E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/13.02.10

Research Article

Solubility Enhancement of Nateglinide by Solid Dispersion and Their Characterization

GOUNIKADI SAI PRAVALLIKA[1], K. RAMESH[2],G.VIJAY KUMAR[3]
[1,2,3]Department Of Pharmacy Kgr Institute of Technology and Management Rampallyvill, Keesara Mdl, M.M Dist-5013, Ts
Received: 04.11.22, Revised: 08.12.22, Accepted: 05.01.23

ABSTRACT
The aim of the present work is to investigate the possibility of obtaining immediate release tablet of Nateglinide with improved dissolution using Solid dispersion technique. The solubility and dissolution rate of Nateglinide can be enhanced by formulating SDs of Nateglinide with PEG 6000.The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wetability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of Nateglinide from its SD and to some extent in PMs. No endothermic peak of Nateglinide was present in of SDs with PEG 6000 suggesting the absence of crystalline Nateglinide. From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between Nateglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed. The identical composition of Superdisintegrants showed that a substantial shorter time require for disintegration can be obtained and immediate release tablet were prepared. The Nateglinide immediate release tablet (F2) showed 78.72% drug release within first 5 min. and 99.50% drug release with in 30 min. The results showed that the formulation satisfied the objective of fast disintegration, dissolution, % friability, hardness, wetting time, water absorption ratio, ease of administration and safety. Success of the present study recommends a detailed investigation in to *in-vivo* studies for its effective use in clinical practice.

Keywords: Nateglinide, Immediate release tablets, Solid dispersion technique, kinetic study, PEG.

INTRODUCTION
Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, highprecision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights. The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance.[1-8] Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated hat50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.[9-10] The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of [11,13]

Nateglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon

functioning beta (ß) cells in the Pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations. Nateglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß- cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

The aim of the present work is to investigate the possibility of obtaining immediate release tablet of Nateglinide with improved dissolution using Solid dispersion technique.

Basic goals in the immediate release tablets are to increase patient compliance, ease of administration, safety and appropriate dosing. Orally disintegrating formulations are provide benefits for pharmaceutical companies like lifecycle management, line extension, market expansion, cost effective drug development programs.

Immediate release tablet has perceived faster onset of action. Nateglinide is a white or half white powder, relatively insoluble in water. It is a class 2 drug according to BCS Classification Solubility and dissolution was improved by formulating solid dispersion. The advantage of this delivery system, in the present study were made to formulate immediate release tablet Nateglinide, which is useful to reduce sudden increased glucose level in the treatment of non-insulin dependent diabetes mellitus (NIDDM).

The direct compression was used to compress the tablets as it is easy way to manufacture tablets. Conventional equipments, commonly available excipients and limited number of processing steps are involved in direct compression and so manufacturing cost is low. Tablets produced by direct compression are relatively strong and hardness and have less friability.

MATERIALS AND METHODS

Chemicals and reagents are taken from different suppliers such as Nateglinide and PEG 6000 from Microlabs, Micro crystalline cellulose from Lobachemi, Mumbai, Sodium Starch Glycolate and Cross Povidone from Research lab fine chem, Mumbai, Sodium alginate and Talc from Lobachemi, Mumbai.

Preformulation

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.[14-15]

Assay

Weighed accurately 10mg of Nateglinide sample and added to 100 ml volumetric flask. Added 1ml of methanol mixed for 10 minutes added 60ml of 0.1 N Hydrochloric acid and dissolved it. Made up the volume to 100ml with 0.1 N Hydrochloric acid. Took 10ml and diluted to 100ml with 0.1 N HCL. Took 1ml and diluted to 10 ml with 0.1 N HCL, absorbance measured at 283nm.

