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DEVELOPMENT OF NATEGLINIDE MODIFIED RELEASE DOSAGE FORM USING ELEMENTARY OSMOTIC PUMP (EOP) AND PUSH-PULL OSMOTIC PUMP (PPOP) METHODS

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Keywords:

Nateglinide, Hyperglycemia, Controlled release, Elementary osmotic pump, Push-pull osmotic pump

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ABSTRACT: Objective: The aim of the study 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:** Initially, pre-compression parameters were studies for the tablet blend in both EOP and PPOP methods. The tablets were prepared by the wet granulation method in both methods. The prepared tablets were evaluated for various physicochemical parameters, *in-vitro* dissolution, and the dissolution data were fitted into kinetic models for knowing the mechanism of drug delivery. The optimized formulation obtained in both methods was further characterized for FTIR and stability studies. **Results**: In EOP method, P1-P14 formulations prepared before coating exhibited 16h drug release, and after coating (F1-F14) all the formulations exhibited 24h prolonged drug release, with F14 showing the highest drug release of 98.82%. In PPOP method, *in-vitro* drug release depended on the effect of plasticizer, effect of drug layer to coating weight gain, and osmogen concentration. Finally, formulation FF14 was optimized with the highest drug release of 99.97%, and also its granules had better flow property. F14 and FF14 were the optimized formulations from EOP and PPOP methods. Both were further characterized for FTIR, which showed no significant interaction and the accelerated studies indicated formulations were stable with no variations in hardness, drug content, and drug release for 3 months. **Conclusion:** To conclude, the EOP and PPOP osmotic tablet of Nateglinide was able to deliver the drug in a controlled pattern for a prolonged period of time.

INTRODUCTION: Various approaches are made in designing the formulations, which will overcome the disadvantages of the conventional dosage forms, which include a sustained/controlled drug delivery system. Osmotic devices are the most promising strategy-based system for controlled drug delivery [1]. The drug can be delivered in a controlled pattern over a long period of time by the process of osmosis.

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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].

The oral osmotically controlled release (OSCR) delivery system provides a uniform concentration/ amount of drug at the absorption site. Thus, after absorption, allows maintenance of plasma concentration within the therapeutic range, which minimizes side effects and reduces the frequency of administration [3]. Drug release from these systems is independent of pH and other physiological parameters to a large extent. It is possible to

modulate the release characteristics by optimizing the properties of the drug and system. Nateglinide is a 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 a 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, propylene-glycol (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 the wet granulation method according to the composition given in **Table 1**. All the ingredients and drugs were accurately weighed and mixed in a mortar with a pestle for 10 minutes to get the uniform mix. The dry blend was granulated with a sufficient quantity of PVP K30, which was dissolved in isopropyl alcohol. The powder mass was dried at 60 ºC in a 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 a 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

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

Coating of Tablets: Coating solutions [4%w/v] were prepared by mixing the 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 **Table 2** and stirred on magnetic stirrer to get homogeneous coating solution. Then the tablets were coated using a 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 of weight gain. The tablets were coated repeatedly until the required weight gain was achieved [5].

Evaluation of Core Tablets:

Micromeritic Properties: The lubricated blend was evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio as per the procedure given in reference to article [6].

Physical Properties: Average weight, hardness, thickness, friability were recorded as per the published reference procedure [8, 9].

% Drug Content: The procedure followed as given in reference and the absorbance of the

resulting solution was measured at 216 nm using a UV-Visible double beam spectrophotometer [10].

***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 a 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. A 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 spectro-photometrically at λ_{max} of 216 nm using a UV-spectrophotometer [10].

Kinetic Model Fitting: To elucidate the mode and mechanism of drug release, the data from the invitro release study were fitted into various kinetic models such as zero-order, first-order, Higuchi's, and Korsmeyer-Peppas model [11, 12].

Stability Studies: Prepared nateglinide coated tablets were placed under a controlled temperature environment inside stability chamber (Thermo Lab, India) with a 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 [13].

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 [14].

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; the speed of pan 30-35rpm; spraying rate 10-15 ml/min; temperature- 20-25°C. The coated tablets had smooth, uniform surfaces without any defects [15].

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:

Pre-compression Parameters:

Micromeritic Properties: Weight variation, hardness, thickness, friability was recorded as per the referred procedures mentioned in EOP method.

