Original Article

Nateglinide Modified Release Dosage Form Using Elementary Osmotic Pump and Push Pull Osmotic Pump Methods: Formulation and in-vivo evaluation

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Abstract

Objective: The aim was to develop osmotic tablets of nateglinide by two methods namely elementary osmotic pump (EOP) and push-pull osmotic pump (PPOP) method for controlled drug release.

Methods: The tablets were prepared by the wet granulation and were evaluated for various physicochemical parameters, in-vitro dissolution and in-vitro dissolution. The optimised formulation obtained in both methods was further characterised for FTIR, stability studies and pharmacokinetic studies.

Results: In EOP method coated tablet F14 showing highest drug release of 98.82%. In PPOP formulation FF14 was optimized with highest drug release of 99.97% and also its granules were having better flow property. Both F14 and FF14 were further characterized for FTIR, which showed no significant interaction and the accelerated studies indicated formulations were stable for 3months. The in-vivo studies in rabbits revealead Cmax of the optimised formulation (FF14) was 469.67±0.034 ng/ml, and the Cmax of the marketed product was 401.27±0.08 ng/ml. The Tmax of the formulation and the pure drug were 6.0±0.07 h and 1.5±0.04 h, respectively. The AUC0-infinity of the FF14 was higher ((2829.83±1.47 ng.h/ml) than the marketed suspension (1310.62±0.82 ng.h/ml). The AUC0-t of the FF14 formulation was significantly higher than that of the marketed product ($p<0.05$).

Conclusion: A better improvement in-vitro dissolution profile and bioavailability of the osmotic tablet of nateglinide was observed using PPOP method.

Keywords: Nateglinide, Hyperglycemia, Controlled release, Push-pull osmotic pump, In-vivo bioavailability studies.

INTRODUCTION

Various approaches are made in designing the formulations, which will overcome the disadvantages of the conventional dosage forms, which include sustained/controlled drug delivery system. Osmotic devices are the most promising strategy-based system for controlled drug delivery 1. Drug can be delivered in a controlled pattern over a long period of time by the process of osmosis. Surveys indicated that dosing more than once or twice daily greatly reduces patient compliance.

Hence, the primary objective of controlling drug release is to deliver a pharmacologically active agent in a predetermined, predictable and reproducible manner 2.

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Oral osmotically controlled release (OSCR) delivery system provides a uniform concentration/amount of drug at the site of absorption and thus after absorption, allow maintenance of plasma concentration within therapeutic range, which minimizes side effects and also reduces the frequency of administration 3. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system. Nateglinide is derivative of D-phenylalanine that stimulates insulin secretion by blocking ATP-sensitive K+ channels in pancreatic cells. It acts by reducing postprandial glycemic elevations in type 2 Diabetes Miletus (DM) patients. Nateglinide is FDA-approved for use in type 2 DM. Nateglinide is metabolized primarily by the liver and should be used cautiously in patients with hepatic insufficiency. Nateglinide was prescribing to patients with Type 2 diabetes over the dose range of 60-240 mg three times a day for one week which is a major limitation of this drug because of reduced patient compliance. Hence the present study was attempted to design a novel drug delivery system for Nateglinide to sustain its release and action for prolonged time 4.

MATERIALS AND METHODS

Nateglinide was gifted from Hetero drugs Ltd, Hyderabad. Cellulose acetate, microcrystalline cellulose (pH 101), talc and magnesium stearate, PEG 400, acetone, Mannitol were purchased from Gattefosse, Mumbai. Sodium chloride (NaCl), lactose, different grades of Polyethylene Oxide (PEO), cellulose acetate with a 39.8 % acetyl content, propyleneglycol (PG) and priethyl citrate (TEC) obtained from S.D. Fine-Chem Ltd. All the chemicals used were of analytical grade. Marketed product (Starlix 60 mg)

Preparation of Nateglinide tablets by elementary osmotic pump (EOP) method

Preparation of core tablets

Osmotic tablets were prepared by wet granulation method according to composition given in table 1. All the ingredients and drug were accurately weighted and mixed in mortar with a pestle for 10 minutes to get the uniform mix. The dry blend was granulated with sufficient quantity of PVP K30 which was dissolved in isopropyl alcohol. The powder mass was dried at 60 ºC in hot air oven for 5 h and pass-through sieve no. 20. The dried granules were mixed with magnesium stearate and talc for 3 min. The blended powder was then compressed by single station rotary tablet compression machine 5.

