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RESEARCH ARTICLE

Dose calculation, design and development of nateglinide matrix tablets using quality by design approach and its pharmacokinetic evaluation in animal model

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Abstract The present work deals with design of zero order sustained release nateglinide matrix tablets by application of statistical design using response surface methodology as a tool. Central composite design was used to investigate the effect of two independent formulation variables (at three levels) such as Kollidon SR (X_1), PVP K 30 (X_2) on dependent variables viz. time required to release 30 % (T30, Y_1), percentage drug released at 6th hour (DR6, Y_2) and time required to release 90 % (T90, Y_3) of drug. Wet granulation technique was employed for tablets preparation. The result showed that release pattern of the optimized formulation was almost equal to the statistically predicted values. There was no chemical interaction observed between drug and polymer based up on FTIR and DSC results. In vitro release studies were performed in 0.1 N HCl containing 0.5 % SLS for first 2 h followed by pH 6.8 phosphate buffer containing 0.5 % SLS. Stability studies were performed to statistically optimized formulation. The release pattern from statistically optimized formulation was followed zero order kinetics with non-Fickian process as drug release mechanism. Pharmacokinetic studies were performed to optimized formulation in comparison with nateglinide suspension in rabbit as animal model. The results of in vivo studies revealed the % relative bioavailability of statistically optimized formulation was found to be 68.87 %.

Keywords Nateglinide sustained release matrix tablets · Response surface methodology · Central composite design · In vitro and in vivo Pharmacokinetic studies

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Introduction

The importance of quality by design (QbD) has been increasing day by day in pharmaceutical formulation development and manufacturing process. Since January 2013, USFDA recommended QbD approach in designing of dosage forms as per regulatory point of view (Jaiprakash et al. 2014). One of the tools in QbD with low experimentation time and low cost for developing and optimizing the dosage form is experimental design/design of experiments (DoE) (Ferreira et al. 2007). DoE is an organized methodology which gives exact output based up on the experimental data, which can be utilized to generate statistical equations and predict the experimental results in the product development process (Montgomery 2001; Porter et al. 1997). Although many experimental designs are available, response surface methodology (RSM) is one of the statistical optimization techniques in the DoE being used extensively now a days. This technique was employed to find out the response of particular variable on the whole experimental process (Long et al. 2012). Central Composite Design (CCD) (one of the statistical experimental tool) is a combination of factorial, axial and central points. In CCD each numerical factor is varied over 3 levels such as plus and minus levels of axial points, plus and minus levels of factorial points and the center point (based up on

Design Expert® Software 8.0.7.1 Version, Stat-Ease Inc., Minneapolis, MN). In CCD all factors are evaluated at a time in all possible variations and combinations (Bhupinder et al. 2004).

Nateglinide (capability to control both fasting and postprandial blood glucose level (FBG, PBG) in the treatment of type 2 diabetes) is a novel D-phenylalanine insulin secretagogue that is similar in action but different in structure from the sulfonylureas (Dunn and Faulds 2000). Chemically, it is a ((-)-*N*-(*trans*-4-isopropylcyclo-hexanecarbonyl)-D-phenylalanine) (Ai et al. 2011). It is official in J.P (Japanese Pharmacopoeia 2011). The terminal elimination half-life is about 1.5–2 h following oral administration of an immediate-release preparation with about 73–75 % bioavailability, but longer with a modified release formulation (Gribble et al. 2001; Makino et al. 2009; Nicholas Tentolouris et al. 2007). The dose range of nateglinide is in between 60–240 mg per *t.i.d.*

A non-swellable and partially water soluble polymer Kollidon SR was used in the study as a drug release retardant. It mainly consists 80 % polyvinyl acetate and 19 % povidone, in a physical mixture (Kolter et al. 2001) with approximately 0.8 % SLS and 0.2 % silica as stabilizers.

The present investigation deals with the development of sustained release matrix tablets of nateglinide using CCD as a statistical tool using Kollidon SR(X_1) and PVP K 30 (X_2) concentrations were considered as independent variables. The effect of these independent variables on dependent variables such as time required to release 30 % (Y_1), percentage drug released at 6th hour (Y_2) and time required to release 90 % (Y3) of drug was studied. Characterization has been done to optimized formulation by DSC and FTIR. Further the statistically optimized dosage form was analysed pharmacokinetically in rabbit as animal model in comparison with nateglinide suspension.

Materials

Nateglinide was received as a gift sample from Ajinomoto Co. Inc., Japan. Kollidon SR was a generous gift sample from Hetero labs Pvt. Ltd, Hyderabad, India. Potassium dihydrogen phosphate, sodium hydroxide and isopropyl alcohol (IPA) were of analytical grade. HPLC grade acetonitrile, methanol were used. Water was distilled before use. All other chemicals and reagents used in the study are analytical grade and used as received.

Dose calculation for nateglinide

The dose for nateglinide sustained release product was calculated using the kinetics of extended release dosage form approach calculations (Shargel et al. 1999).

The amount of drug required in a sustained release dosage form is determined by the pharmacokinetics of the drug, the desired therapeutic level of the drug, and the intended duration of action. In general, the total dose required (D_{Tot}) is the sum of maintenance dose (D_m) and initial dose (D_I) released immediately to provide a therapeutic blood level.

$$D_{Tot} = D_I + D_m \quad (1)$$

In practice, D_m (mg) is released over a period of time and is equal to the product of t_d (the duration of drug release) and the zero-order rate k_r^0 (mg/h). Therefore, Eq. 1 can be expressed as

$$D_{Tot} = D_I + k_r^0 t_d \quad (2)$$

Ideally, the maintenance dose (D_m) is released after D_I has produced a blood level equal to the therapeutic drug level (C_p). However, due to the limitations of formulations, D_m actually starts to release at $t = 0$. Therefore, D_I may be reduced from the calculated amount to avoid "topping".

$$D_{Tot} = D_I - k_r^0 t_p + k_r^0 t_d \quad (3)$$

Equation 3 describes the total dose of drug needed, with t_p representing the time needed to reach peak drug concentration after the initial dose.

For a drug that follows a one-compartment open model, the rate of elimination (R) needed to maintain the drug at a therapeutic level (C_p) is

$$R = K_e V_d C_p \quad (4)$$

where V_d is apparent volume of distribution and K_e is elimination rate constantWhere k_r^0must be equal to R in order to provide a stable blood level of the drug, Eq. 4 provides an estimation of the release rate (k_r^0) required in the formulation. The above equation may also be written as

$$R = C_p Cl_t \quad (5)$$

where Cl_t is the clearance of the drug since $Cl_t = K_e V_d$.

In designing a sustained release product, D_I would be the loading dose in the sustained release formulation that would raise the drug concentration in the body to C_p, and the total dose needed to maintain therapeutic concentration in the body would be simply

$$D_{Tot} = D_I + C_p Cl_t T \quad (6)$$

For many sustained release drug products, there is no built-in loading dose (i.e. $D_I = 0$) (Shargel et al. 1999; Brahmankar 2008). This could be due to the use of hydrophilic polymers as release retardants which require some lag time for swelling and during which the loading dose will be released and the remaining drug in the dosage form acts as maintenance dose and hence Eq. 6 is modified to Eq. 7 ignoring the loading dose in the calculation. The

dose needed to maintain a therapeutic concentration for T hours is

$$D_{Tot} = C_p Cl_t T \quad (7)$$

(where T is dosing interval and $Cl_t = K_e V_d$).