Physical Properties: Average weight, hardness, thickness, friability was recorded [8].

%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 an osmotic drug delivery system, a coating of semi-permeable polymer is given in order to control water entry into the system. The water inflow can be modulated by different plasticizers. Hence, to determine the effects of plasticizers on drug release formulations, water-soluble (PG) and water-insoluble (TEC) plasticizers were made.

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: 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, 75, and 100 rpm. The samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µm nylon membrane filters.

Drug Release Kinetics of Nateglinide PPOP Tablets: Referred procedures mentioned under the EOP method.

Characterization of Nateglinide PPOP Tablets: The optimized tablet formulation was analyzed for FTIR as per the referred methods in the EOP method.

Stability Studies: Referred procedures mentioned under EOP method.

RESULTS AND DISCUSSION:

Micromeritic Properties of Nateglinide Granules for EOP Tablets: Granules prepared for compression of nateglinide EOP tablets were evaluated for their flow properties.

The bulk densities of all the formulations P1 to P14 were measured, and they are ranged from 0.46± 0.56g/cc³ to 0.53±0.62g/cc³.

The tapped density of all the formulations P1 to P14 was measured, and they are ranged from 0.48±0.96g/cc³ to 0.56±0.42 g/cc³.

The angle of repose of all the formulations was found to be good. The formulation P14 was found to be 25.82±0.80, having excellent flow property.

The compressibility index values were found to be in the range of 6 to 15%, and carrs index values ranged between 1.11±0.41 to 1.16±0.39. These findings indicated that all the batches of formulations exhibited good flow properties.

Physicochemical Properties: The value of hardness, weight variation of the prepared core

tablet is recorded. The hardness, friability, weight variation, uniformity of content of the prepared coated tablet is recorded. Here tablets before coating were coded as P1-P14. These same tablets were after coating coded as F1-F14. This different coding is given to differentiate the evaluation tests done in two different steps.

The results for weighing variation of core tablets passed the test and were within limits.

The weight variation of all the coated formulations is within limits; adequate tablet hardness is a necessary requisite for consumer acceptance and handling.

The measured hardness of the tablets of each batch of all formulations, *i.e.*, F1 to F14 was ranged between 4.4 to 4.9Kg/cm^2.

The thickness of the tablets was found to be almost uniform in all formulations F1 to F14.

The thickness of all the formulations ranged between 4.3-4.9 mm.

The friability of all prepared formulations between 0.15-0.21. the friability properties limits are between 0-1%.

The drug content of all formulation is between 97.21-99.34%, drug content with highest exhibited by F14 formulation and depends on the angle of repose because 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.

***In-vitro* Dissolution Study: Table 8** and **Fig. 1** shows that without coating (P1 - P14) none of the batches give controlled release and release of drug limited to 16 h only which are not meeting the objectives, and all the batches show good and satisfactory release data and selected for the next step for coating them. In porous osmotic pump tablets, the drug release rate depends on the concentration of osmotic agent and pore former used. The osmotic agent concentration increases, then the osmotic pressure created inside the tablet also increases; 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. The pore former is added here in the 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 microporous, were used in for the release of the drug from tablets. **Table 9** (F1- F14) shows that all 14 batches are showing release up to 24 h and in that F14 is optimized with (98.82%) release profile as shown in **Fig. 2**.

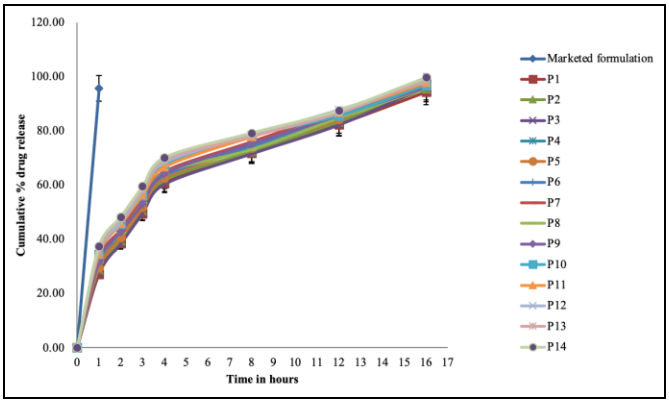

FIG. 1: CUMULATIVE PERCENTAGE DRUG RELEASE OF NATEGLINIDE MARKETED FORMULATION AND NATEGLINIDE EOP CORE TABLETS (P1-P14)