Table 1: Composition of core tablet

Ingredients	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**
Nateglinide	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Sodium chloride	100	110	120	130	140	150	160	0	0	0	0	0	0	0
Fructose	0	0	0	0	0	0	0	100	110	120	130	140	150	160
PVP K30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
MCC	200	190	180	170	160	150	140	200	190	180	170	160	150	140
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mg. stearate	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Total weight of core tablets	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Coating of tablets

Coating solutions[4%w/v] were prepared by mixing required quantity of cellulose acetate (semi-permeable membrane forming agent), PEG 400 (pore forming agent) and castor oil [20% v/w of total solid CA] (plasticizer) in acetone as specified in the table 2 and stirred on magnetic stirrer to get homogeneous coating solution. Then the tablets were coated using small size coating pan made up of stainless steel with rotation speed of 25 rpm and 55° C temperature of hot air. Then the tablets were kept in oven at 40° C for about 24 hours and weighed to calculate the percentage weight gain. The tablets were coated repeatedly until the required weight gain was achieved 5.

Table 2: Composition of coating solution

Ingredients	**Amount**
Ratio of CA: PEG400	75:25:00
Castor oil (ml)	0.15
Weight gain (%)	3
Total weight after coating (F1-F14)	**412**

Evaluation of core tablets

Physical properties

Average weight, hardness, thickness, friability was recorded as per the published reference procedure 6,7

%Drug content

The procedure followed as given in reference and the absorbance of the resulting solution was measured at 216nm using a UV-Visible double beam spectrophotometer 8.

In vitro drug release studies

The dissolution study of tablets was conducted using dissolution testing USP apparatus II (paddle method) in 900ml 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 24 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 analysed spectrophotometrically at □max of 216 nm using a UV-spectrophotometer.8

Stability studies

Prepared nateglinide coated 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 EOP tablets

FTIR

FT-IR spectra were recorded on samples in potassium bromide disks using shimadzu FTIR 8400S spectrophotometer and procedure followed as mentioned in reference. 9.

Preparation of nateglinide tablets by push pull osmotic pump (PPOP) method

Bilayered osmotic tablets of Nateglinide were prepared using conventional wet granulation technology. Drug and excipients as shown in table 3 were mixed together to produce tablets. The alcohol (Isopropyl alcohol) solution of PVP K 30 was added to produce a damp mass, which was passed through a # 16 sieve and dried in a hot air oven at 45° C for 30 minutes. The dried granules were then passed through a # 30 sieve and mixed with lubricants. Granules for the push compartment were prepared in a similar fashion and for identification a coloring agent (Iron oxide) was added to the push layer. The tablets were compressed at an average weight of 400 mg. The weight of the push compartment was adjusted to 40mg and the pull compartment weight was adjusted. Prepared granules were compressed as bilayer tablets using concave punches on rotary compression machine 10.

Table 3: Formulation table of core tablet

Ingredients	**PP1**	**PP2**	**PP3**	**PP4**	**PP5**	**PP6**	**PP7**	**PP8**	**PP9**	**PP10**	**PP11**	**PP12**	**PP13**	**PP14**
Drug Layer:														
Drug	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Lactose	110	110	110	80	80	90	90	90	80	80	80	70	70	70
PEO 200K	30	30	30	60	60	60	60	60	60	60	60	60	60	60
Nacl	0	0	0	0	0	0	0	0	10	10	10	20	20	20
PVP K30	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8

Mg. stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Push Layer:														
PEO 7000K	30	30	30	30	30	30	30	30	30	30	30	30	30	30
NaCl	0	0	0	0	0	20	40	60	20	40	60	20	40	60
Lactose	150	150	150	150	150	120	100	80	120	100	80	120	100	80
PVP K30	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Iron Oxide (red)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Mg. stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3
total weight	400	400	400	400	400	400	400	400	400	400	400	400	400	400

Coating of bilayer tablets

The tablets were coated with cellulose acetate (5%w/v) in dichloromethane:ethanol (90:10) along with a suitable plasticizer as shown in table 4. The coating process parameters were optimized as follows: Pan diameter-6 inch; spray gun (pilot scale); baffles- 4; speed of pan 30-35rpm; spraying rate10-15 ml/min; temperature-20-25° C. The coated tablets had smooth, uniform surfaces without any defects 10.