Drug-Excipient Compatibility Study By Ftir

Infra-red spectroscopy is one of the most widely used tools for purity analysis of drugs in pharmaceutical Industry. Fourier Transform IR spectra were recorded using bruker Germany. IR spectrophotometer. KBr powder was used to prepare pellet for sampling. The scanning range was 4000- 40cm

Preparation of Standard Curve

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 283nm The Standard solution in Nateglinide in pH acetate buffer 10mg of Nateglinide is accurately weighed and dissolved in 10ml containing methanol in a volumetricflask. The various concentrations of Nateglinide prepared are 10, 20, 30, 40, 50, 60, ug/ml. The absorbance of various solutions of Nateglinide are determined spectrophotometricaly at 283nm employing UV double beam spectrophotometer usingacetate buffer of pH.

Preparation of Solid Dispersion and Physical Mixture Solid dispersions prepared by melting the carrier

Solid dispersions (SDs) preparations containing different weight ratios of Nateglinide in PEG6000 (1:1, 1:3, 1:5) were prepared by the melting method. Nateglinide was added to the melted PEG 6000 at 75°C and the resulting homogenous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24h.Subsequently, the dispersion was ground in a mortar and sieved through 100#

Physical Mixture

Physical mixture (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of Nateglinide and PEG 6000 in a mortar until a homogenous mixture was obtained. The resulting mixture were sieved through a 100# sieve and denoted as PM.

Characterization of solid dispersions of Nateglinide with PEG 6000

Drug content

About 10mg of drug equivalent of physical mixture and solid dispersion (theoretical) were weighed accurately and transferred to 50ml volumetric flask to which 10ml methanol was added and sonicated for 15min and volume was made up with methanol. From this stock solution further dilution were done and assayed using ultraviolet spectrophotometer measured at 283nm.

Phase-Solubility Study

Phase-solubility studies were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess amount of drug to flask containing 10ml of aquous solutions containing increasing concentrations of PEG6000. The flask were placed in a mechanical shaker at 75rpm and room temperature for 24hour. After 24 Hours the solutions were filtered and analysed by UV-Spectrophotometer at 283nm.

Dissolution Studies

Dissolution studies of Nateglinide in powder form, SDs, and PMs were performed by using the USP type II paddle apparatus at the paddle rotation speed of 75 rpm in 900ml of pH 5 acetate buffers as a dissolution medium at 37±0.5 °C. The SDs or PMs Equivalent to 2mg of Nateglinide was weighed using a digital balanceand added into the dissolution medium. At the specified times (every 10 min for 2 hours), 10ml samples were withdrawn by using syringe filter (0.45 μm) and then assayed for Nateglinide content by measuring the absorbance at 283 nm using a UV- Visible spectrophotometer. Fresh medium (10ml), which was prewarmed at 37 °C, was added to the dissolution medium after each sampling to maintain its constant volume throughout the test.

Fourier transforms IR spectroscopy

Fourier- transform infrared (FT-IR) spectra were obtained by using Bruker Germany FTIR. The samples (Nateglinide or SDs or PMs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

Formulation of Immediate Release Tablets of Nateglinide

Different Nateglinide Immediate Release Tablets were prepared according to the proportions given in the table no 1. The raw materials passed through a screen (# 60). Prior to mixing powdered separately the Nateglinide Solid dispersion, and weighed the amount equivalent to 10 mg Nateglinide, was mixed with other excipients and compressed proton mini press tablet punching machine. All formulation prepared according to the following formulation table.

Table 1: Formulation of Immediate Release Tablet.

S. No.	IngredientName	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	1:5Solid Dispersion equivalent to2mg Nateglinide	10	10	10	10	10	10	10	10	10	10	10	10
2	Micro crystallineCellulose	92	92	92	92	92	92	92	92	92	92	92	92
3	Mannitol	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0
4	Isphagol Mucilage	10	12.0	-	-	-	-	-	-	-	-	-	-
5	IsphagolPowder	-	-	10.0	12.0	-	-	-	-	-	-	-	-
6	Iphagol husk powder	-	-	-	-	10.0	120	-	-	-	-	-	-
7	Cross Povidone	-	-	-	-	-	-	10.0	12.0	-	-	-	-
8	CMC		-	-	-	-	-	-	-	-	-	10.0	12.0
9	SSG	-	-	-	-	-	-	-	-	10.0	12.0	-	-
10	Talc	2	2	2	2	2	2	2	2	2	2	2	2
11	Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
12	Aerosil	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
13	Orange Flavour	1	1	1	1	1	1	1	1	1	1	1	1
	Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of Immediate Release Tablet

Physicalappearance

Prepared immediate release Tablets were evaluated for the smoothness and absence of cracks, chips and other undesirable characteristics.