The available pharmacokinetic data for nateglinide is i.e. half life ($t_{1/2}$) is 1.4 h, K_e is 0.495 h^{-1} (0.693/1.44), C_p (drug at therapeutic level) is 2.40 mg/L and volume of distribution (V_d) is 10.1 L (McLeod 2004). From the pharmacokinetic data the clearance of the drug was found to be 5 L/h.

In the present investigation it was planned to develop nateglinide sustained release formulation capable of acting for over 12 h (T) with zero order release approach. The total dose required was calculated based on this assumption. According to Eq. 7

$$D_{Tot} = 2.40 \times 5 \times 12 = 144 \text{ mg}$$

Thus from the above calculations the total dose obtained for design of matrix tablets of nateglinide for 12 h duration was 144 mg and for the convenience it was rounded to 150 mg. As the drug belonging to anti diabetic category and it has the ability to control both FBG, PBG (Chisato et al. 2006), it was assumed that in the first 2 h 30–40 % of drug should be released as loading dose (i.e. nearly ~45–60 mg of drug from total 150 mg dose like conventional tablet) so that the drug can minimize both fasting and postprandial blood glucose levels in body and then the remaining amount can be useful to maintain the glucose levels in controlled form. Based on the above assumption, the theoretical release profile has been predicted and around 40, 64, 88, 94 and 100 % drug should be released at 2, 6, 10, 11 and 12 h respectively.

Statistical design

Based up on previous experimental results it was found that Kollidon SR and PVP K 30 have greater impact on the drug release rate. Hence Kollidon SR (Y_1) and PVP K 30 (Y_2) were considered as independent variables and their range was found to be in between 10–20 mg and 3.5–10.5 mg respectively. The various combinations of independent variables which were yielded by CCD for nateglinide matrix tablets are summarized in Table 1.

Preparation of nateglinide matrix tablets

Nateglinide matrix tablets were prepared by wet granulation technique. All the ingredients required for 100 tablets in each batch according to the formulae available in Table 2 were weighed accurately and passed through sieve # 40 (420 μm). Drug, Kollidon SR, PVP K 30 and lactose (diluents) were mixed geometrically for proper homogenous blending and sufficient quantity of isopropyl alcohol was added to the above materials to form dough mass. The dough mass was passed through sieve # 18 (1000 μm) for the formation of granules. The wet granules were dried in hot air oven at 50 °C for half an hour. The dried granules were shifted through sieve # 24 (710 μm). Required quantities of talc and magnesium stearate were thoroughly mixed with these granules in a polyethylene bag for lubrication of granules and were compressed as tablets using 8 mm flat faced round punch on a 16 station rotary tablet machine (M/s Cadmach Machinery, Co. Pvt. Ltd, India) using compression force sufficient to obtain hardness of 4–5 kg/cm^2.

Table 1 Central composite design formulations for nateglinide matrix tablets

Point type	Nateglinide formulation	
	Kollidon SR (X_1, mg)	PVP K 30 (X_2, mg)
Center (0,0)	15	7
Center (0,0)	15	7
Center (0,0)	15	7
Center (0,0)	15	7
Center (0,0)	15	7
Axial (0,−1.414)	15	2
Axial (0,+1.414)	15	12
Axial (+1.414,0)	22	7
Axial (−1.414,0)	8	7
Factorial (−1,−1)	10	3.5
Factorial (−1,+1)	10	10.5
Factorial (+1,−1)	20	3.5
Factorial (+1,+1)	20	10.5

In vitro drug release studies

In vitro drug dissolution studies were performed using USP type II apparatus (paddle). Initially drug release studies were performed in 900 ml of 0.1 N HCl containing 0.5 % SLS for 2 h followed by 900 ml of pH 6.8 phosphate buffer containing 0.5 % SLS (JP XVI) for rest of time at 50 rpm paddle speed and 37 ± 0.5° C. In each dissolution study the dose of nateglinide tested was equivalent to 150 mg. During each time interval 5 ml of sample was collected and filtered through a 0.22 μm membrane filter sintered glass disc (Millipore) and absorbance of the sample was determined using double beam UV–Visible Spectrophotometer at 210 nm. The percent of drug dissolved at various time intervals was calculated and plotted against time. Each dissolution study was replicated three times and average values are reported.

Table 2 Formulae of nateglinide matrix tablets

Ingredients (mg)	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13
Nateglinide	150	150	150	150	150	150	150	150	150	150	150	150	150
Kollidon SR	15	15	15	15	15	15	15	22	8	10	10	20	20
PVP K 30	7	7	7	7	7	2	12	7	7	3.5	10.5	3.5	10.5
Lactose	175	175	175	175	175	180	170	168	182	183.5	176.5	173.5	166.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total	350	350	350	350	350	350	350	350	350	350	350	350	350

Drug release kinetics

In vitro drug release kinetics such as zero order (Lazarus and Cooper 1961) and first order (Wagner 1969), mechanism of drug release like diffusion (Higuchi 1963) or erosion (Hixson and Crowell 1931) and Peppas-Korsemeyer (Korsmeyer et al. 1983; Peppas 1985) equations for determining the Fickian or non-Fickian diffusion were performed. The drug transport mechanism was finding out according to Korsmeyer-Peppas equation based up on the release exponent 'n' value for a dosage form which is in cylindrical shape.

Statistical analysis of the data

The obtained data from in vitro release studies was fitted simultaneously to linear, quadratic and cubic or interaction models available in Design Expert Software and analyzed for best fit model in comparison with each other. Based up on the comparison of parameters viz. coefficient of variance (CV), multiple correlation coefficient (R^2), adjusted multiple correlation coefficient (adjusted R^2), predicted residual sum of squares (PRESS), F test and p value, the best fit model was selected. The polynomial equation was developed to the best fit model followed by correlation between independent and dependent variables were studied by generating response surface plots. 3D surface plots and contour plots were developed with the existing data to study the effect of variables on responses effectively followed by optimization using numerical and graphical approaches.

Optimization

The obtained responses were statistically optimized using a numerical target approach and overlay plots by multi criteria decision approach. The criteria for the responses Y_1, Y_2, Y_3 for nateglinide were fixed as 1.5–2 h, 60–65 % and 10.5–11.5 h. These values were fixed based up on theoretical drug release profile calculations. From the above criteria the overlay plots were obtained and the statistically optimized formula was selected based up on the highest desirability value. The statistically optimized formula was further compared with predicted responses to validate the design.

Determination of difference and similarity factors

The in vitro drug release profile of the formulations (test) was compared with the theoretical release profile (reference) of developed nateglinide matrix tablets by determining the 'difference factor', f_1 and 'similarity factor', f_2 (Geoffroy et al. 1998; Hamed and Sakr 2001). The difference factor (f_1) measures the percent error between the two curves over all time points and was calculated by using the following Eq. 8

$$f_1 = \left| \sum_{j=1}^{j=n} (R_j - T_j) \Big/ \sum_{j=1}^{j=n} R_j \right| \times 100 \tag{8}$$

$$f_2 = 50 \times \log \left\{ \left| 1 + (1/n) \sum_{j=1}^{j=n} \left(R_j - T_j\right)^2 \right|^{-0.5} \times 100 \right\} \tag{9}$$

The similarity factor (f_2) is a logarithmic transformation of sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated based upon Eq. 9.

In order to consider the similar dissolution profiles, f_1 value should be lower than 15 (i.e. 0–15) and f_2 value higher than 50 (i.e. 50–100). In the present investigation, f_1 and f_2 were calculated for optimized formulations against theoretical release profile of the respective drugs.