Table 4: Formulation table of coated tablet

Coating:														
Ingredients	**FF1**	**FF2**	**FF3**	**FF4**	**FF5**	**FF6**	**FF7**	**FF8**	**FF9**	**FF10**	**FF11**	**FF12**	**FF13**	**FF14**
Cellulose acetate	34	34	68	34	68	34	34	34	34	34	34	34	34	34
Propylene Glycol	6	0	0	0	0	0	0	0	0	0	0	0	0	0
TEC	0	6	12	6	12	6	6	6	6	6	6	6	6	6
Wt. Gain	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
total weight after coating	440	440	480	440	480	440	440	440	440	440	440	440	440	440

Drilling of bilayer tablets: The bilayer coated tablets were drilled by Cameron microdrill press

Evaluation of nateglinide PPOP tablets

Physical properties

Average weight, hardness, thickness, friability was recorded 6.

%Drug content

Drug content was determined as per the referred procedures mentioned in EOP method.

In vitro release of nateglinide PPOP tablets

In vitro drug release studies were carried out and recorded as per the referred procedures mentioned in EOP method.

Effect of plasticizer on drug release: In osmotic drug delivery system coating of semi permeable polymer is given

in order to control water entry in to the system. The water in flow can be modulated by different plasticizers. Hence to determine the effects of plasticizers on drug release formulations were made using water soluble (PG) and water insoluble (TEC) plasticizers.

Effect of pH of dissolution medium on drug release: An osmotically controlled release system delivers its contents independent of external variables. Hence to assess the effect of pH on the in vitro release profile, dissolution studies were carried out in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

Effect of agitation intensity: In order to assess the effect of the agitational intensity of the release media, the release studies of the optimized formulation were carried out in a dissolution rate test apparatus II at various rotational speeds. The paddle rotation speed was adjusted at rates of 50, 75and 100 rpm. The samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µm nylon membrane filters.

Characterization of nateglinide PPOP tablets

The optimized tablet formulation analyzed for FTIR as per the referred methods in EOP method.

Stability studies

Referred procedures mentioned under EOP method.

Pharmacokinetic studies

Pharmacokinetic studies of Nateglinide in rabbit plasma

Animal preparation

Eighteen Albino male rabbits were (weighing 2–3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25°C, RH 45%, and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. An in vivo pharmacokinetic study was conducted in accordance with the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee (IAEC NO : 1447/PO/Re/S/11/CPCSEA-59/A).11

Study Design

Rabbits were randomly divided into 3 groups (GROUP A, B and C) each group contains six animals. The Group A rabbits were fed with nateglinide optimized osmotic tablet formulation made into mini tablets with equivalent weight to rabbits dose with a Ryle's tube with a diameter of 4 mm, rabbits were given minitablets and Group B fed with marketed reference product (Starlix 60mg) triturated and diluted with Carboxymethylcellulose sodium (CMC-Na) with equivalent dose to animal body weight. 12. Group C was kept control for the study.

Blood sampling

Blood samples (approximately 0.5 ml) were obtained with syringes by marginal ear vein at regular intervals 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20, and 24 h post doses. During collection, blood sample has been mixed thoroughly with heparin to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5 min to 10 min and stored frozen at −20°C until analysis.

Determination of Nateglinide in Rabbit plasma by HPLC method 13

CHROMATOGRAPHIC CONDITIONS

A manual rheodyne injector with a 20-l fixed loop, an LC-20AT Prominence solvent delivery module, and an SPD-20A Prominence UV-visible detector made up a high-performance liquid chromatograph (Shimadzu, Kyoto, Japan). At room temperature, separation was carried out on a Phenomenex C18 column (paricle size 5m; 250 mm 4.6 mm i.d.; Phenomenex, Torrance, USA) after an ODS guard column (10 m; 10 mm 5 mm i.d.). A Spinchrom Chromatographic Station® CFR Version 2.4.0.195 (Spinchrom Pvt. Ltd., Chennai, India) was used to capture and process the chromatographic data.