Weight Variation

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weightvariation was calculated. As per Indian Pharmacopoeia specification, tablet with an average weight between 80 – 250 mg, percentage deviation should not more than ±o.5% and the tablet with an average weight more than 250 mg should not be more than ± 10 %.

Friability

Friability of the tablets was checked by Roche friabilator. In this device, tablets subjected to combined effects of abration and shock by utilizing a plastic chamber that revolves at 75 rpm, dropping the tablets at a distance of6 inches in each revolution. Pre weighed tablets were placed in friabilator, which was then operated for100revolutions. The tablets were dusted and reweighed.

Thickness

The thicknesses were measured using vernier caliper and values were tabulated. Three tablets of each batch were measured. Average and standard deviation was calculated.

Hardness

Monsanto hardness tester was used for the determination of hardness. For eachformulation 3 tablets were determined.

Disintegration Time

A disintegration time of6 tablet from each formulation was determined by using USP disintegration apparatus. Disintegration test was carried out in 900ml buffer pH 6.8 at 37 ± 2 ^{0}Cand apparatus operated for 3 minutes, six tablets were taken and one tablet was introduced in each tube, disc was placed and basket and the disintegration time in seconds was noted.

Wetting Time

This is carried out as a measure of hydrophilicity of tablets. Wetting time is a length of time required to wet the tablet. A piece of tissue paper (12 x 10.75). folded twice was placed in the small Petri dish (I.D 6.5cm) containing 6 ml of buffer pH 6.8 simulated to salivary pH, tablet was placed on the paper and time for complete wetting was measured. Three trials of each batch were performed and standard deviation was determined.

Uniformity of Dispersion Test

Two tablets from each batch were separately kept in 100 ml water and gently stirred for 2 minutes. The dispersion was passed through 22 mesh. The tablets were considered to pass the test if no residue remained on the screen.

Assay

Standard Preparation

Weigh accurately 100 ml volumetric flask, dissolved in minimum quantity of methanol. The volume made up to 100 ml with 0.1 N hydrochloric acid. Took 10 ml of that solution and diluted to 100 ml with 0.1 N hydrochloric acid. Took 1 mlfrom that solution and diluted to 10 ml with 0.1 N hydrochloric acid.

Sample Preparation

Mixed well and volume made up to 100ml. Filtered the solution and 10 ml of this solution diluted to 100 ml. From that took 1ml and diluted to 10 ml.

Dissolution Studies

Dissolution studies were carried out using USP type II (paddle apparatus) at 75rpm pH 5 acetate buffer was used as dissolution medium. Temperature was maintained at 37 ±0.5 ^{0}C. Aliquots of dissolution media was withdrawn at specific time intervals and it was filtered. Same quantity of fresh media was replaced. The filtered solution was used to determine the estimation of drug content. The absorbances were measured at 283 nm by UV/Visible spectophtometer. The test was carried out for 30 minutes.

Kinetic Study

The release data obtained from optimized formulation was studied further for the fitness of data in different kinetic models like, zero order, first order, Higuchi'sand korsmeyer – Peppa's.

Accelerated Stability Studies

Selected formulation were subjected to stability studies as per I.C.H guidelines. Following conditions were used for stability testing. 40^0 C / 75% RH analyzed every month for a period of two months as per I.C.H guidelines. By keeping 40 ± 2^{0}C /RH the formula analyzed every month for a period of 3 months.