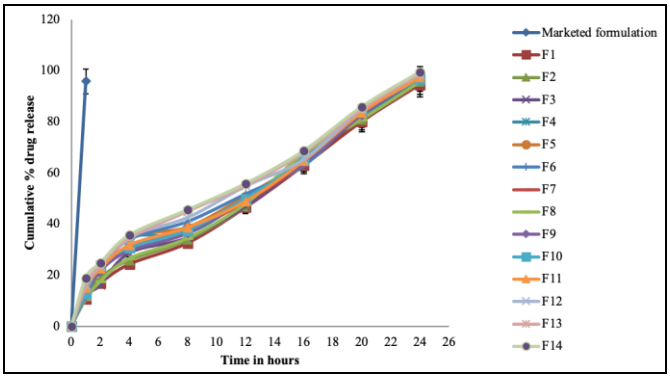

FIG. 2: CUMULATIVE PERCENTAGE DRUG RELEASE OF NATEGLINIDE MARKETED FORMULATION AND NATEGLINIDE EOP COATED TABLETS (F1-F14)

Drug Release Kinetics: From the results **Fig. 3** to **6** it is apparent that the regression coefficient value (R^2) of optimized formulation (F14) is closer to unity in the case of zero-order plot, *i.e.,* 0.998 indicates that the drug release follows a zero-order mechanism. Hence it can be concluded that the major mechanism of drug release follows zero-order kinetics. Further, the results from the Korsmeyer Peppas plot with R^2 value equal to 0.9745 and the n value obtained from the Korsmeyer-Peppa plots, *i.e.,* 1.3875, suggesting that the drug release from tablets was anomalous non- Fickian diffusion super case II transport.

Marketed Formulation: From the above results **Fig. 7** to **10** the (R^2) value closer to unity in case of First-order plot i.*e.*, 0.984 indicates that the drug release follows a first-order mechanism. Hence, it can be concluded that the major mechanism of drug release follows first-order kinetics.