With ACN:10 mM KH2PO4 buffer solution (PBS) (adjusted to pH 3.0 with H3PO4) (70:30, v/v) as the mobile phase, the analysis was isocratic at 1.0 ml/min flow rate. Every day, the mobile phase was freshly prepared. Before usage, the mobile phase was degassed by sonication after being premixed, filtered through a 0.2 m membrane filter to eliminate any particulate matter, and pre-filtered. In addition to being interference-free, the absorbance of Nateglinide (NTG) and Gliclazide (GLZ) as internal standard (IS) was higher at 203 nm than at the more popular 210 nm. The peaks that were eluted were therefore found at 203 nm.

The ideal absorption wavelength was chosen after doing a prior UV (190-280 nm) scanning. The detector's sensitivity was adjusted to 0.01 AUFS. The substance's peak area ratio of NTG to IS was used to calculate its weight. The column was equilibrated for at least 30 min with the mobile phase running through the system prior to injecting solutions. According to the NTG/IS peak area ratio, the relative standard deviation (R.S.D.) had to stay below 1.0% for each solution that was injected in triplicate.

Preparation of solutions

In methanol, 500 g/ml stock solutions of NTG and GLZ were created and kept there between 2 and 8 °C until needed.

To get 30 g/ml of NTG and GLZ, aliquots of these solutions were diluted incrementally with the mobile phase. The proposed method's optimization was carried out using this solution.

The appropriate aliquots of stock solutions were diluted with HPLC grade water to create the spiking solutions of NTG (8g/ml) and GLZ (8g/ml). To achieve NTG concentrations in the analytical range of 10 to 2500 (10, 25, 100, 250, 500, 1000, and 2500) ng/ml and GLZ concentrations of 2500 ng/ml for calibration curve, appropriate aliquots of the

spiking solutions were spiked to plasma.

The total chromatographic run time is 10.0 min with retention times for nateglinide and gliclazide at 5.48 min and 4.62 min respectively.

RESULT AND DISCUSSION

Physicochemical properties

The results for physical properties of core and coated tablets passed the test and were within the limits.

The drug content of all formulation is in between 97.21-99.34%, drug content with highest exhibited by F14 formulation. 14

In vitro dissolution study

Figure 1 shows that without coating (P1 - P14) none of the batch give controlled release and release of drug limited to 16 hr only which are not meeting the objectives and all the batches shows good and satisfactory release data and selected for the next step for coating them. In porous osmotic pump tablet the drug release rate is depends on the concentration of osmotic agent and pore former used. The osmotic agent concentration increases then osmotic pressure created inside the tablet also increase; the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug so the release of the drug also will increase 15. The pore former is added here in coating solution so, it will cause easy leaching out of the drug from the formulation. Here the mechanical drilling was done for orifice formation after drying of the coating layer. So here the dual concepts of EOP as well as micro porous were used in for release of the drug from tablets. Figure 2 (F1- F14) shows that all 14 batches are showing release up to 24hrs and in that F14 is optimized with (98.82%) release profile.

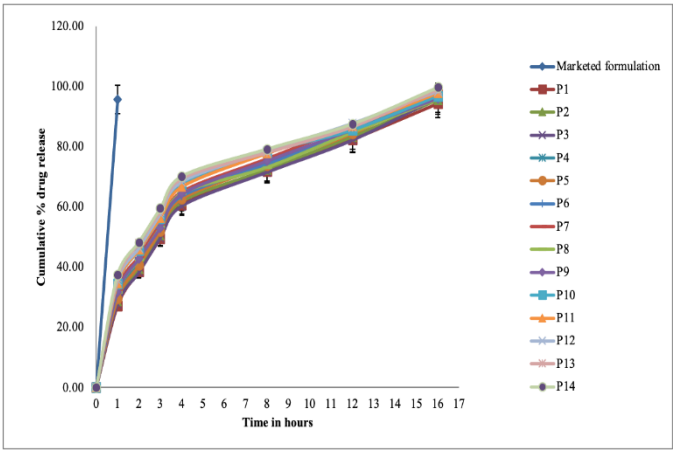

Figure 1: Cumulative percentage drug release of nateglinide marketed formulation and nateglinide EOP core tablets (P1-P14)

