMC K100, nateglinide, solid dispersion

INTRODUCTION

Solid dispersions (SD) are dispersions of active pharmaceutical ingredients in carriers in solid state that efficiently enhances dissolution of sparingly water-soluble drugs. The solubility of drug is the major exigent aspect in formulation of drugs which impacts the bioavailability of drug. About 60–65% of compelling drugs are deprived of water solubility. The SD technique is proved to efficiently increase drug release and bioavailability of variety of hydrophobic drugs.[1,2] The controlled-release (CR) formulations are advantageous over conventional dosage forms, as they provide consistent and protracted therapeutic effect for better patient compliance, minimal drug dosage, reduced side effects, and increased drug effectiveness. The SD incorporated controlled release formulations comprise the advantages of both SD and CR for enhancing solubility of sparingly soluble drug. These systems facilitate immediate availability of drug for quick onset of action and also continued drug release to maintain drug plasma concentration of poorly water-soluble drugs over extended durations of time. The controlled release SD formulations can bypass the risk of burst release as the

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drug is homogeneously dispersed in the SD formulation. The drug release is also controlled by matrix that comprises of hydrophilic or hydrophobic polymeric excipients.[3-5]

Nateglinide is antihyperglycemic drug used for treating non-insulin-dependent diabetes mellitus. It belongs to meglitinide class of short-acting insulin secretagogues that bind to β cells of pancreas and stimulate release of insulin. It shows pH-dependent solubility and uneven bioavailability. The weak acidic nature and pH-dependent solubility of nateglinide are chief restraints during oral dosage design.[6] Various designs of proficient oral dosage were reported in literature.[7-9]

MATERIALS AND METHODS

The drug nateglinide, HPMC K 4M, HPMC K 15M, HPMC K 100M, and crospovidone were gifted from Hetero drugs Ltd, Hyderabad. The excipients Soluplus, Kolliphor ELP, and Kolliphor RH40 were purchased from Gattefosse, Mumbai. Lactose, talc, polyvinylpyrrolidone (povidone K-30), magnesium stearate, sodium lauryl sulfate (SLS), and PEG 4000 were purchased from SD Fine chemicals, Mumbai, and used without further purification.

Preliminary solubility studies of nateglinide

Excess nateglinide stirred with 25 ml of carriers (crospovidone, croscarmellose, eudragit, Labrafac PG, Kolliphor RH 40 and GMS II, Soluplus, Kolliphor ELP, PEG 2000, PEG 4000, and urea) for 24 h. The suspension clarified through a Whatman filter paper no.1 and filtered solution is diluted with methanol for spectroscopic analysis of drug at 216 nm.[10]

Preparation of nateglinide SD

Nateglinide weighed and mixed with various polymers (PEG 4000, Soluplus, Kolliphor ELP, Kolliphor RH 40, and crospovidone) and 0–2% SLS surfactant in different drug-polymer-surfactant ratios (1:1:1, 1:2:1.5, and 1:3:2). Fifteen SDs prepared by adopting solvent evaporation method [Table 1], in which the mixture is dissolved in minimal amount of CH_3OH, followed by its evaporation at temperature 50°C. The SDs prepared were pulverized, sieved through 45 μm sieve, and stored in desiccator for further investigations [Table 2].[11]

Evaluation of nateglinide SD

Solubility study of nateglinide SD

Solubility study carried out by preparing suspensions of SD and agitating for 48 h, and then filtered through Whatman filter paper, filtrates estimated for nateglinide at 216 nm [Table 3].[12]

Percentage practical yield estimation

The percent yield of nateglinide SD can be determined using the following expression:[13]