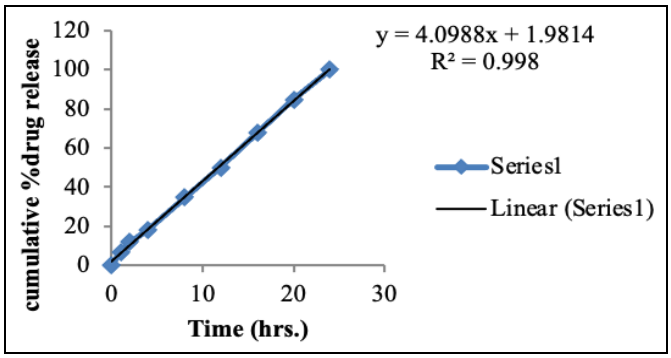

FIG. 3: % DRUG RELEASE *vs.* TIME PLOT OF F14 SHOWING ZERO ORDER KINETICS

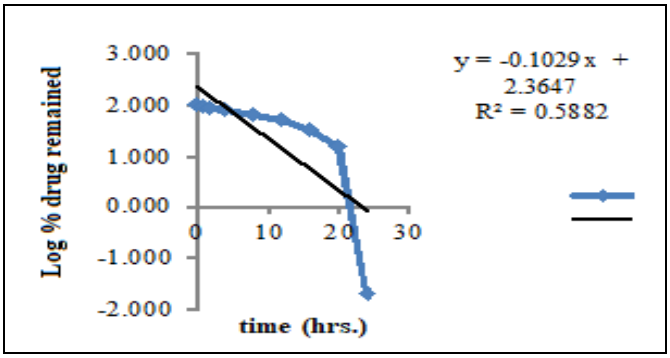

FIG. 4: LOG % DRUG REMAINED *vs.* TIME PLOT OF F14 SHOWING FIRST ORDER KINETICS

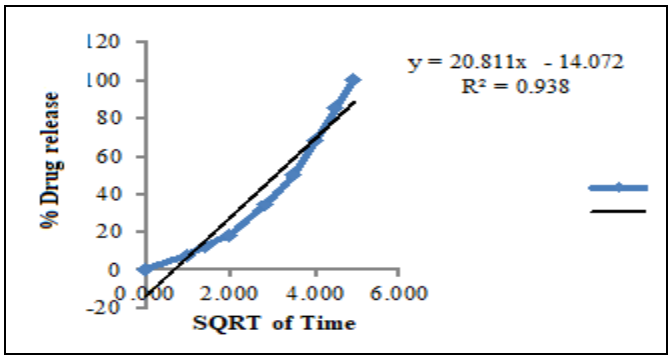

FIG. 5: % DRUG RELEASE *vs.* SQUARE ROOT OF TIME PLOT OF F14 SHOWING HIGUCHI'S MODEL

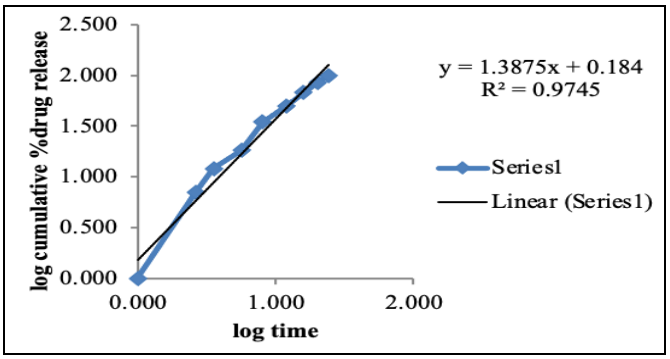

FIG. 6: LOG % DRUG RELEASE *vs.* TIME PLOT OF F14 SHOWING KORSMEYER-PEPPA'S MODEL

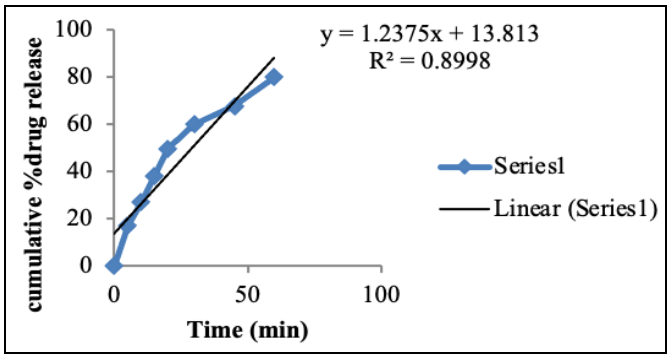

FIG. 7: % DRUG RELEASE *vs.* TIME PLOT OF MARKETED FORMULATION SHOWING ZERO

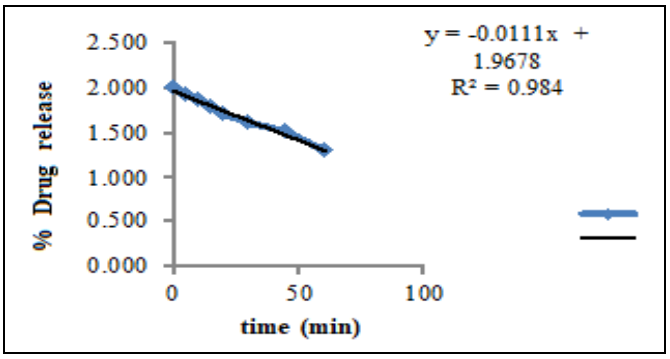

FIG. 8: % DRUG RELEASE *vs.* TIME PLOT OF MARKETED FORMULATION SHOWING FIRST ORDER KINETICS

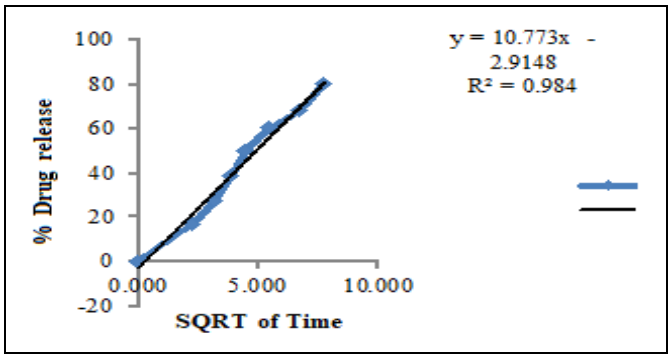

FIG. 9: % DRUG RELEASE *vs.* SQUARE ROOT OF TIME PLOT OF MARKETED FORMULATION SHOWING HIGUCHI'S MODEL

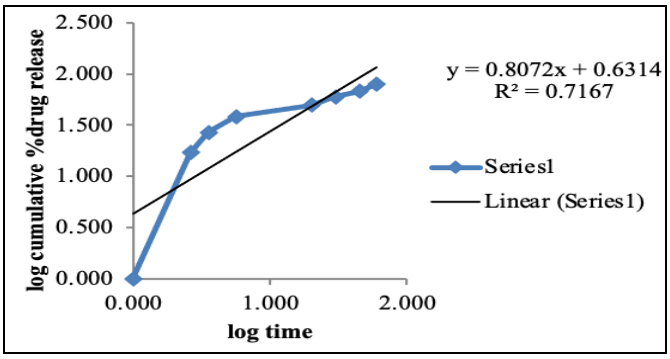

FIG. 10: LOG % DRUG RELEASE *vs.* TIME PLOT OF MARKETED FORMULATION SHOWING KORSMEYER-PEPPA'S MODEL