RESULTS AND DISCUSSION

Preformulation Studies Organlopetic Properties

These tests were performed as per procedure given in The results were illustrated in table no.2.

Table 2: Organoleptic Properties.

Test	Specification/Limits	Observations
Color	White to half-white powder	White powder
Odour	Odourless	Odourless

Loss on Drying

This test was done as per procedure stated in 6.1.2. The results wereillustrated in table no.3.

Table 3: Loss on Drying.

Test	Specification/Limits	Observations
Loss on drying	Not more than 0.5%	0.085%

Flow Properties (Angle of repose)

It was determined as per procedure given in 6.1.3. The results were illustrated in tables No. 4.

Table 4: Flow properties.

Material	Angle of repose
Nateglinide	27.85``

*Average of three determinations

Determination of Density

It was determined as per procedure given in 6.1.4. The results wereillustrated in table no. 11.

Table 11: Density.

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Nateglinide	0.24	0.35

*Average of three determinations

Powder compressibility

It was determined as per procedure given in 6.1.5. The results wereillustrated in table no. 12.

Table 12: Powder Compressibility.

Materials	Compressibility index	Hausner ratio
Nateglinide	14.23%	1.84%

Average of three determinations

Solubility

It was determined as per procedure given in 6.1.6. The results wereillustrated in table no. 13.

Table 13: Solubility.

Test	Specification	Result
Solubility in water, Methanol, Methylene chloride.	Practically insoluble in water, freelysoluble in methylene chloride, soluble in methanol	Complies

pH of the solutions

Table 14: pH.

Test	Specification	Observation
pH	5.5	5

Table 15: Assay.

Test	Specification	Observation
Assay	90.8-101.75 %	101.18%

Drug excipients compatability study by ftir

FTIR Studies

The spectral details for the drug and physical mixtures are shown as follows FT-IR Peak Of Various Components.

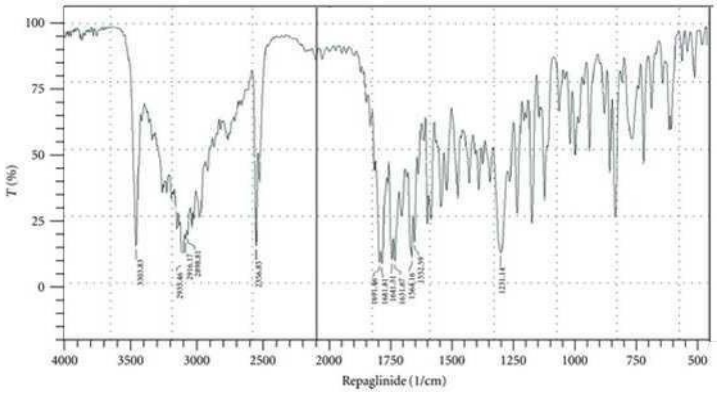

Fig. 1: IR spectrum of Nateglinide.

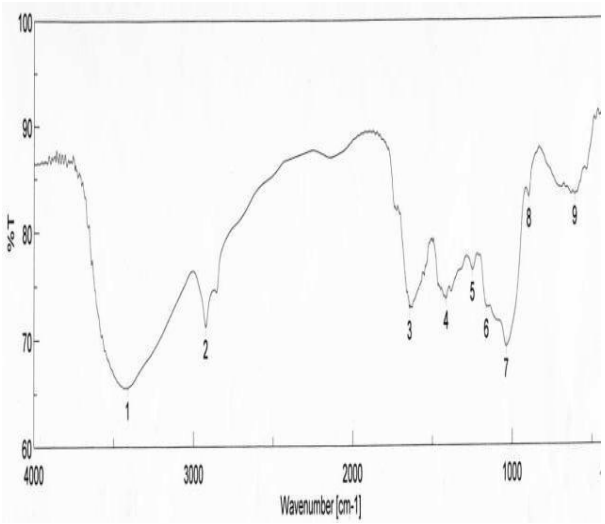

Fig. 2: Ispagol Mucilage.