Validation of statistically optimized formula

The responses were compared with statistically predicted values to validate the statistical design using the following formula to find out the percentage relative error.

$$\% \text{ Relative error} = \left[\frac{\text{predicted value} - \text{experimental value}}{\text{predicted value}} \right] \times 100 \tag{10}$$

Characterization

Compatibility studies by FTIR

Compatibility studies between drug and polymer were performed by pressed pellet technique using Fourier transform infrared spectroscopy (FTIR) (BRUKER Optics, Model- Alpha 200218). The pellet was prepared by compression of small pinch of the material (drug, polymer) with potassium bromide (KBR) and the vibrations of functional groups were analyzed at the wave number range 4000–500 cm^{-1}.

Differential scanning calorimetry (DSC)

The thermal analysis of pure nateglinide, physical mixture and optimized formulation was performed using differential scanning calorimetry (Perkin Elmer DSC 4000). The samples were sealed in aluminium pan and heated at 10 °C/min rate from 20–200 °C with the aluminium pan having pinch of iridium was kept as reference sample. Throughout the study nitrogen gas was supplied to DSC instrument.

Stability studies

Screw capped HDPE (high density polyethylene) containers were used for the study. The statistically optimized formulation coded N14 was packed in container and kept in stability chamber (Kemi-KHO-3A, Kadavil Electro Mechanical Industries, Kerala, India) maintained at 30 ± 2° C/70 ± 5 % RH, and 40 ± 2° C/75 ± 5 % RH as per ICH guidelines (ICH 2003). This has been particularly recommended for zone III and zone IV. India is one of the countries included in these zones (Grimm 1998). Samples were withdrawn from the stability chamber after 3 and 6 months in case of samples stored at real time conditions (30 ± 2° C/70 ± 5 % RH) and after 1, 2, 3 and 6 months in case of accelerated stability conditions (40 ± 2° C/75 ± 5 % RH).

In vivo pharmacokinetic studies

The pharmacokinetic studies were performed for statistically optimized formulation of nateglinide (N14) matrix tablets in comparison with pure drug. Nateglinide 10 mg/Kg body weight was used for the pharmacokinetic study. The dose was calculated based on the conversion factor of adult dose to rabbit dose as shown below (Ghosh 2005).

$$\text{Rabbit dose per Kg body weight} = \text{Human dose} \times 0.07 = 10\ \text{mg/Kg}$$

Nateglinide matrix tablets for rabbit administration were prepared using 3 mm punches having same hardness of N14. The prepared tablets of nateglinide were further denoted as N15 and were tested for their drug release pattern and compared with that of N14.

The protocol was approved by Institutional animal ethical committee at Shri Vishnu College of Pharmacy, Andhra Pradesh, India (33/IAEC/VCP/PhD/2013-14). The experiments were conducted as per CPCSEA guidelines. The rabbits were divided into two groups each containing six animals. They were fasted over night and freely accessed to water before dose administration. The tablet was administrated to rabbit using mouth gauge. One group of animals received nateglinide matrix tablet (N15) and another group received pure drug (10 mg/Kg) in suspension form (0.1 % w/v sodium carboxy methyl cellulose). During each period, approximately 1 ml of blood was collected from marginal ear vein of rabbit into micro centrifuge tubes containing EDTA. Blood samples were collected at 0, 0.5, 1, 2, 4, 6, 8, 10, 12 and 18 h. Plasma was separated from blood immediately by centrifugation after withdrawing from animas and stored at −20 °C until drug analysis. The plasma samples were analysed by high performance liquid chromatography (HPLC). The pharmacokinetic parameters such as C_{max}, t_{max}, elimination rate constant (Ke), AUC, AUMC, and biological half life was estimated after analysis of the plasma samples.

HPLC assay

A gradient HPLC (Shimadzu, Class VP series) with 2 LC-10AT VP pumps, variable wavelength programmable Photo Diode Array (PDA) detector, SPD-M10A VP was used. The HPLC system was equipped with Empower software (Version 2). Samples were chromatographed on a reversed phase C_{18} column (5µ, 250 × 4.6 mm). Equal quantities of methanol and acetonitrile were added to plasma followed by vortexed on cyclomixture for continuous mixing and centrifuged at 5000 rpm for 15 min for drug separation. The supernatant was collected in eppendrof tube and again centrifuged for 15 min to complete removal of plasma proteins if any. The obtained supernatant after second centrifugation was separated and filtered through 0.45 µm membrane filter and an aliquot of 20 µl was injected directly into HPLC loop injector. The pure nateglinide HPLC chromatogram was obtained by directly injecting the nateglinide solution into HPLC loop. Calibration curve was constructed between concentration and peak area obtained with respective concentration of the solution.

Analysis was isocratic at 1.0 ml/min flow rate with acetonitrile: 10 mM phosphate buffer solution (adjusted to pH 3.0 with phosphoric acid). The mobile phase was prepared freshly everyday prior to the experiment and

premixed, filtered through 0.2 μm membrane to remove any particulate matter and degassed by sonicator before use. The eluents was monitored using UV detection at 203 nm. The sensitivity of the detector was set at 0.01 AUFS (Jolly et al. 2007).

Results and discussion

In vitro drug dissolution studies

Nateglinide matrix tablets were prepared as per CCD yielded combinations and in vitro drug dissolution studies were conducted to study the release profiles from respective formulations. The mean percentage drug release from the nateglinide matrix tablets are summarized in Table 3.

The results indicated that nateglinide release was slow and sustained from the matrix tablets in the range of 6–15 h in formulation batches developed with Kollidon SR as release rate retardant and PVP K 30 as binder. Those formulations developed with 15 mg of Kollidon SR and 7 mg of PVP K 30 (i.e. center points of the design) (N1-5), drug release profiles were almost similar with each other and complete drug release was observed (~99 %) nearly in 12 h. From the drug release profiles it was observed that concentration of PVP K 30 has major role on drug release pattern. The formulation developed with low quantity of PVP K 30 i.e. 2 mg, 15 mg Kollidon SR (axial points) (N6) 99.35 % of drug was released in 6 h. Formulations N7 and N12 released the complete drug (~100 %) in 13 h and the plateau observed in formulation N7 was due to change in dissolution buffer from 0.1 HCl to 6.8 phosphate buffer solutions. Formulations N8 (axial points) and N13 (factorial points) took 14 h for complete release of drug. The formulations developed with (factorial points) 8 mg polymer and 7 mg binder (N9), 10 mg of polymer and 3.5 mg of binder (N10) showed almost similar pattern in drug release rate and 8 & 9 h time required to release 100 % of drug. The formulations developed with (axial points) 15 mg of polymer, 12 mg binder (N7) and (factorial points) 20 mg polymer, 3.5 mg binder (N12) showed similar release patterns.

Dissolution profiles from the nateglinide matrix tablets indicated that the drug release was retarded with increase in the polymer concentration. Additionally the drug release was also sustained even with lower concentrations of polymer with high binder concentration and with increase in both Kollidon SR and PVP K 30 concentrations. This may be due to mutual effect of polymer and binder on each other on release pattern of drug.