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 ±2°C /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). Confirmation 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 **Fig. 11**. The peaks of polymer PVP K30 at 2957.06 cm^{-1} -CH_3 stretch, at 1290.14 cm^{-1} and 1223.1 cm^{-1} correspondings to -C-H bend, at 737.78 cm^{-1} N-H bendss also appeared in optimized formulation, indicating no interaction between drug and excipients.

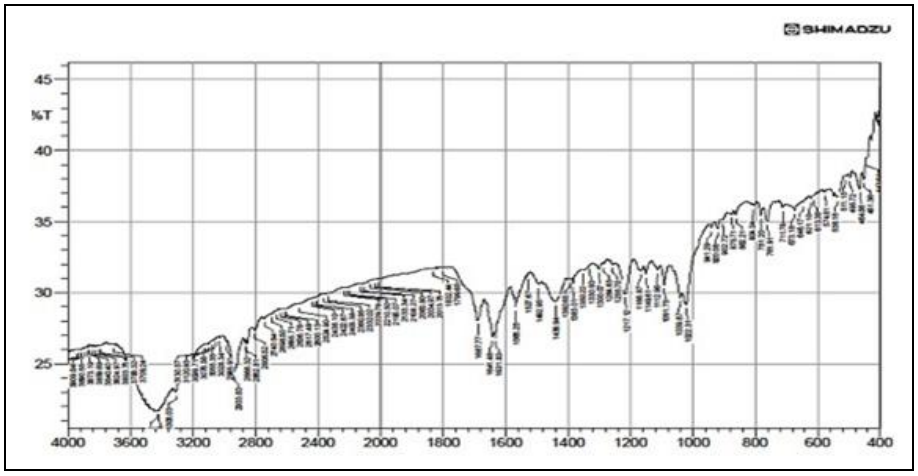

FIG. 11: FTIR SPECTRA OF PURE DRUG

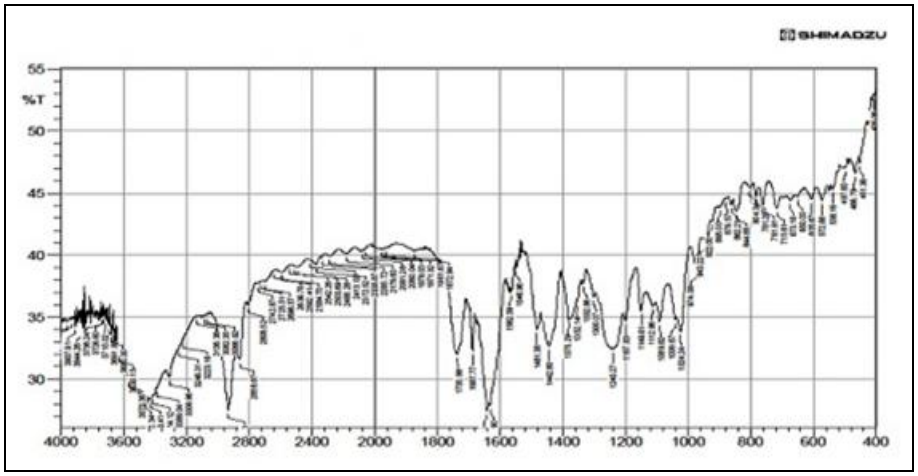

FIG. 12: FTIR SPECTRA OF NATEGLINIDE OPTIMIZED FORMULATION (F14)

The FTIR spectrum of nateglinide with excipients showed all the peaks for nateglinide, suggesting no significant interaction observed between them **Fig. 12.**

Results of Nateglinide PPOP Tablets:

Micromeritic Properties of Nateglinide granules for PPOP Tablets: Granules prepared for compression of nateglinide PPOP tablets were evaluated for their flow properties.