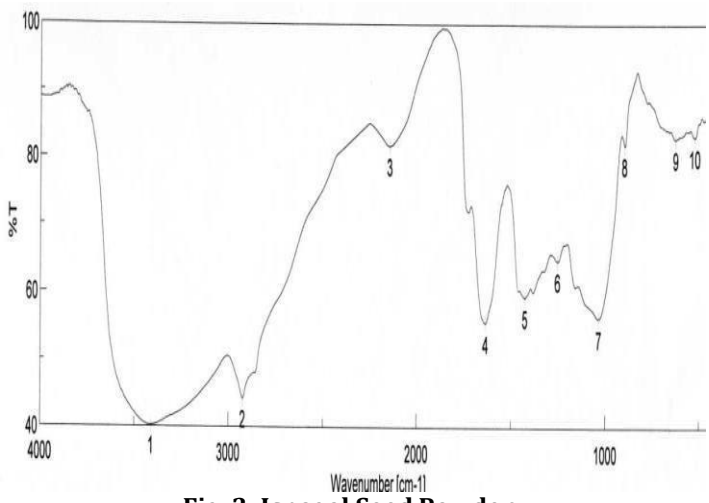

Fig. 3: Ispagol Seed Powder.

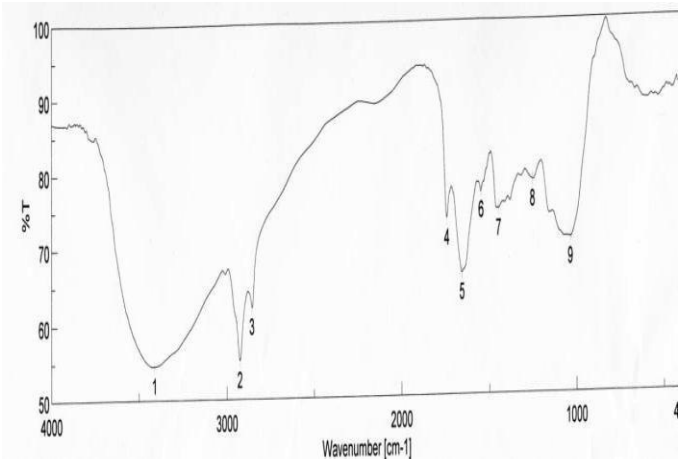

Fig. 4: Ispagol Husk Powder.

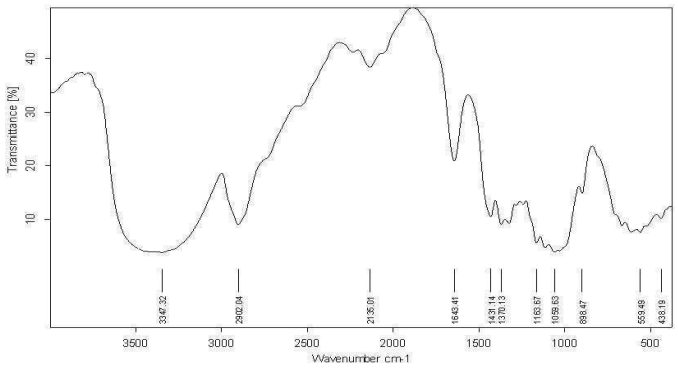

Fig. 5: IR Spectra of Microcrystalline Cellulose.