Table 3 Cumulative % drug released versus time from nateglinide matrix tablets

Time (h)	% drug released (mean ± SD, n = 3)												
	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13
0.5	13.26 ± 0.06	12.81 ± 0.17	8.17 ± 0.71	13.28 ± 0.78	8.78 ± 0.93	12.9 ± 0.1	9.32 ± 0.15	7.32 ± 0.04	8.16 ± 0.03	11.84 ± 0.52	8.62 ± 0.36	8.14 ± 0.02	7.37 ± 0.11
1	22.05 ± 0.19	23.34 ± 2.03	18.54 ± 2.6	18.82 ± 0.41	15.99 ± 0.51	25.96 ± 0.09	21.23 ± 1.24	16.56 ± 0.07	24.81 ± 3.04	21.21 ± 0.39	16.5 ± 1.24	23.4 ± 0.5	14.69 ± 0.18
2	31.42 ± 0.93	35.99 ± 0.42	31.8 ± 4.94	35.73 ± 0.9	30.6 ± 0.2	42.63 ± 0.15	30.83 ± 0.45	28.26 ± 0.09	36.68 ± 0.22	34.4 ± 0.36	31.86 ± 2.9	32.18 ± 0.01	24.75 ± 0.88
3	37.36 ± 2.01	37.84 ± 0.45	34.55 ± 0.52	36.58 ± 0.5	33.97 ± 0.92	57.15 ± 1.11	31.93 ± 0.25	29.29 ± 0.07	49.6 ± 4.45	39.69 ± 0.34	35.88 ± 4.6	36.02 ± 0.61	26.64 ± 0.13
4	44.63 ± 0.96	44.47 ± 0.39	44.25 ± 0.67	41.03 ± 0.35	39.57 ± 0.57	73.69 ± 1.72	33.52 ± 0.34	31.22 ± 0.2	60.44 ± 0.87	46.43 ± 0.64	43.54 ± 1.79	49.41 ± 0.22	29.33 ± 0.12
5	54.07 ± 1.08	53.12 ± 0.55	53.66 ± 2.92	50.85 ± 0.47	50.23 ± 0.36	82.66 ± 1.6	43.86 ± 0.21	38.18 ± 0.24	69.4 ± 1.81	55.42 ± 0.77	53.59 ± 0.37	54.21 ± 0.26	39.52 ± 0.31
6	64.95 ± 0.44	59.33 ± 0.66	61.8 ± 6.08	56.53 ± 0.3	59.55 ± 0.56	99.35 ± 0.75	50.11 ± 0.53	47.5 ± 0.2	78.9 ± 1.34	65.6 ± 0.52	60.31 ± 1.34	60.73 ± 0.26	48.53 ± 0.38
7	75.48 ± 0.80	63.94 ± 0.95	71.64 ± 3.53	66.3 ± 0.34	68.7 ± 0.3		61.25 ± 0.27	54.27 ± 0.45	84.78 ± 0.65	75.11 ± 0.4	69.36 ± 0.14	69.27 ± 0.15	57.94 ± 0.46
8	83.06 ± 0.32	72.85 ± 0.54	76.67 ± 2.38	73.81 ± 1.03	77.39 ± 1.11		72.81 ± 0.95	60.91 ± 0.32	92.46 ± 0.58	85.59 ± 0.28	78.21 ± 0.24	75.22 ± 0.13	67.8 ± 0.4
9	86.98 ± 0.69	76.56 ± 0.84	80.29 ± 0.64	78.23 ± 0.4	82.26 ± 0.56		76.59 ± 0.54	67.15 ± 0.46	98.46 ± 0.5	91.89 ± 0.58	84.56 ± 0.87	79.05 ± 0.48	71.02 ± 0.87
10	89.29 ± 0.94	82.13 ± 0.44	85.88 ± 2.01	83.61 ± 1.54	88.52 ± 0.38		81.82 ± 0.52	74.06 ± 0.44		99.26 ± 0.36	90.44 ± 0.85	84.16 ± 0.26	78.89 ± 0.29
11	94.56 ± 0.98	89.97 ± 0.89	91.25 ± 0.58	88.57 ± 0.79	92.05 ± 0.78		84.45 ± 0.45	78.19 ± 0.32			99.09 ± 0.48	88.59 ± 0.45	81.05 ± 0.43
12	99.73 ± 0.19	99.01 ± 0.89	99.04 ± 0.45	97.96 ± 0.7	98.05 ± 0.56		88.05 ± 0.43	84.29 ± 0.24				92.16 ± 0.26	85.06 ± 0.2
13							99.32 ± 0.47	91.26 ± 0.29				99.34 ± 0.13	88.34 ± 0.48
14								99.88 ± 0.69					91.04 ± 0.37
15													99.98 ± 0.57

Drug release kinetics

The zero and first order correlation coefficient values (r) for nateglinide formulations are shown in Table 4. According to the values of correlation coefficient all formulations exhibited zero order release except the N2, N3 and N12. The last three followed first order release kinetics.

To find out the drug release mechanism in vitro dissolution data of nateglinide matrix tablets was fitted to Higuchi and Hixson-Crowell models and according to those models the highest correlation coefficient values were found in diffusion model than the erosion except in formulations N13, N7, N8 and N12.

The correlation coefficient (r) values were in the range of 0.9759–0.9960 indicating that the drug release followed Korsemeyer-Peppas model also. The exponent "n" value was used to find out the exact release mechanism. The values were found to be in between 0.5993 and 0.7945 indicating that the nateglinide release from the matrices followed non-Fickian (anomalous) process as drug release mechanism.

Observed responses for the dependent variables

The responses of nateglinide matrix tablets were observed from in vitro release studies of all the formulations are summarized in Table 5. The values of T30, DR6 and T90 were ranged from 1.0–4.0, 47.45–78.9 and 5.15–13.45 respectively. From the obtained responses it was observed that drug release was sustained with increase in Kollidon SR and PVP K 30.

Data analysis

The obtained data from established in vitro release profiles were simultaneously fitted to models available in Design Expert Software. The ANOVA test was also performed, polynomial regression equation was developed using ANOVA. Contour plots (2D) and 3D response surface plots were developed between independent variables to find out their effect on the dependent variables/responses. The summary of model statistics of T30, DR6 and T90 are given in Table 6. The ANOVA of all the responses for nateglinide matrix tablets is summarized in Table 7.

Table 5 Response values of nateglinide matrix tablets

Tablet code	T30 (h) (Y_1)	DR6 (%) (Y_2)	T90 (h) (Y_3)
N1	2	59.55	10.5
N2	1.4	56.53	11
N3	1.5	61.8	10
N4	1.4	59.33	10.5
N5	1	64.95	10.1
N6	1.25	99.35	5.15
N7	2	50.11	10.1
N8	3.5	47.45	12.1
N9	1.4	78.9	8
N10	1.45	65.6	9
N11	1.5	61.8	10
N12	1.4	60.73	11.2
N13	4.0	48.53	13.45

Table 4 Drug release kinetics and mechanisms data of nateglinide matrix tablets

Tablet code	Zero order		First order		Higuchi R	Hixson-Crowell r	Peppas		Mechanism
	K_0 (%/time)	r	K_1 (hrs^{-1})	r			r	n	
N1	8.742	**0.9883**	0.095	0.9824	0.9917	0.9743	**0.9956**	0.6403	Non-Fickian
N2	7.2327	0.9853	0.068	**0.9906**	0.9903	0.9519	**0.9934**	0.5956	Non-Fickian
N3	7.8387	0.987	0.0811	**0.9914**	0.9957	0.9726	**0.9932**	0.7387	Non-Fickian
N4	7.4758	**0.9869**	0.1013	0.9036	0.989	0.9696	**0.9933**	0.6194	Non-Fickian
N5	8.0152	**0.9910**	0.1152	0.9274	0.9922	0.9837	**0.9964**	0.7595	Non-Fickian
N6	16.06	**0.9870**	0.142	0.9748	0.9832	0.9531	**0.9923**	0.793	Non-Fickian
N7	7.123	**0.9856**	0.0742	0.9797	0.9801	**0.9888**	0.9821	0.669	Erosion
N8	6.6211	**0.9915**	0.0604	0.9783	0.9825	**0.9841**	0.9876	0.7152	Erosion
N9	10.669	**0.9808**	0.1634	0.9346	0.9989	0.9874	**0.9812**	0.7945	Non-Fickian
N10	9.5657	**0.9919**	0.1056	0.9583	0.9884	0.9598	**0.996**	0.6851	Non-Fickian
N11	8.737	**0.9924**	0.09429	0.9714	0.9928	0.9624	**0.9961**	0.7603	Non-Fickian
N12	7.2997	0.9783	0.0847	**0.9873**	0.997	**0.9971**	0.9836	0.6885	Erosion
N13	6.5845	**0.9887**	0.0724	0.9843	0.9859	**0.9946**	0.9921	0.7513	Erosion