The bulk densities of all the formulations PP1 to PP15 were measured, and they are ranged from 0.47±0.28g/cc³ to 0.53±0.98g/cc³.

The tapped density of all the formulations PP1 to PP12 was measured, and they are ranged from 0.50±0.47g/cc³ to 0.57±0.63 g/cc³.

The angle of repose of all the formulations was found to be good. The formulation P14 was found to be 25.51±0.51, having excellent flow property.

The compressibility index values were found to be in the range of 7 to 14 %, and carrs index values ranged between 1.10±0.26 to 1.13±0.22. These findings indicated that all the batches of formulations exhibited good flow properties.

Physicochemical Properties: The value of hardness, weight variation of the prepared core tablet is recorded. The hardness, friability, weight variation, uniformity of content of the prepared coated tablet is recorded. Here tablets before coating were coded as PP1-PP14. These same tablets were after coating coded as FF1-F14. This different coding is given to differentiate the evaluation tests done in two different steps.

The results for weighing variation of core tablets (PP1-PP14) passed the test and were within limits.

The weight variation of all the coated formulations (FF1-FF14) is within limits.

The measured hardness of the tablets of each batch of all formulations, *i.e.*, FF1 to FF14 was ranged between 4.4 to 4.8 Kg/cm^{2,} and the results are shown in **Table 12**.

The thickness of the tablets was found to be almost uniform in all formulations FF1 to FF14.

The thickness of all the formulations ranged between 4.3-4.8 mm.

The friability of all prepared formulations between 0.11-0.21. the friability properties limits are between 0-1%.

The drug content of all formulation is between 94.9-99.61%, drug content with highest exhibited by F14 formulation and depends on angle of repose because 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.

***In-vitro* Drug Release:** The effect of plasticizer, effect of drug layer to coating weight gain and osmogen on drug release **Fig. 13** 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 an extended period of time. The formulation containing PG released the drug quickly, and more than 80% of the 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 was unable to release more than 75% of the drug in 24 hours.

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

Effect of Osmogen on Drug Release: Formulations FF6 to FF14 was formulated with different ratios of Sodium chloride in both layers. Formulations FF6, FF7, and FF8 contain osmogen only in the push layer at the level of 10%, 20%, and 30% weight of the 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 had better flow property with a regression coefficient (zero-order) of 0.999 **Table 15**.

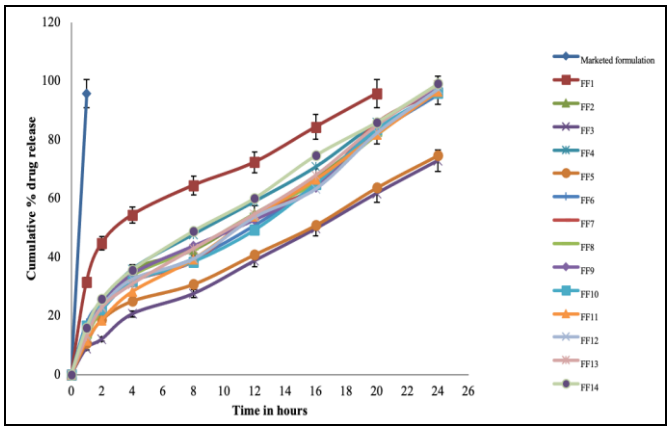

FIG. 13: CUMULATIVE PERCENTAGE DRUG RELEASE OF NATEGLINIDE MARKETED FORMULATION AND NATEGLINIDE PPOP TABLETS (FF1-FF14)

Characterization of PPOP Optimized Formulation FF14:

Effect of pH: When formulation FF14 was subjected to in vitro release studies in buffers of different 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 **Fig. 14**.