Percent yield = (weight of prepared SD/weight of drug + carriers) × 10

Table 1: Composition of nateglinide SD's

Formulation code	Drug and ingredients ratios	Nateglinide (mg)	Soluplus (mg)	PEG 4000 (mg)	Kolliphor ELP (mg)	Kolliphor RH 40 (mg)	Crospovidone (mg)	SLS (mg)	Methanol (mL)
SD1	1:1:1	60	60	-	-	-	-	60	Qs
SD2	1:2:1.5	60	120	-	-	-	-	90	Qs
SD3	1:3:2	60	180	-	-	-	-	120	Qs
SD4	1:1:1	60	-	60	-	-	-	60	Qs
SD5	1:2:1.5	60	-	120	-	-	-	90	Qs
SD6	1:3:2	60	-	180	-	-	-	120	Qs
SD7	1:1: 1	60	-	-	60	-	-	60	Qs
SD8	1:2:1.5	60	-	-	120	-	-	90	Qs
SD9	1:3:2	60	-	-	180	-	-	120	Qs
SD10	1:1:1	60	-	-	-	60	-	60	Qs
SD11	1:2:1.5	60	-	-	-	120	-	90	Qs
SD12	1:3:2	60	-	-	-	180	-	120	Qs
SD13	1:1:1	60	-	-	-	-	60	60	Qs
SD14	1:2:1.5	60	-	-	-	-	120	90	Qs
SD15	1:3:2	60	-	-	-	-	180	120	Qs

SLS: Sodium lauryl sulfate

Table 2: Formulation table of nateglinide SD incorporated controlled release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Nateglinide SDs	360	360	360	360	360	360	360	360	360	360	360	360
HPMC K 4M	40	40	60	60	-	-	-	-	-	-	-	-
HPMC K 15 M	-	-	-	-	40	40	60	60	-	-	-	-
HPMC K 100M	-	-	-	-	-	-	-	-	40	40	60	60
Cederela gum	0	30	0	30	0	30	0	30	0	30	0	30
PVP K30	30	0	30	0	30	0	30	0	30	0	30	0
Lactose	60	60	40	40	60	60	40	40	60	60	40	40
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight (mg)	500	500	500	500	500	500	500	500	500	500	500	500

SD: Solid dispersion

Table 3: Solubility of physical mixture of nateglinide pure drug+polymer in 1:1 ratio

Nateglinide drug+polymer (1:1) physical mixture	Solubility (mg/ml)
Pure drug	0.36±0.46
Drug+Crospovidone	9.12±0.87
Drug+Croscarmellose	3.21±0.46
Drug+Eudragit	2.54±0.78
Drug+Labrafac PG	0.86±0.23
Drug+Kolliphor RH 40	4.65±0.67
Drug+Kolliphor GMS II	2.87±0.54
Drug+Soluplus	3.89±0.39
Drug+Kolliphor ELP	5.87±0.98
Drug+PEG 2000	2.57±0.34
Drug+PEG 4000	4.98±0.62
Drug+Urea	0.94±0.17

Above parameters are communicated as Average±Standard deviation; (*n*=3)

% Drug content estimation

An accurately weighed quantity of SD equivalent to 10 mg were transferred into 10 ml standard flasks, made up to 10 ml with methanol The content of nateglinide was determined spectrophotometrically at 216 nm against suitable blank using ultraviolet (UV)-visible spectrophotometer (T60 PG Instruments).[14]

In vitro dissolution study of nateglinide SD

The dissolution of nateglinide from SDs prepared was investigated in 900 ml phosphate buffer (pH 6.8) using USP apparatus (type II) with a stirring speed of 50 rpm at a temperature of 37 ± 0.5°C. 5 ml aliquots of dissolution medium were withdrawn at an interval of 5 min and filtered through 0.45 µm filter. An equal volume withdrawn from dissolution medium was replaced. The collected sample solution is diluted, assayed at 216 nm and the data compared to that of pure drug.[15]

Stability study of nateglinide SD

Prepared SDs were placed under controlled temperature in stability chamber (Thermo Lab, India) at 75% ± 5% RH and 40°C ± 2°C for accelerated stability studies as mentioned in ICH guidelines. Samples withdrawn after 1st, 2nd, and 3rd months were evaluated.

Characterization of nateglinide SD

The nateglinide SD was characterized by Fourier transforms infrared (FTIR) spectroscopic analysis using Shimadzu FTIR 8400S spectrophotometer,[16] X-Ray diffractometer using Shimadzu, Japan[17] and SEM using Hitachi, Japan[17] according to the procedure referred.

Formulation of nateglinide SD incorporated controlled release tablet

Pre-compression parameters

The lubricated blend was evaluated for angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio as per the referred procedures.[18,19]

Preparation of nateglinide SD incorporated controlled release tablets

The nateglinide SD incorporated controlled release tablets prepared by wet granulation method.[20] In this HPMC K 100 M/HPMC K 15 M/HPMC K 4 M were employed as rate controlling polymers. Lactose is used as diluent, Cederela gum (natural gum) and PVP K 30 are used as binders and magnesium stearate is used as lubricant [Table 2].