The bold format describes release kinetics and mechanism of respective formulation

Table 6 Summary of model statistics of T30, DR6 and T90 of nateglinide matrix tablets

Model	Sum of squares	Degree of freedom	Mean square	R^2	Adjusted R^2	Predicted R^2	PRESS	SD	F-value	p-value Prob > F	Remark
Response 1 (Time required to release 30 % of drug, T30)											
Linear	3.78	6	0.63	0.557	0.4684	0.1501	8.23	0.65	4.92	0.0725	
Interactive	2.15	5	0.43	0.7249	0.6331	0.3677	6.12	0.54	3.36	0.1317	
Quadratic	0.35	3	0.12	0.9105	0.8466	0.657	3.32	0.35	0.92	0.5064	Suggested
Response 2 (% drug release at 6th hour, DR6)											
Linear	829.53	6	138.25	0.6181	0.5418	0.1864	1851.66	9.32	14	0.0117	Suggested
Interactive	811.89	5	162.38	0.6259	0.5012	−0.2006	2732.34	9.73	16.44	0.009	
Quadratic	637.9	3	212.63	0.7024	0.4897	−1.0203	4597.87	9.84	21.53	0.0063	
Response 3 (Time required to release 90 % of drug, T90)											
Linear	17.56	6	2.93	0.6188	0.5425	0.1843	38.91	1.35	18.64	0.0068	Suggested
Interactive	17.17	5	3.43	0.627	0.5026	−0.0542	50.29	1.41	21.87	0.0053	
Quadratic	10.37	3	3.46	0.7694	0.6047	−0.5668	74.74	1.25	22.02	0.006	

The responses follows those models which were underlined

Table 7 Summary of ANOVA for the responses T30, DR6 and T90

Parameter	Sum of squares	df	Mean squares	F value	p value Prob > F	Remark
T30 (Quadratic model)						
Model	8.82	5	1.76	14.24	0.0015	Significant
Lack of fit	0.35	3	0.12	0.92	0.5064	Not significant
Pure error	0.51	4	0.13			
DR6 (Linear model)						
Model	1406.8	2	703.4	8.09	0.0081	Significant
Residual	869.03	10	86.9			
Lack of fit	829.53	6	138.25	14	0.0117	Significant
Pure error	39.5	4	9.88			
T90 (Linear model)						
Model	29.52	2	14.76	8.12	0.0081	Significant
Residual	18.19	10	1.82			
Lack of fit	17.56	6	2.93	18.64	0.0068	Significant
Pure error	0.63	4	0.16			

df degree of freedom, *VIF* Variance inflation factor, *CI* Confidence interval

The effect of independent variables of nateglinide matrix tablets such as Kollidon SR (X_1) and PVP K 30 (X_2) on responses T30, DR6 and T90 were found effectively by generating contour (2D) plots. Similarly 3D response surface plots were developed to find out the role of independent variables on dependent variables. 2D contour plots and 3D response surface plots are shown in Figs. 1 and 2. From the contour plots it was observed that Kollidon SR and PVP K 30 have distant effect on drug release rate. It was found that decrease in percentage drug release rate was observed with increase in Kollidon SR (X_1) and PVP K 30 concentration (X_2). This may be due to a synergistic effect of both polymer and binder on each other as well as the concentration range of polymer was increased, this leads to decrease in the drug release rate.

It was also observed that decrease in the concentrations below 15 mg of Kollidon SR and 7 mg of PVP K 30, the time required to release the desired quantity of the drug was decreased. Thus the time required to release 30 %, % drug release at 6th hour and 90 % of the drug release from matrices was decreased with decrease in both Kollidon SR and PVP K 30 concentrations.

It was found that from the above results the concentration of Kollidon SR and PVP K 30 has considerable effect on drug release rate and it caused the alteration in time required to release desirable quantity of the drug from matrix tablets.

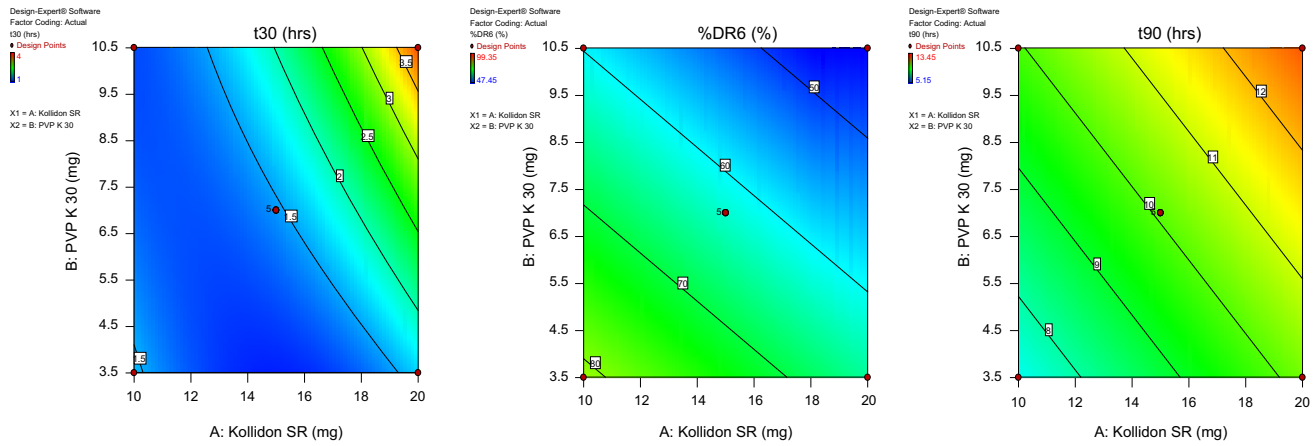

Fig. 1 Contour plot showing the influence of Kollidon SR (X_1) and PVP K 30 (X_2) on T30, DR6 & T90