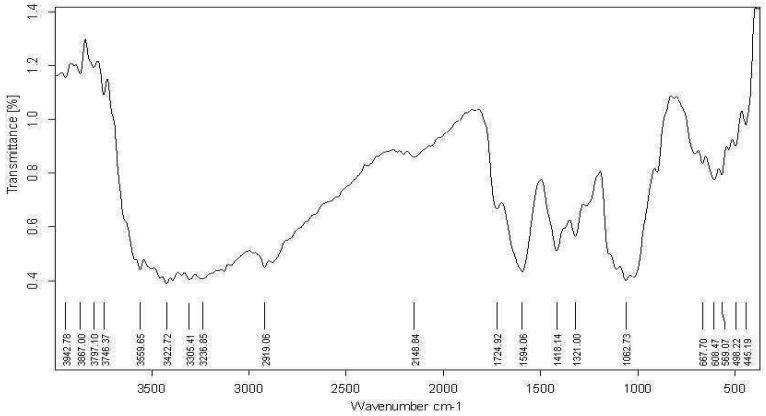

Fig. 6: IR Spectra of Crospovidone.

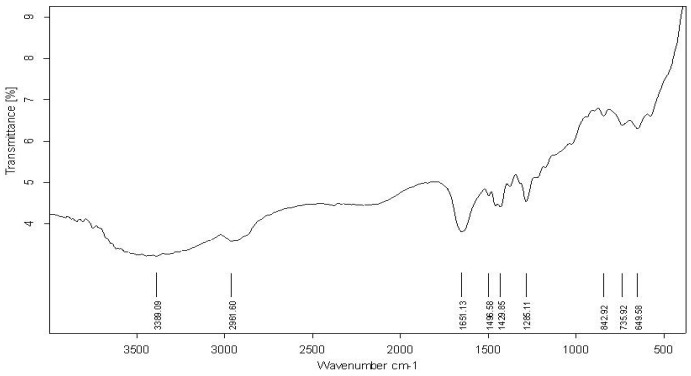

Fig. 7: IR Spectra of Croscarmellose Sodium.

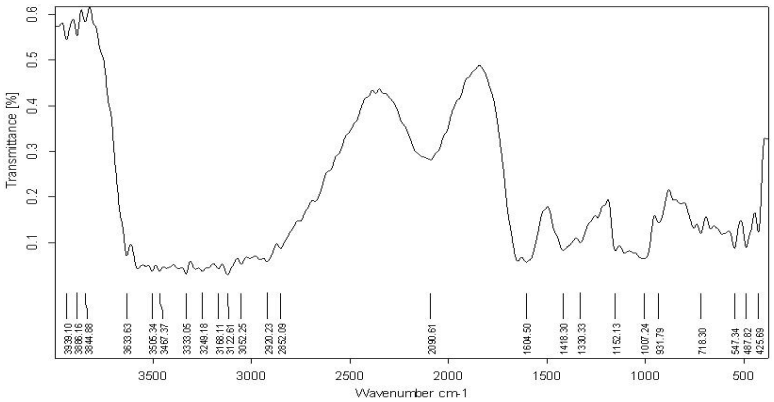

Fig. 8: IR Spectra of Sodium Starch Glycolate.

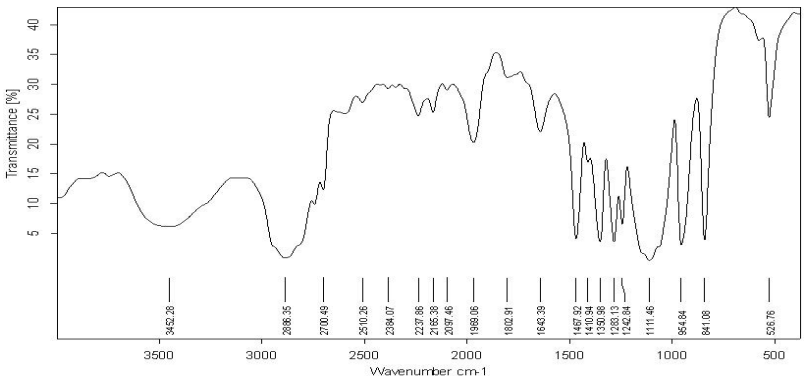

Fig. 9: IR Spectra of PEG 6000.