Accurate quantity of the nateglinide, lactose, hydroxypropyl methyl cellulose (HPMC K-100M/HPMC K15M/HPMC K4M), and magnesium stearate was weighed and sifted through #40 separately. The mixture was then granulated with purified water, in which Cederela gum/PVP K30 is dissolved. The wet mass died in hot air oven, and then it is lubricated with magnesium stearate and the lubricated blend is compressed into tablets.

Evaluation of nateglinide SD incorporated controlled release tablets

Average weight, hardness, thickness, weight variation, and friability were recorded as per the referred procedures.[21,22]

In vitro dissolution study of nateglinide SD incorporated controlled release tablets

The dissolution study of tablets was conducted using dissolution testing USP apparatus II (paddle method) in 900 ml of pH-6.8 phosphate buffer was placed in the vessel and assembled. The medium was allowed to equilibrate to temperature of 37 ± 0.5°C. A tablet was placed in the vessel and covered; the apparatus was operated up to 16 h at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 216 nm using a UV-spectrophotometer.[20]

Drug release kinetics nateglinide SD incorporated controlled release tablets

To describe the kinetics of the drug release from nateglinide SD incorporated controlled release tablets, mathematical models such as zero-order, first order, and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or-fit test.[23]

Stability studies

Prepared nataglinide SD incorporated controlled release tablets were placed under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75% ± 5% RH and temperature of 40°C ± 2°C for accelerated stability studies as mentioned in ICH guidelines. Samples were removed after 1, 2, and 3 months and evaluated.

Characterization of nateglinide SD incorporated controlled release tablets

The optimized tablet formulation analyzed for FTIR[19] as per the referred methods.[24,25]

RESULTS

Preliminary solubility studies of nateglinide

The solubility results show that pure drug solubility is 0.36 ± 0.46 mg/ml. Nateglinide showed maximum solubility in solvent 6.8 pH buffer (1.59 ± 0.79 mg/ml), and in the physical mixture of nateglinide drug with crospovidone shown highest drug solubility, that is, 9.12 ± 0.87 mg/ml, almost 25-fold enhanced compared to pure drug [Table 3].

Preparation of nateglinide SD

Total 15 (SD1-SD15) nateglinide SD formulations were prepared by solvent evaporation method using different polymers.

Solubility studies of nateglinide SD

All SDs formulated exhibited enhanced solubility compared to that of pure drug and the solubility exhibited by the physical mixtures reflected in SDs. The solubility studies of nateglinide SD with crospovidone (SD13, SD 14, and SD15) exhibited greater solubility and SD15 showed highest among all formulations 17.32 ± 0.26 mg/ml which was almost 48-fold increase when compared to pure drug solubility [Table 4].

Percentage practical yield (%PY) and drug content of nateglinide SD

The %PY for all nateglinide SD's found within 94.19 ± 0.5–98.53±0.46%. Maximum yield of 98.96 ± 0.25% observed

Table 4: Solubility of nateglinide SD formulations (SD1-SD15)

Nateglinide SD	Solubility (mg/ml)
Nateglinide	0.36±0.46
SD1	12.54±0.19
SD2	12.98±0.05
SD3	13.3±0.72
SD4	14.09±0.56
SD5	14.38±0.83
SD6	14.69±0.24
SD7	15.09±0.87
SD8	15.39±0.31
SD9	15.57±0.53
SD10	13.38±0.50
SD11	13.71±0.90
SD12	14.01±0.23
SD13	15.75±0.38
SD14	16.03±0.36
SD15	17.32±0.26

Above parameters are communicated as Average±Standard deviation; (*n*=3). SD: Solid dispersion

for formulation SD15. The % drug content of all nateglinide SD's lie within 95.35 ± 0.64–99.68 ± 0.68% with SD15 exhibiting maximum drug content [Table 5].