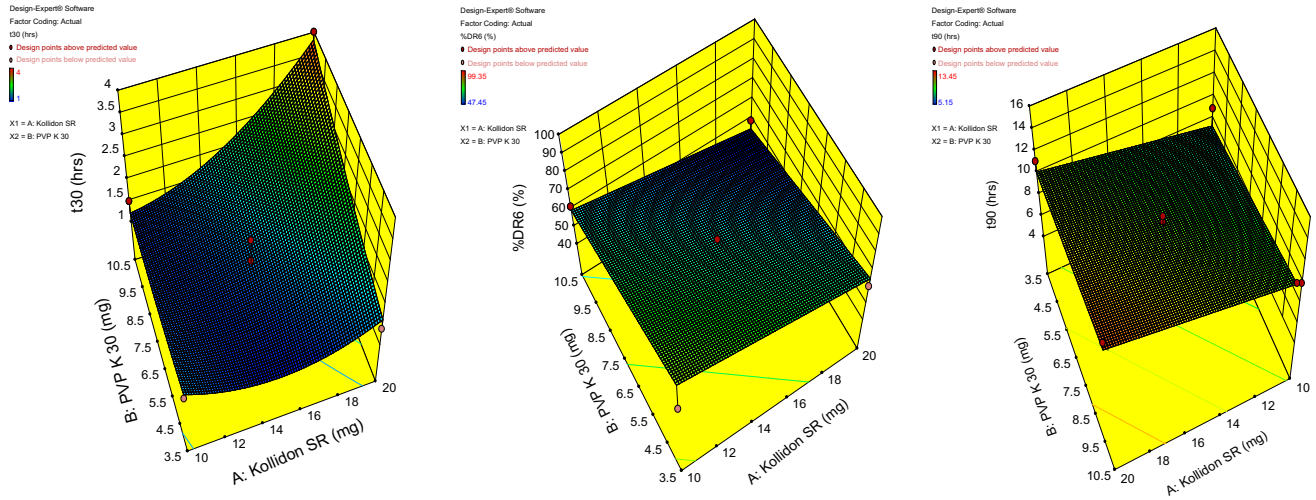

Fig. 2 Response surface plot showing the influence of Kollidon SR (X_1) and PVP K 30 (X_2) on T30, DR6 & T90

The in vitro data was subjected to statistical analysis using Design Expert Software with the constraints. The data analysis suggested quadratic model for response Y_1 (T30) and linear models for the other two responses Y_2 (DR6) and Y_3 (T90).

The Prob >F values of T30, DR6 and T90 were 0.0015, 0.0081 and 0.0081 respectively, and all the Prob >F values were found to be <0.0500 indicated that the responses are significant. The goodness of the fit was checked by coefficient of determination (R^2). The coefficient of determination (R^2) values of the responses Y_1, Y_2 and Y_3 were 0.9105, 0.6181 and 0.6188 respectively. The difference between predicted and adjusted R^2 values for response Y_1 was less than 0.2. However for the responses $Y_2$and Y_3 more difference was observed (approximately 0.35–0.36). Hence the optimization was done based on overall mean of the responses as per Design Expert software. When the signal to noise ratio was greater than 4 adequate precision values of responses will be considered to be desirable for navigating the design space. In the present study it was found that all the adequate precision values of the responses Y_1, Y_2 and Y_3 were found to be 11.9, 8.3 and 8.4 respectively and hence considered desirable and used for navigating the design space. The variance inflation factor (VIF) values for all the models were found to be one, indicating good estimation of coefficient.

The application of the RSM yielded the polynomial regression equations which are as follows

$$T30 = +1.46 + 0.68 \times A + 0.46 \times B + 0.64 \times AB + 0.51 \times A^2 + 0.095B^2$$

$$PD6 = +62.66 - 7.83 \times A - 10.70 \times B$$

$$T90 = +10.08 + 1.43 \times A + 1.28 \times B.$$

Optimization

The optimization was done by multiple criteria approach using numerical optimization technique by desirability

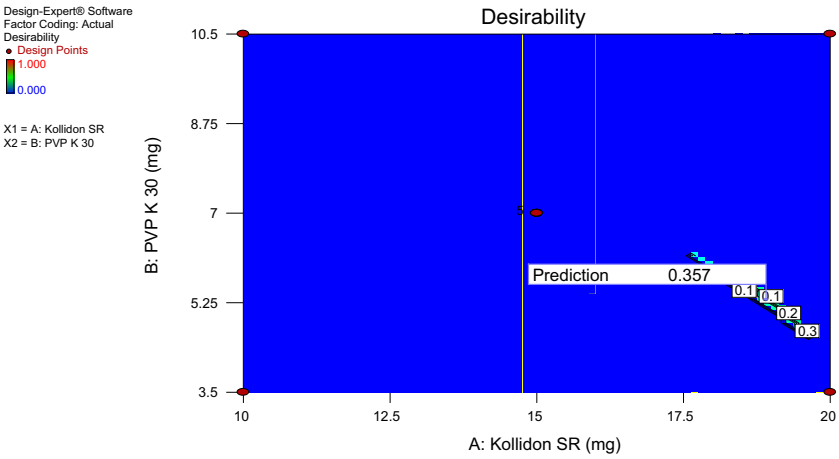

Fig. 3 Desirability plot for nateglinide matrix tablets

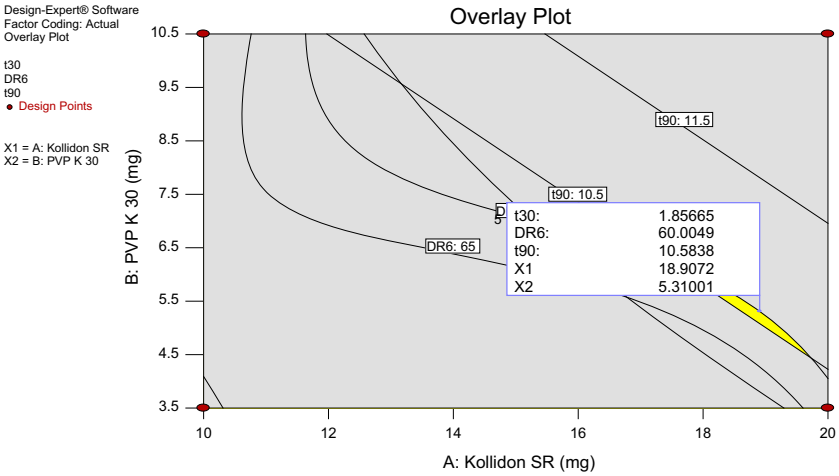

Fig. 4 Overlay plot for nateglinide matrix tablets

function and graphical optimization technique using overlay plots. The respective plots are shown in Figs. 3 and 4. The optimized formula was selected based up on highest desirability value. The recommended concentrations of the independent variables were calculated using Design Expert Software based up on response surface plots and overlay plots.

The optimized formulations of nateglinide matrix tablets contained 18.9 mg of Kollidon SR and 5.31 mg of PVP K 30.

Preparation, evaluation and cross validation of optimized formulation

The statistical optimized nateglinide matrix tablets were prepared and further denoted as N14. The prepared matrix tablets were evaluated for the in vitro drug release studies as described in the earlier sections. The dissolution data of optimized formulation comparison with theoretical profile is mentioned in Table 8.

The results from in vitro dissolution release studies revealed that the dissolution profile of statistically optimized nateglinide matrix tablet f_1 value was 5.21 and f_2 value was 56.18. The f_1 and f_2 values of statistically optimized simvastatin matrix tablet were 2.79 and 74.31 respectively. From the above results it was observed that the f_1 and f_2 values of the matrix tablet was below 15 and above 50 respectively indicated similarities between the optimized formulation and theoretical release profiles.

The predicted responses for the optimized model for nateglinide matrix tablets were found to be 1.85 h, 60 % drug release and 10.5 h for T30, DR6 and T90 respectively. The observed responses for nateglinide were found to be 1.9 h, 60.08 % and 10 h. The % relative error between observed and predicted responses was found to be less than 5 indicating the fitness of the model.

The dissolution data was analyzed for drug release kinetics and drug release mechanism. The statistical optimized nateglinide matrix tablet followed zero order release kinetics and non-Fickian process as drug release mechanism.