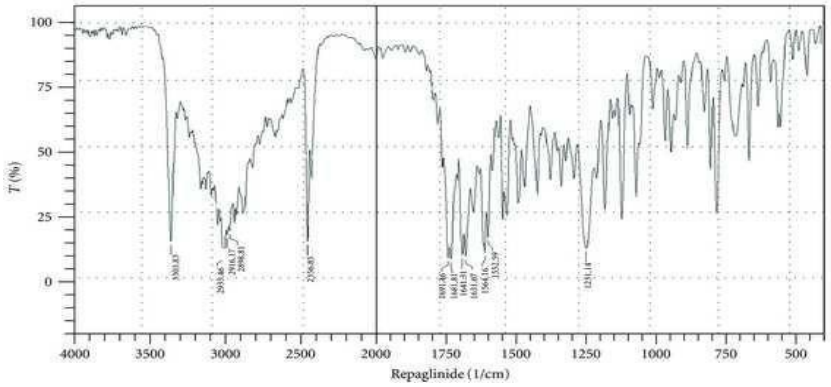

Fig. 10: IR Spectra of Nateglinide & Excipient Mixture.

Table 16

Characteristic bands	Pure drug	Physical mixture
O-H	3103.54cm-1	3005.14cm-1
N-H	1599.09cm-1	1739.03cm-1
C-O	1108.83cm-1	1365.64cm-1
C=C	3005.90 cm-1	1477.26cm-1
C-N	2825.87 cm-1	1579.39cm-1

Preparation of Standard Curve

A UV spectrophometric method given in IP is used for dissolution samples of Nateglinide tablet. Absorbance scans of drug is pH5 acetate buffer, showed maximum at 283nm, which is selected as the analytical wavelength. Standard curve of Nateglinide in Calibration curve of Nateglinide was determined by plotting absorbance versus concentration (µg/ml) at 283nm. The results obtained were as follows. Nateglinide standard calibration curve in pH 5 Acetate buffer at 283 nm.

Table 17

Concentration (µg/ml)	Absorbance at 283nm
10	0.121
20	0.283
30	0.455
40	0.651
50	0.810

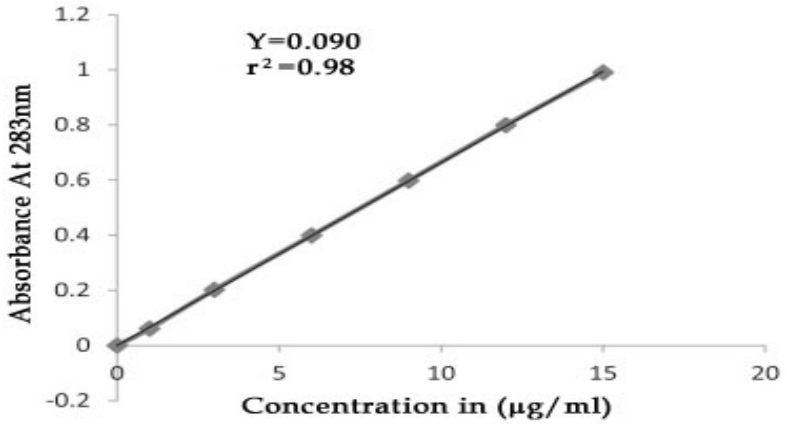

Fig. 11: Calibration curve in pH 5 Acetate buffer at 283 nm.

Preparation of Solid Dispersion And Physical Mixture

As per the method given in 6.4.1 and 6.4.2 solid dispersion and physicalmixture were prepared.

Characterization of solid dispersions of Nateglinide with PEG 6000

Drug content

It was determined as per procedure given in 6.5.1. The results wereillustrated I table no. 18.

Table 18: Drug content in physical mixtures and solid dispersions.

Solid dispersion (drug to PEG massratio)	Drug content(%)	Physical mixture (drug to PEG massratio)	Drug content(%)
SD 1:1	97.54	PM 1:1	98.05
SD 1:3	96.25	PM 1:3	97.96
SD 1:5	98.42	PM 1:5	98.18

Phase solubility Study

It was determined as per procedure given in 6.5.2. The results were illustrated below.