In vitro drug dissolution studies of nateglinide SD

A significant raise in dissolution rate is observed in all the formulated SDs of nateglinide than the pure drug (30.84 ± 1.62%) in 1 h. As the polymer ratio increased there was an increase in dissolution rate, and among all 15 formulations, formulations containing crospovidone exhibited greater dissolution. Formulation SD15 containing high amount of crospovidone showed highest dissolution rate of 99.93 ± 1.09% in 1 h [Figure 1].

Table 5: % PY and drug content for nateglinide SD

Nateglinide SDs	%PY	Drug content
SD1	94.34±0.53	95.35±0.64
SD2	95.56±0.86	96.57±0.87
SD3	96.44±0.57	97.36±0.24
SD4	95.12±0.36	95.68±0.76
SD5	95.32±0.98	96.46±0.54
SD6	96.46±0.46	97.25±0.87
SD7	94.19±0.5	96.74±0.13
SD8	95.38±0.87	97.68±0.86
SD9	96.69±0.24	98.42±0.62
SD10	95.51±0.65	95.47±0.47
SD11	95.66±0.86	97.43±0.53
SD12	96.45±0.35	98.39±0.27
SD13	96.96±024	97.47±0.38
SD14	97.61±0.46	98.25±0.48
SD15	98.53±0.46	99.68±0.68

Above parameters are communicated as Average±Standard deviation; (*n*=3). SD: Solid dispersion

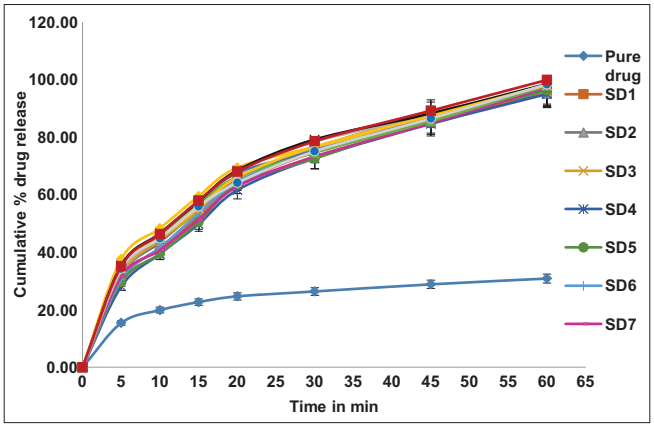

Figure 1: *In vitro* drug dissolution of pure nateglinide and nateglinide SD (SD1-SD15)

Stability study of nateglinide SD

Optimized formulation (SD15) was subjected to stability study for 90 days at accelerated stability conditions as per the ICH guidelines. The formulation SD15 was found stable during study period. Results indicate that optimized formulation (SD15) is stable with no variations in its physical properties [Table 6].

Characterization of nateglinide SD

FTIR studies

The FTIR spectrum of pure nateglinide displayed sharp bands at 2924.52 and 2859.92 cm^{-1} for aliphatic C-H, 1649.80 and 1713.44 cm^{-1} for ketonic C=O, and 1240.97 cm^{-1} for C-O and O-H of COOH. The peak at 3299.61 cm^{-1} (-NH stretching) of 2^0 amine. A band at 1540.85 cm^{-1} for C=C, band at 756.92 cm^{-1} and 700.03 cm^{-1} for mono-substituted benzene [Figure 2]. The FTIR spectra of drug mixed with crospovidone, SLS displayed all prominent peaks for nateglinide suggesting no significant interaction amongst them [Figure 3].

PXRD study

The PXRD of pure nateglinide exposed a drug pattern with strong and sharp peaks, illustrative of crystalline nature. The X-ray diffractogram of nateglinide displayed sharp and strong peak at 2θ° equivalent to 10°, 13°, 14.25°, 19°, 20°, and 23° indicated crystalline in nature [Figure 4]. No significant changes observed in 2θ values of nateglinide and physical mixture [Figure 5] but there was a significant difference between the 2θ