Table 8 Cumulative % drug released from optimized nateglinide matrix tablet

N14	Cumulative % drug dissolved	Theoretical release profile (%)
0.5	12.97 ± 0.98	–
1	20.47 ± 1.28	20
2	31.78 ± 1.47	40 ± 5
3	38.47 ± 0.85	46
4	44.46 ± 1.56	52
5	51.78 ± 1.98	58
6	60.08 ± 1.34	64
7	68.44 ± 2.36	70
8	76.77 ± 1.28	76
10	89.96 ± 1.22	88
11	94.25 ± 0.78	94
12	99.47 ± 0.98	100

Drug – polymer interaction studies

FTIR studies

Fourier transform infrared spectroscopy analysis was performed to pure drug, physical mixture and statistically optimized formulation and presented in Fig. 5. The FTIR spectrum of nateglinide shown 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 CH_3 –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 Kollidon SR and statistically optimized

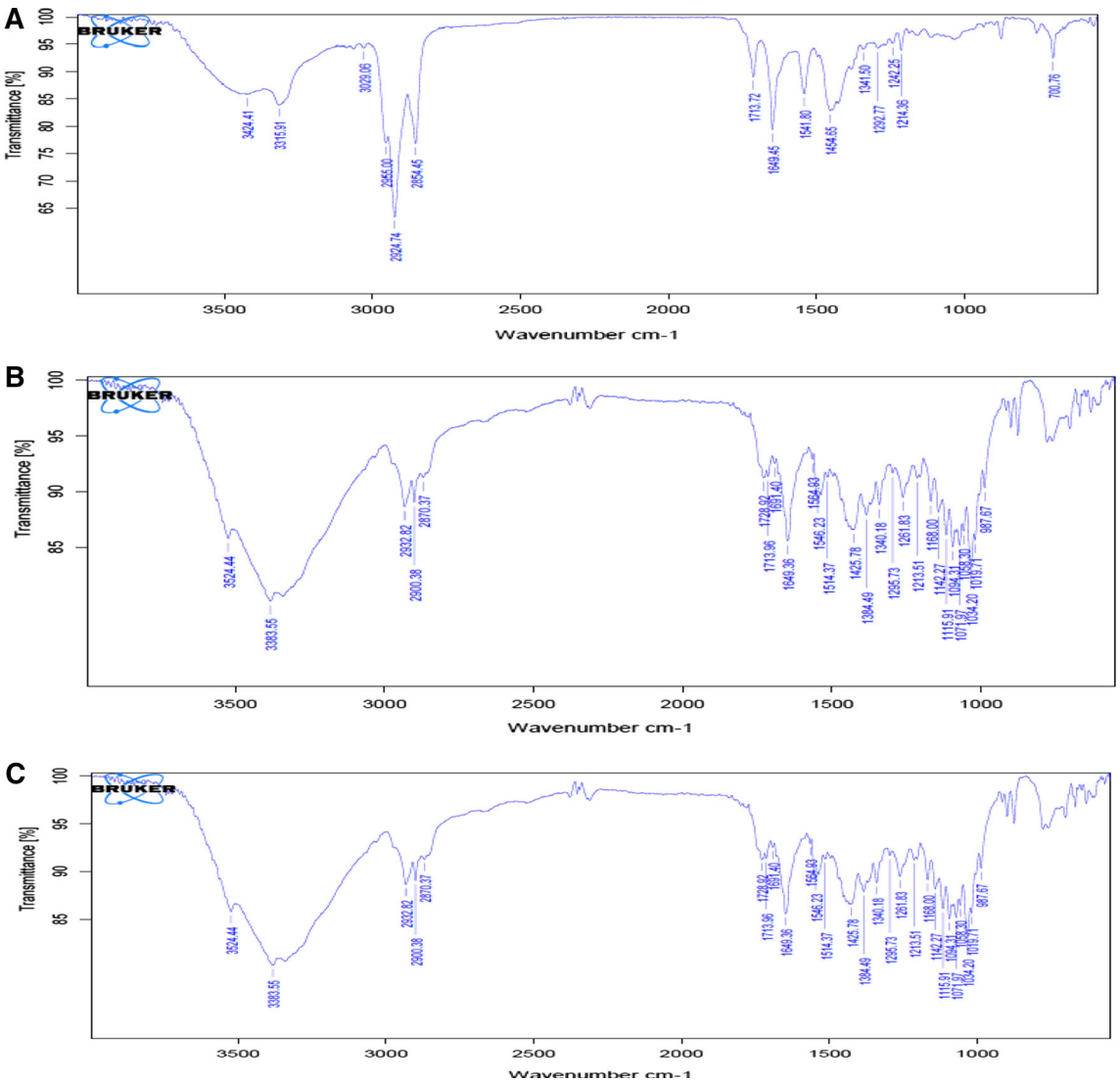

Fig. 5 FTIR spectra of **a** Nateglinide **b** Nateglinide + Kollidon SR physical mixture **c** Statistically optimized tablet (N14)