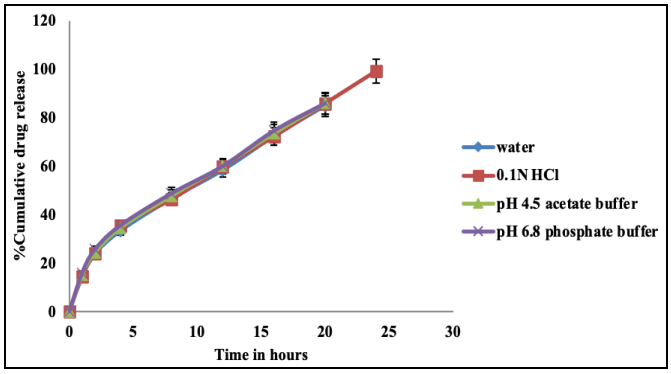

FIG. 14: EFFECT OF pH ON PPOP OPTIMIZED FORMULATION FF14

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 **Fig. 15**.

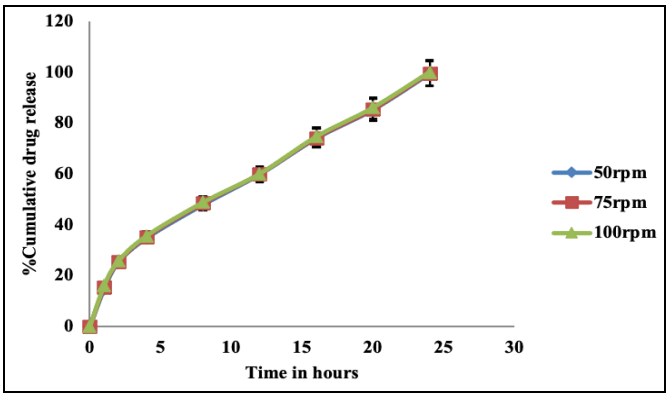

FIG. 15: EFFECT OF AGITATION INTENSITY ON PPOP OPTIMIZED FORMULATION FF14

Drug Release Kinetics: From the results (fig 16 to 19) the R^2 value of optimized formulation (FF14) is closer to unity in the case of zero-order plot, *i.e.*, 0.999 indicates that the drug release follows a zero-order mechanism. Hence it can be concluded that the major mechanism of drug release follows zero-order kinetics.

Further, the results from the Korsmeyer Peppas plot with R^2 value equal to 0.9723 and the n value obtained from the Korsmeyer-Peppa plots, *i.e.*, 1.3736, suggest that the drug release from tablets was anomalous non- Fickian diffusion super case II transport.

Marketed formulation release kinetics referred under EOP method **Fig. 7** to **10**.