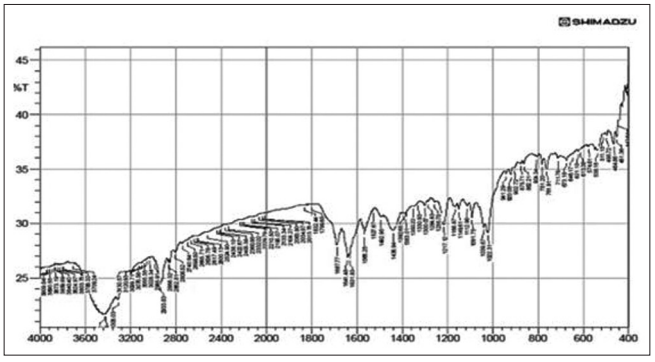

Figure 2: Fourier transforms infrared spectra of pure drug

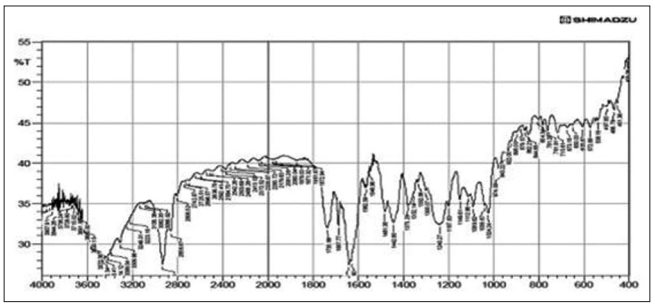

Figure 3: Fourier transforms infrared spectra of nateglinide solid dispersion optimized formulation (SD15)

values of the pure drug and final SD15 formulation [Figure 6]. A reduction in crystallinity observed in SD15.

The results indicate the conversion of nateglinide from the crystalline state to the amorphous on SD. The development of an amorphous formulation verifies that the dispersion of drug in molecular state within the polymers.

SEM studies

SEM studies conducted on optimized nateglinide SD for determination of surface morphology. The monogram of SDs exhibited size uniformity with spherical shaped, porous, and rough surfaced particles. The roughness of surface is adhered to moisture loss from wet surfaces which, in turn, resulted in porous. The wrinkled surface of the SDs showed up surge in surface area that play key role in increasing the solubility [Figures 7 and 8].

Preparation of nateglinide SD incorporated controlled release tablets

Nateglinide controlled release tablets were round in shape, white in color with smooth appearance.

Table 6: Stability studies of SD15

Retest time for optimized formulation SD15	Drug content (%)	*In-vitro* drug release profile (%)
0 days	99.68±0.68	99.93±1.09
30 days	99.25±0.46	99.34±1.35
60 days	98.61±1.02	98.56±1.86
90 days	97.98±0.26	98.04±1.27

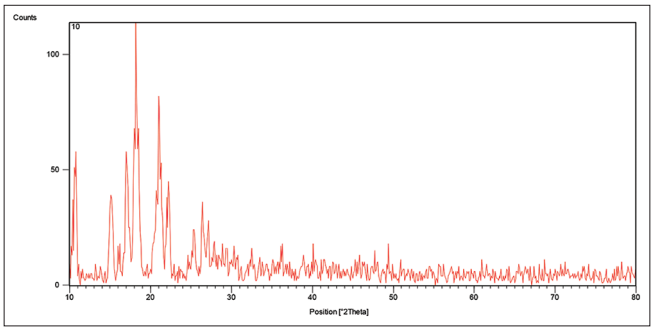

Figure 4: X-ray diffractogram of nateglinide pure drug

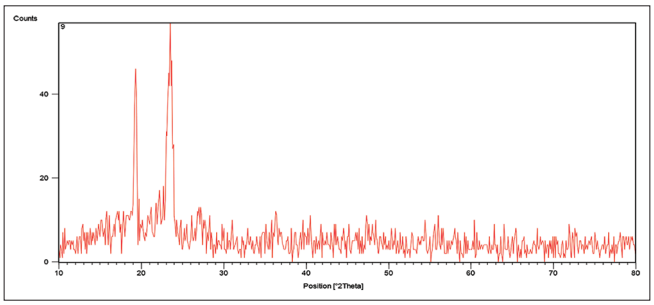

Figure 5: X-ray diffractogram of nateglinide physical mixture

Evaluation studies of nateglinide SD incorporated controlled release tablets

Micrometric properties of nateglinide controlled release tablets lubricated blend