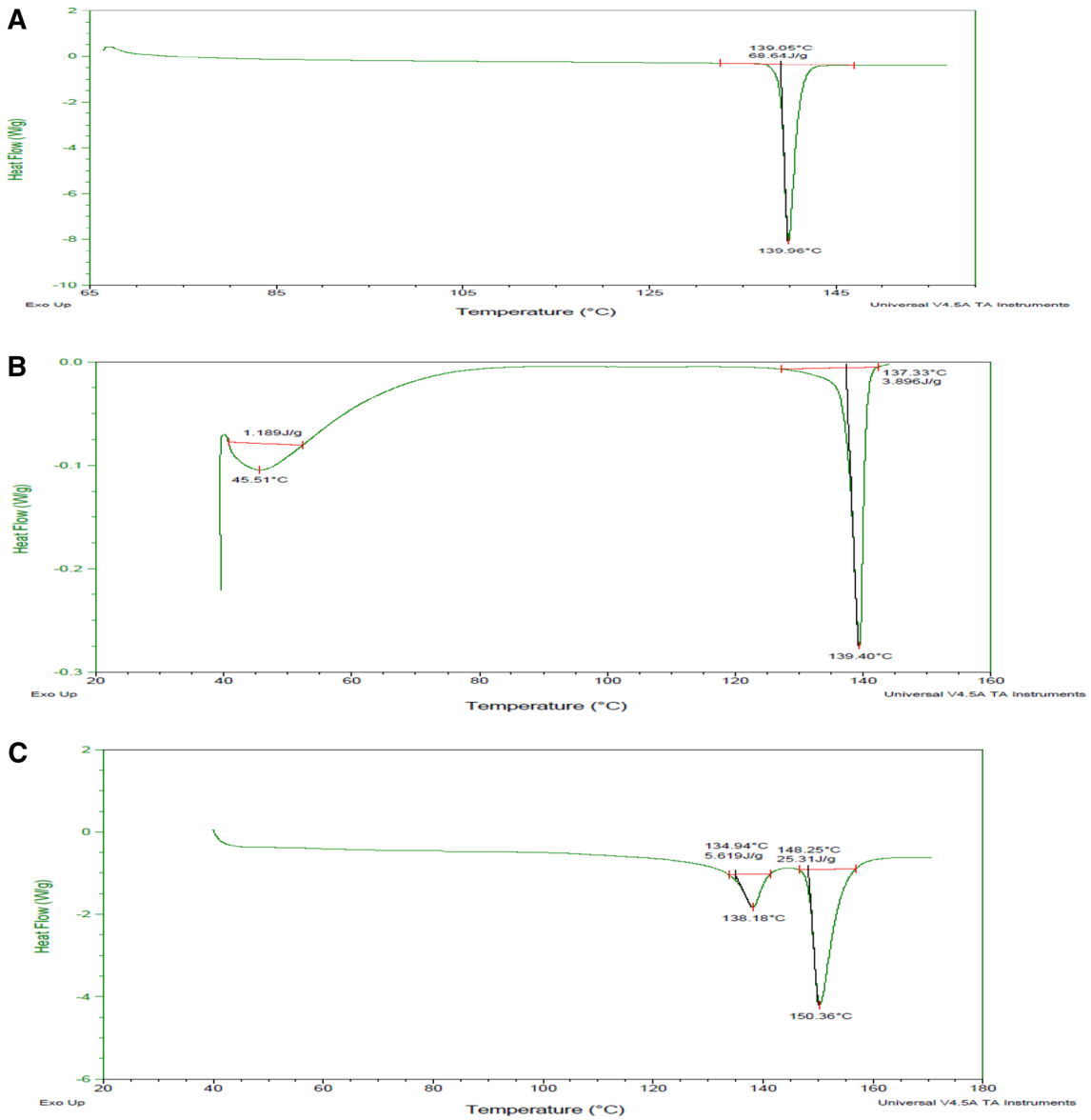

Fig. 6 DSC thermograms of **a** Nateglinide **b** Nateglinide + Kollidon SR physical mixture **c** Statistically optimized product (N14)

product with minor shifts. From the FTIR data it concluded that there were no considerable changes even after development of tablet with references to the respective spectrums.

DSC analysis

The DSC thermograms are presented in Fig. 6. The sharp peak obtained at 139.96° C corresponding to melting point of pure nateglinide. The sharp peak was evident that there was no moisture present in the pure drug. In physical mixture of nateglinide and Kollidon SR thermogram the broad peak obtained at 45.51° C represented the melting point of Kollidon SR, the broad peak indicated that there was a negligible quantity of moisture present in the polymer and another peak obtained at 139.96 °C represented nateglinide melting point, from the results of DSC thermogram of physical mixture it was observed that there was no change in the melting point of nateglinide suggested compatibility between drug and polymer. The thermograms obtained at 138.18 °C and 150.36 °C represented the melting points of nateglinide and lactose in developed formulation (Tablet). Due to very less quantity of polymer in comparison with drug (15 mg of polymer in 150 mg drug) the polymer peak was not observed even at 30 °C. In conclusion even after formulation development there was no change in drug melting point indicated that there was no change in the drug characteristics.

Table 9 Pharmacokinetic parameters (mean ± SD, n = 6) of nateglinide matrix tablet and nateglinide suspension

Parameters	SR	Drug suspension
C_{max} (ng mL^{-1})	131.20 ± 9.10	204.21 ± 6.50
t_{max} (h)	2	1
AUC_{0-12} (ng h mL^{-1})	466.8 ± 20.43	723.48 ± 25.82
$AUC_{0-\infty}$ (ng h mL^{-1})	515.09 ± 20.22	748.60 ± 28.02
$AUMC_{0-12}$ (ng h^2 mL^{-1})	1855.03 ± 158.68	2599.47 ± 114.91
$AUMC_{0-\infty}$ (ng h^2 mL^{-1})	2684.37 ± 218.29	2989.02 ± 135.24
K_a (h^{-1})	0.227 ± 0.03	0.295 ± 0.01
K_{el} (h^{-1})	0.175 ± 0.02	0.304 ± 0.02
$t_{1/2}$ (h)	3.99 ± 0.52	2.27 ± 0.14
$MRT_{0-\infty}$ (h)	5.24 ± 0.33	3.98 ± 0.04

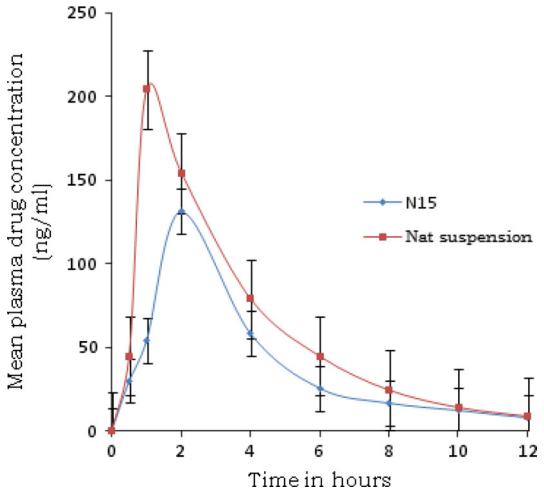

Fig. 7 Comparision of mean plasma concentration–time curves of matrix tablet and nateglinide suspension

Stability studies

No visible physical changes were observed after storage at different conditions. The average weight and drug content in all the formulations were found to be satisfactory and within the limits. No significant changes in the hardness, friability and weight variation were observed for nateglinide matrix tablets. There was no significant difference between the initial and after storage dissolution profiles indicating the stability of the tested nateglinide matrix tablets.

Pharmacokinetic evaluation in white albino rabbits

Due to very low concentration it was not possible to quantify the drug at 18th hour. The mean pharmacokinetic parameters of N15 and nateglinide suspension were estimated from the in vivo experiments and the results are shown in Table 9. A comparative mean plasma concentration–time curve of sustained and pure drug suspension is shown in Fig. 7.

It was observed from the above results that the peak plasma concentration values of N15 were lowered in comparison with that of nateglinide suspension. When compared to nateglinide suspension the T_{max} of N15 was high and which may be due to slow release of drug from matrix tablets (N15). The K_{el} values were calculated from the slope of the terminal portion of log plasma concentration versus time curve. From the $t_{1/2}$ values of the respective formulations it was observed that the half life of N15 was more than that of nateglinide suspension half life, this may be due to the sustained action of the drug in N15. The K_a values were obtained by the application of Wagner-Nelson method to the plasma concentration data. From the results of $MRT_{0-\infty}$ values of N15 and nateglinide suspension, $MRT_{0-\infty}$ for N15 was increased in comparison with suspension which indicated that N15 maintained effective plasma concentration for longer periods of time than nateglinide suspension. The % relative bioavailability of optimized formulation N15 was found to be 68.8 %. The possible reason could be the poor solubility of the drug in biological environment as well as sustained release of drug, whereas it was compared with suspension in which the drug is in powder form. The comparison could not be made with immediate release tablet as the dose administered to rabbits is low and no products are available in the market with that dose.

Conclusion

A trail has been made to prepare zero order sustained release nateglinide matrix tablets since it is not available in the market till date, to reduce dosage frequency and enhance patient compliance. Statistically optimization technique, i.e. CCD was used for the prediction of optimized concentrations of influenced variables on the product parameters. The statistically optimized formulation of nateglinide matrix tablets contained 18.9 mg of Kollidon SR and 5.31 mg of PVP K 30, the drug release from the statistically optimized product was sustained up to 12 h with zero order release kinetics and non-Fickian process as drug release mechanism. It was concluded from the observed results from pharmacokinetic studies that if the nateglinide matrix tablet bioavailability could be enhanced than nateglinide suspension, as the biological half life and mean residence time of nateglinide matrix tablet are higher than nateglinide suspension, it may be useful to diabetic patients for reduction in dosage frequency and over come from hypoglycemic state. Hence further studies on nateglinide matrix tablets are required to be performed for

investigating the possible causes for less bioavailability and solutions for the enhancement of the same.

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