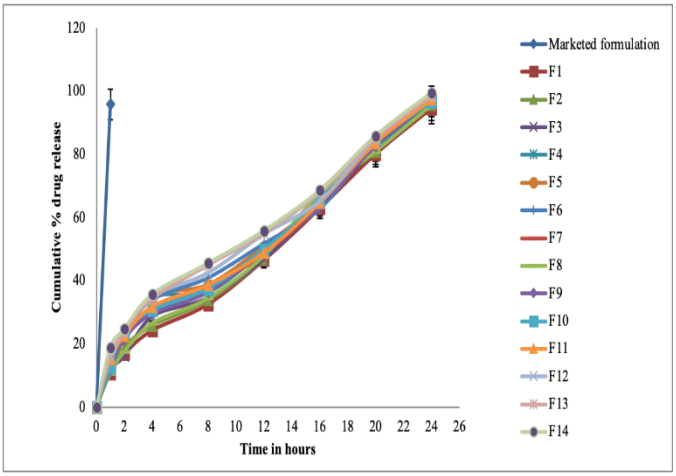

Figure 2: Cumulative percentage drug release of nateglinide marketed formulation and nateglinide EOP coated tablets (F1-F14)

Stability studies

Optimized formulation (F14) was subjected to stability study for 90 days at accelerated as per ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (F14) is stable with no variations in its physical properties (table 5).

Table 5: Stability studies of F14 stored at 40 ±20C /75±5% RH

Retest Time for Optimized formulation F14	**Drug content (%)**	***In-vitro* drug release profile (%)**	**Hardness (kg/cm^2)**
0 days	99.34±0.25	98.82±1.83	4.32±0.12
30 days	98.81±1.72	98.21±1.83	4.32±0.47
60 days	98.37±0.16	97.62±0.37	4.32±1.47
90 days	97.75±1.37	97.23±1.83	4.32±1.25

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

FTIR Studies

The FTIR spectra of pure nateglinide is taken into account it showed an absorption band at 2924.52 cm-1 (aliphatic C-H stretching; asymmetric), 2859.92 cm-1 (aliphatic CH stretching; symmetric), 1649.80 & 1713.44 cm-1 (C=O stretching for Ketone). Conformation of C-O stretching OH bending of carboxylic acid spectra was given by the band at 1240.97 cm-1 owing to hydrogen bonded O-H of COOH. The peak at 3299.61 cm-1 is attributed to secondary amide (-NH stretching). The absorption band at 1540.85 cm-1

corresponds to alkene C=C stretching bonds. The sharp band at 756.92 cm-1& 700.03 cm-1 indicates the mono-substituted benzene (Figure 3). The peaks of polymer PVP K30 at 2957.06 cm-1 -CH3 stretch, at 1290.14 cm-1and 1223.1 cm-1 corresponding to -C-H bend, at 737.78 cm-1 N-H bend also appeared in optimised formulation indicating no interaction between drug and excipients.

The FTIR spectrum of nateglinide with excipients showed all the peaks for nateglinide suggesting no significant interaction observed between them (Figure 4).