Granules prepared for compression of nateglinide controlled release tablets evaluated for flow properties and results tabulated [Table 7]. The bulk densities of F1 to F15 were measured and they ranged from 0.458 ± 0.74g/cc³ to 0.51 ± 0.56g/cc³ .The tapped density of all the formulations F1 to F12 ranged from 0.49 ± 0.78g/cc³ to 0.54 ± 0.63g/cc³. Angle of repose of all 15 formulations was good with F12 exhibiting value of 25.21 ± 0.36° indicative of excellent flow property. The compressibility index ranged between 9% and

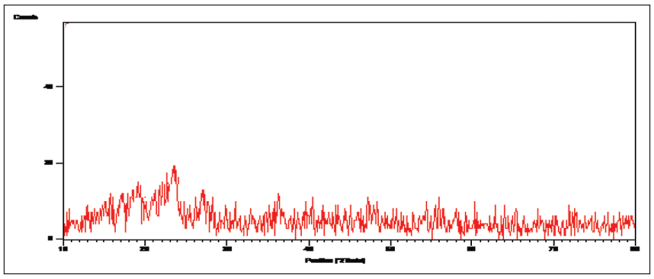

Figure 6: X-ray diffractogram of nateglinide solid dispersion optimized formulation (SD15)

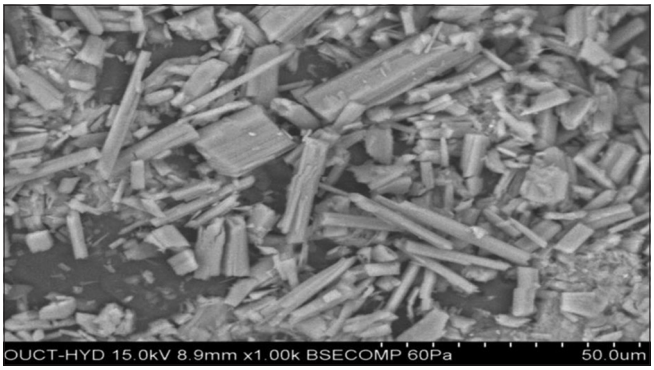

Figure 7: SEM image of nateglinide pure drug

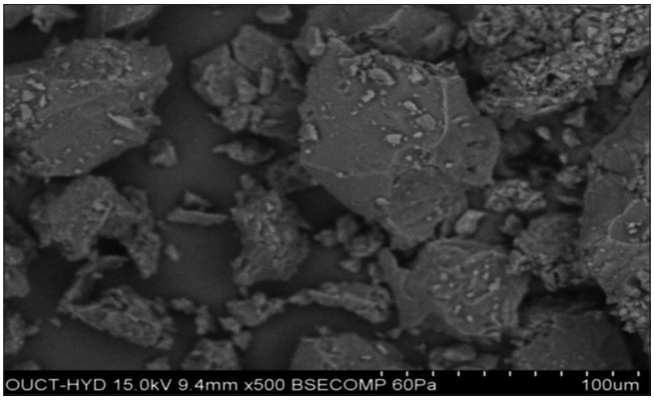

Figure 8: Nateglinide solid dispersion optimized formulation (SD15)

15%. These findings indicated that the all the batches of formulations exhibited good flow properties [Table 7].

Physical evaluation of nateglinide controlled release tablets

The results of the physical properties of nateglinide controlled release tablets are shown in Table 8. The results of the physical tests of the prepared blends were within the limits, the weight variation of all the formulations is within limits, and the adequate tablet hardness is necessary requisite for consumer acceptance and handling. The hardness of the tablets made of formulations, that is, F1–F12 was ranged between 6.0 and 8.0 kg/cm^2. The thickness of all tablets found to be uniform. The thickness ranged between 4.3 mm and 4.7 mm. The friability ranged between 0.15 and 0.21 is within limits between 0% and 1%. The drug content ranged between 96.43% and 99.93%, [Table 8] with highest exhibited by F12 formulation and depends on angle of repose; if the angle of repose is excellent then drug content is also uniform and the flow property is good; hence, the drug is evenly distributed in the formulation [Table 8].

In vitro dissolution studies

The drug released versus time plot is shown in Figures 9 and 10 for all formulations. Due to the high viscosity of rate controlling polymers and using lactose as filler in the formulation sustained release of nateglinide was achieved. Formulation F12 containing higher amount of rate controlling polymer (HPMC K 100M) with natural gum Cederela and lactose exhibited highest drug release of 99.98% up to 16 h whereas marketed product released 97.43% up to 8 h Hence, out of all formulation F12 is selected as best optimized formulation and further studied for its characterization [Figures 9 and 10].