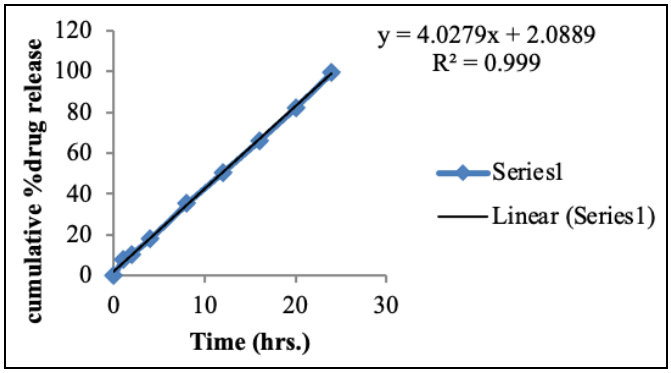

FIG. 16: % DRUG RELEASE *vs.* TIME PLOT OF FF14 SHOWING ZERO ORDER KINETICS

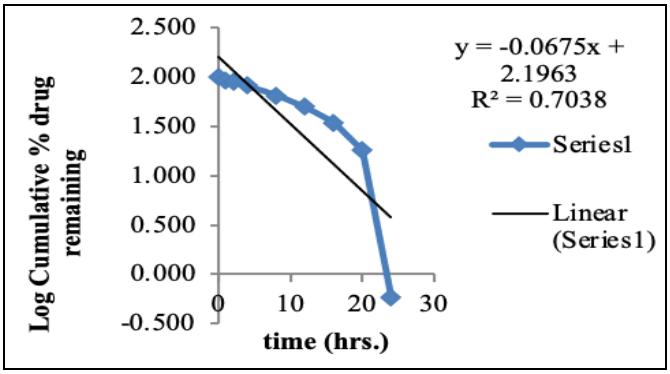

FIG. 17: LOG % DRUG REMAINED *vs.* TIME PLOT OF FF14 SHOWING FIRST ORDER

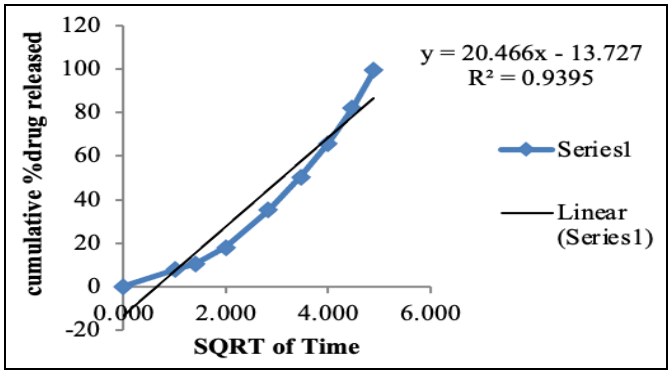

FIG. 18: % DRUG RELEASE *vs.* SQUARE ROOT OF TIME PLOT OF FF14 SHOWING HIGUCHI'S MODEL

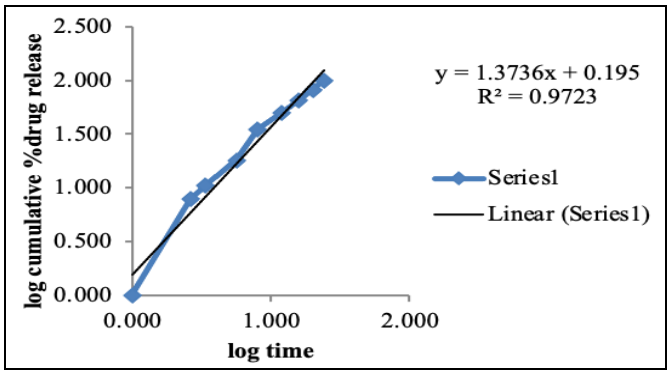

FIG. 19: LOG % DRUG RELEASE *vs.* TIME PLOT OF FF14 SHOWING KORSMEYER-PEPPA'S

FTIR Studies: The FTIR spectra of pure nateglinide are referred under EOP method **Fig. 11**. The FTIR spectrum of nateglinide with PVP K30 and NaCl showed all the peaks for nateglinide, suggesting no significant interaction observed between them **Fig. 20**.

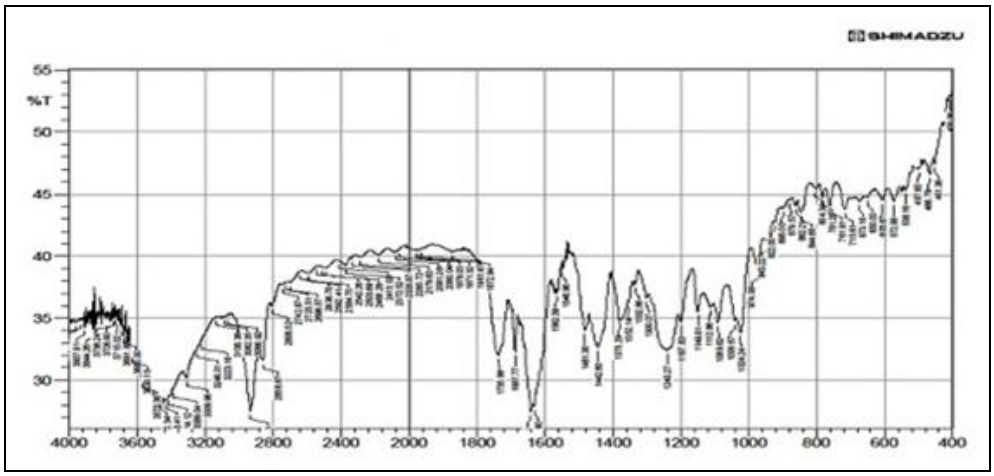

FIG. 20: FTIR SPECTRA OF NATEGLINIDE OPTIMIZED FORMULATION (FF14)

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 ±2°C /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)

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. To conclude, the push-pull osmotic tablet was able to deliver the drug in a controlled pattern for a prolonged period of time. This type of formulation can be used in conditions like hyperglycemia, where patient compliance can be improved by reducing the dosing frequency, and the plasma drug levels can be maintained.

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CONFLICTS OF INTEREST: Nil

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