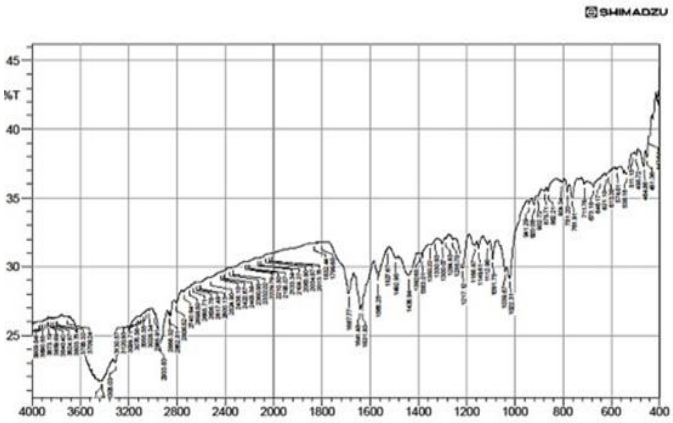

Figure 3: FTIR Spectra of pure drug

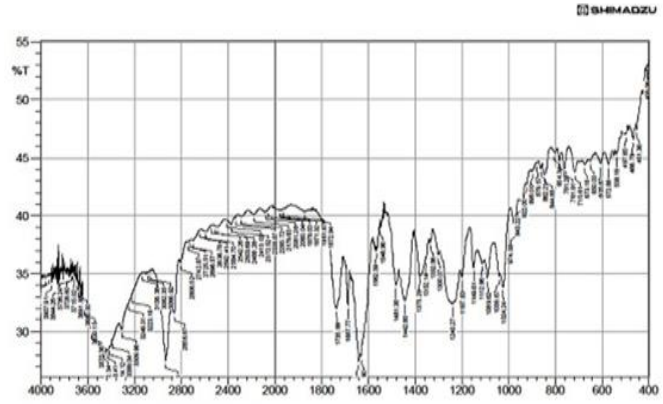

Figure 4: FTIR Spectra of nateglinide optimized formulation (F14)

Results of nateglinide PPOP tablets

Physicochemical properties

The hardness, friability, weight variation, uniformity of content of prepared coated tablet is recorded and found to be satisfactory.

The drug content of all formulation is in between 94.9-99.61%, drug content with highest exhibited by FF14 formulation.

In-vitro drug release: The effect of plasticizer, effect of drug layer to coating weight gain and osmogen on drug release (figure 5) is studies as follows:

Effect of type of plasticizer on Drug Release: Initial batches (FF1 and FF2) were prepared using different plasticizers. The core tablet formulation was kept constant and the plasticizer was optimized to provide zero-order drug release kinetics for extended period of time. The formulation containing PG released drug quickly and more than 80% of drug was released in 16 hours. In case of TEC drug release was consistent and it was able to prolong drug release up to 24 hours.

Effect of drug layer polymer and coating wt. gain on drug release: Formulations FF2, FF3, FF4 and FF5 were formulated with different ratios of Drug: PEO WSR N80 (1:0.5 and 1:1) and coating wt. gain (10% and 20%). The formulations with 20% wt. gain were unable to release more than 75% of drug in 24 hours 16.

Formulation FF4 (10% wt. gain and 1:1 ratio of Drug: PEO WSR N80) released more than 80% of drug in 24 hours with regression coefficient (zero order) of 0.98. So, it was used for further optimization.

Effect of Osmogen on drug release: Formulations FF6 to FF14 were formulated with different ratios of Sodium chloride in both layers. Formulations FF6, FF7 and FF8 contains osmogen only in push layer at the level of 10%, 20% and 30% weight of push layer respectively. In formulations FF9-FF14 Sodium chloride is present in both layers in different ratios. From all batch's formulations FF10, FF11, FF13 and FF14 were able to control the drug release for up to 24 hours. Formulation FF14 was optimized because its granules were having better flow property.

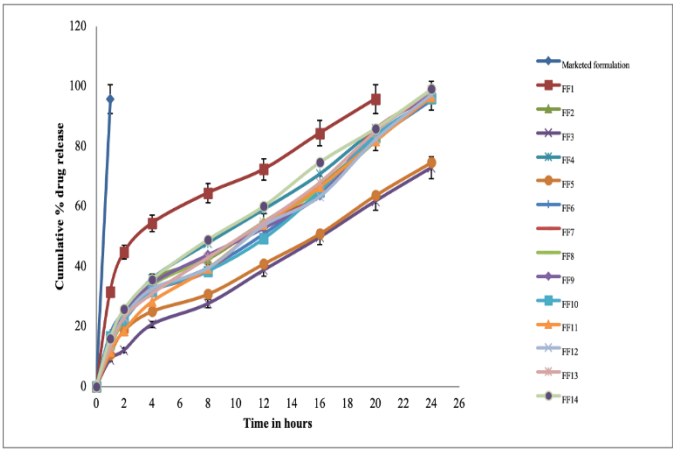

Figure 5: Cumulative percentage drug release of nateglinide marketed formulation and nateglinide PPOP tablets (FF1-FF14)

Characterization of PPOP optimized formulation FF14

Effect of pH: When formulation FF14 was subjected to in vitro release studies in buffers of differing pH and in distilled water, no significant difference in release profiles was observed. In other words, the developed push-pull osmotic tablet was found to exhibit pH independent release kinetics (figure 6).