Table 7: Micrometric properties of nateglinide controlled release tablets lubricated blend

Micrometric properties	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Angle of repose (°)
F1	0.47±0.35	0.52±0.67	12.47±0.64	1.14±0.67	27.78±0.87
F2	0.49±0.46	0.54±0.45	14±0.76	1.16±0.54	27.34±0.34
F3	0.46±0.77	0.51±0.59	15.09±0.56	1.17±0.36	27.87±0.98
F4	0.46±0.23	0.50±0.35	14.87±0.87	1.16±0.67	28.53±0.42
F5	0.51±0.33	0.50±0.66	15.25±0.90	1.15±0.34	27.87±0.76
F6	0.48±0.87	0.49±0.78	14.74±0.53	1.17±0.78	27.46±0.45
F7	0.47±0.45	0.54±0.63	15.78±0.63	1.15±0.84	28.89±0.67
F8	0.49±0.24	0.51±0.93	13.54±0.34	1.16±0.60	27.31±0.23
F9	0.48±0.76	0.54±0.63	14.67±0.74	1.16±0.73	26.56±0.89
F10	0.458±0.74	0.53±0.25	12.86±0.42	1.15±0.87	26.63±0.54
F11	0.47±0.23	0.49±0.37	11.75±0.85	1.16±0.23	26.43±0.97
F12	0.51±0.56	0.50±0.71	9.46±0.63	1.17±0.98	25.21±0.36

Above parameters are communicated as Average±Standard deviation; (*n*=3)

Table 8: Physical properties of nateglinide controlled release tablets

Parameters	Average weight (in mg)	Thickness (in mm)	Hardness (in KP)	Friability (%)	Drug content
F1	498.35±0.35	4.5±0.67	7.1±0.45	0.15±0.45	96.43±0.65
F2	498.50±1.9	4.6±0.43	6.8±0.35	0.17±0.34	96.56±0.35
F3	499.20±0.35	4.62±0.17	6.8±1.25	0.18±0.45	97.34±0.97
F4	499.77±1.76	4.45±0.23	7.61±0.46	0.19±0.07	97.45±0.67
F5	499.15±2.64	4.67±0.45	6.8±1.86	0.20±0.1	97.59±0.78
F6	500.2±2.68	4.34±0.56	6.8±0.47	0.21±0.32	97.89±0.67
F7	498.8±0.36	4.32±0.46	7.1±1.53	0.16±0.05	98.43±0.65
F8	499±1.35	4.37±0.87	7.8±0.39	0.18±0.03	98.34±0.24
F9	500.8±4.2	4.39±0.89	6.9±0.36	0.19±0.05	98.68±0.53
F10	499.35±3.68	4.45±0.34	6±1.45	0.19±0.32	98.79±0.75
F11	499.8±2.46	4.48±0.025	6.6±0.46	0.18±0.15	98.92±0.46
F12	500.2±1.47	4.5±0.14	7.9±0.67	0.19±0.56	99.93±0.46

Above parameters are communicated as Average±Standard deviation; (*n*=3)

The results show that optimized formulation (F12) is closer to unity in case of zero-order plot, that is, 0.9991 indicates that the drug release follows a zero-order mechanism This data indicate a lesser amount of linearity when plotted by the first-order equation. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppa's plots. The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one, that is, 0.932 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer-Peppa's plots, that is, 1.3531 suggest that the drug release from tablets was anomalous non-Fickian diffusion super Case II transport.

From the above results, formulation F12 was chosen optimal among all the other formulations.

Stability studies

Optimized formulation (F12) was subjected to stability study for 90 days at accelerated as per the ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (F12) is stable with no variations in its physical properties [Table 9].