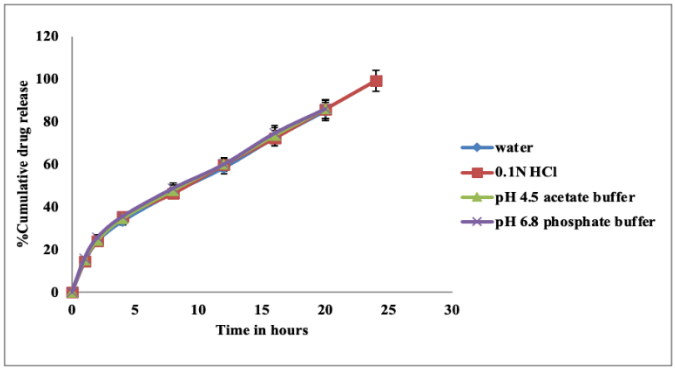

Figure 6: Effect of pH on PPOP optimized formulation FF14

Effect of agitation Intensity: The effect of different agitation rate on formulation FF14 was also studied at 50, 75 and 100 rpm. There was no significant change in the drug release rate was observed. Hence, it can be concluded that the release rate of push-pull osmotic tablet was independent of agitational intensity (figure 7).

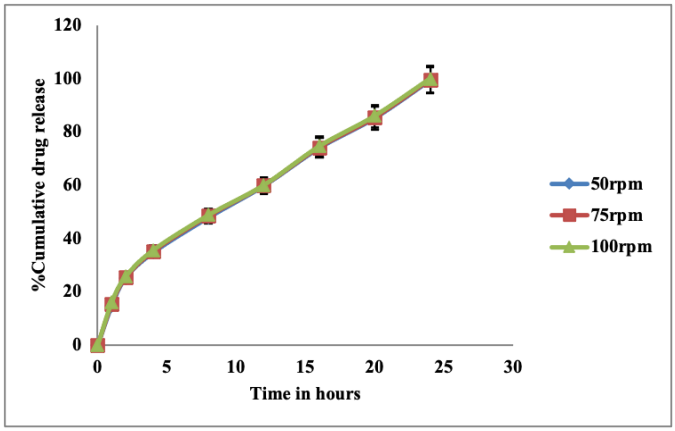

Figure 7: Effect of agitation intensity on PPOP optimized formulation FF14

FTIR studies

The FTIR spectra of pure nateglinide referred under EOP method (fig 3). The FTIR spectrum of nateglinide with PVP K30 and NaCl showed all the peaks for nateglinide suggesting no significant interaction observed between them (Figure 8).

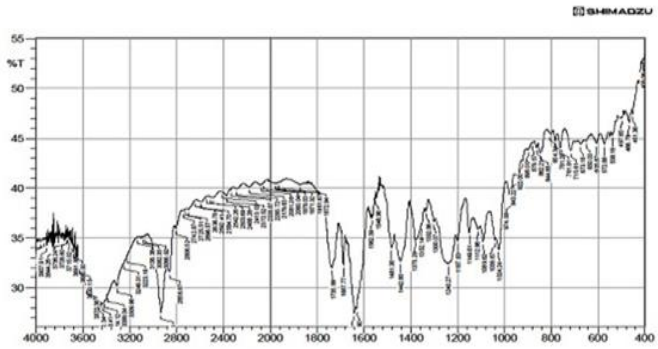

Figure 8: FTIR Spectra of nateglinide optimized formulation (FF14)

Stability studies

Optimized formulation (FF14) was subjected to stability study for 90 days at accelerated as per ICH guidelines. The optimized formulation was stable during 3 months period. Results indicate that optimized formulation (FF14) is stable with no variations in its physical properties (table 6).

Table 6: Stability studies of FF14 stored at 40 ±20C /75±5% RH

Retest Time for Optimized formulation F14	**Drug content (%)**	***In-vitro* drug release profile (%)**	**Hardness (kg/cm^2)**
0 days	99.61±0.36	99.97±1.87	4.3±0.49
30 days	98.92±0.58	99.51±1.57	4.31±0.25
60 days	98.51±0.42	99.12±0.25	4.31±0.69
90 days	98.10±1.48	98.86±1.57	4.31±0.14

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

Pharmacokinetic data of Nateglinide marketed reference and nateglinide osmotic tablet FF14

Nateglinide concentrations in plasma following oral administration of nateglinide marketed reference and optimized nateglinide osmotic tablet administered oral route are given in Table 7 and respective plasma concentration-time curves are shown in Figure 9.

Cmax of the osmotic tablet 401.27±0.08 ng/ml was significant ($p<0.05$) as compared to the nateglinide marketed reference formulation 469.67±0.034 ng/ml. Tmax

of both osmotic tablet formulation and nateglinide marketed reference was 6.0±0.07 h and 1.5±0.04 h, respectively. AUC0-∞ infinity for osmotic tablet formulation was higher (2829.83±1.47ng. h/ml) than the nateglinide marketed reference formulation 1310.62±0.82 ng.h/ml. Statistically, AUC0-t of the osmotic tablet formulation was significantly higher ($p<0.05$) as compared to nateglinide marketed reference formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Nateglinide from osmotic tablet formulation when compared to the nateglinide marketed reference and also in vivo pharmacokinetic studies in rabbits confirmed the prolonged release by showing increase in bioavailability for Nateglinide from osmotic tablet formulation as compared to the nateglinide marketed reference formulation.

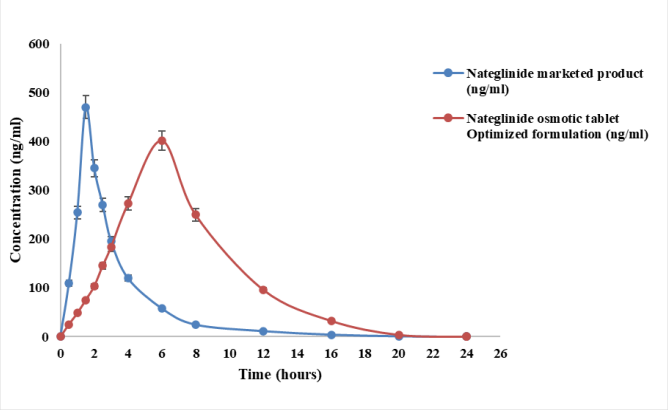

Figure 9: Plasma concentration profiles of Nateglinide osmotic tablet and marketed reference in rabbit plasma

Table 7: Pharmacokinetic Parameters of Nateglinide osmotic tablet formulation and marketed reference in rabbit plasma

Pharmacokinetic parameters	Nateglinide marketed reference	Nateglinide–osmotic tablet Optimized Formulation
C_{max} (ng/ml)	469.67±0.034	401.27±0.08
AUC_{0-t} (ng. h/ml)	1282.3±2.06	2702.4±1.36
AUC_{0-inf} (ng. h/ml)	1310.62±0.82	2829.83±1.47
T_{max} (h)	1.5±0.04	6.0±0.07
$t_{1/2}$ (h)	2.21±0.05	6.23±0.06

Conclusion

In the current research work, elementary osmotic and push pull osmotic tablets were prepared for Nateglinide which is used for the treatment of hyperglycemia (type 2 diabetes). Evaluation studies were performed namely weight variation, hardness test, friability, drug content and dissolution. All the results were found to be within the limit. The dissolution results showed that the release profile was sustained for a period of 24h with F14 showing 98.82% prepared by EOP method and FF14 showing 99.97% prepared by PPOP method which were best optimized formulations. The excipients used in the study did not alter any physicochemical properties of the drug as examined by FTIR. The selected formulation which was subjected to accelerated stability studies at Rh 75% ± 5% and 40 ºC ± 2 ºC for three months was found to be stable. The optimised osmotic tablet formulation (FF14) had a Cmax of 401.27 ng/ml while the commercial version had a Cmax of 469.67 ng/ml. Tmax was 6.0 and 1.5 hours for the FF14 and marketed, respectively. FF14 had a greater AUC0- ∞ than commercial suspension. The AUC0-t of the osmotic tablet formulation was statistically higher than the AUC0-t of the marketed products. Compared to the marketed product, higher drug concentrations in the blood showed enhanced systemic absorption of nateglinide.

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