Table 9: Stability studies of F15 stored at 40±2°C/75±5% RH

Retest time for optimized formulation F15	Drug content (%)	*In-vitro* drug release profile (%)	Hardness (kg/cm²)
0 days	99.93±0.46	99.98±1.82	7.9±0.67
30 days	99.44±0.89	99.23±1.67	7.9±0.65
60 days	98.79±1.35	98.56±1.12	7.9±0.23
90 days	97.65±0.68	98.02±0.23	7.9±0.35

Above parameters are communicated as Average±Standard deviation; (*n*=3)

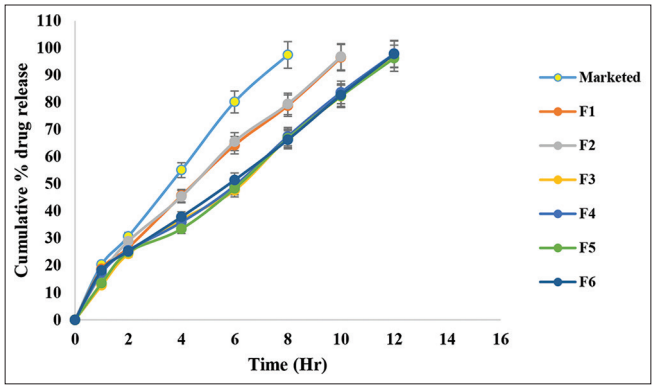

Figure 9: Percentage drug release of nateglinide formulations F1 to F6 and marketed product

Characterization of F12 tablet formulation

FTIR studies

FTIR spectrophotometric method was developed to establish the compatibility of nateglinide pure drug and nateglinide controlled release tablets. Figure 2 represents the FTIR of pure nateglinide. The spectra were compared for confirmation of common peaks. Similar peaks were observed and showed no disposition/disappearance in the spectra of nateglinide controlled release tablets [Figure 11] suggesting that drug and recipients were compatible.

DISCUSSION

In the current research, the SD tablets of nateglinide were formulated using hydrophilic polymer and hydrophobic polymer for controlled drug release. The nateglinide SD prepared using crospovidone and SLS, evaluated for percentage yield, drug content, and drug release. The formulation SD15 with higher values of drug content and drug release of 99% was chosen optimal for incorporating into tablet formulation by wet granulation technique. The controlled release tablet blend was initially evaluated for pre-compression parameters and results show that formulation F12 exhibited excellent flow properties. The post-compression parameters were also found within acceptable limit. The drug release of formulation F12 comprising HPMC K 100M, Cederela and lactose displayed highest drug release of 99.98% up to 16 h whereas marketed product released

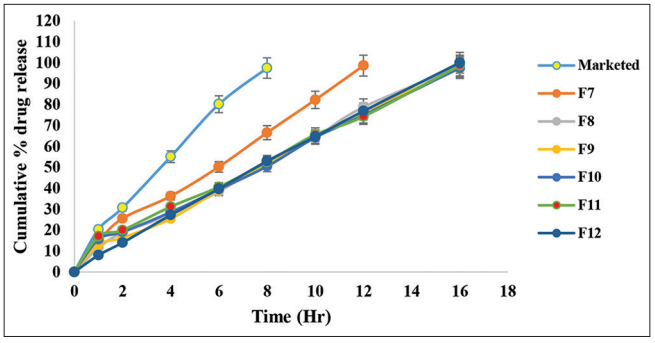

Figure 10: Percentage drug release of nateglinide formulations F9 to F15 and marketed

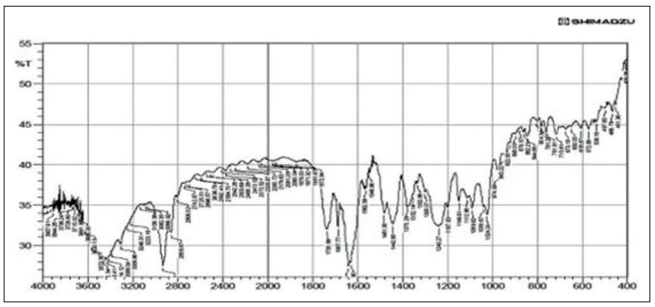

Figure 11: Fourier transforms infrared of optimized formulation F12 of nateglinide controlled release tablet

97.43% within 8 h. The drug excipient compatibility study for FTIR and DSC shows that the combination is compatible.

The results conclude that this formulation of nateglinide SD incorporated controlled release tablets enhanced the solubility and dissolution rate of the drug which further extended the therapeutic effect of the drug. This technique also helps in reduction of dosage frequency with increased patient compliance.

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