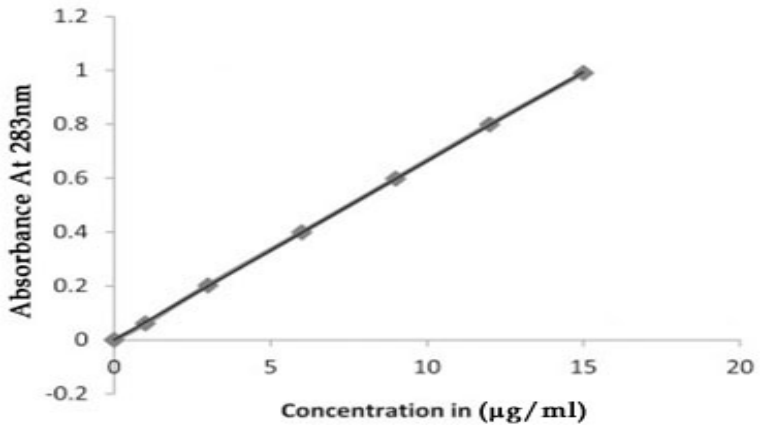

Fig. 12: Solubility diagram of Nateglinide in presence of PEG 6000.

Fig no.11 represented the effect of different polymers concentration at different temperature on the solubility of Nateglinide. The plots of drug solubility against the polymer concentration at the investigated temperatures indicated a linear relationship between drug solution and polymer concentration. The result shown that in both cases, the solubility of Nateglinide increased with increasing temperature and carrier concentration. Solubility of Nateglinide in pure water at 25°C was 0.01 (µg/ml). At the highest polymer concentration (10% w/w), the solubility increased approximately 4 fold for PEG 6000 at 25°. The same tendency was observed for other temperatures.

Dissolution studies

It was determined as per procedure given in 6.5.3. The results were illustrated in table no. 20.

Table 20: *In-vitro* Dissolution Profile of Nateglinide Physical Mixture of Nateglinide and Solid Dispersion of Nateglinide in pH 1.2 Buffers.

Sr. No.	Formulation	Percentage drug released after 30 minutes (DR)
A1	Drug	31.23 □ 2.25 %
A2	PM 1:1	41.54 □ 2.58 %
A3	PM 1:2	44.86 □ 2.69%
A4	PM 1:5	51.12 □ 2.50%
A5	SD 1;1	87.89 □ 2.25 %
A6	SD 1:2	93.46 □ 2.35 %
A7	SD 1:5	98.35 □ 2.76 %

Fourier transforms IR spectroscopy

The following figures were illustrated results.

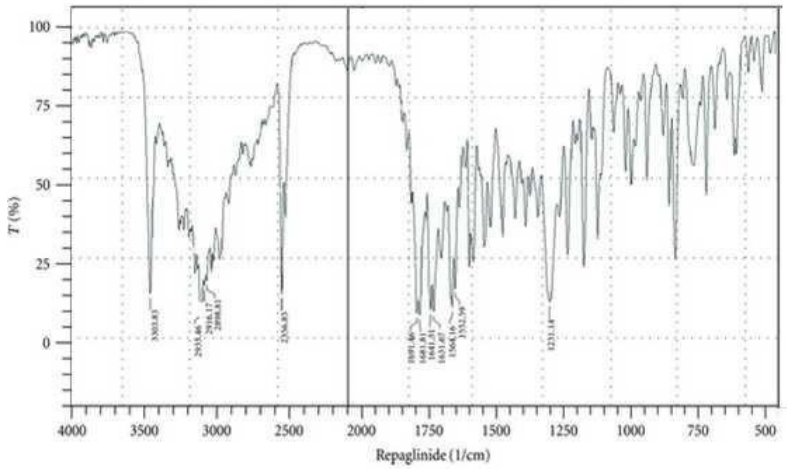

Fig. 13: IR Spectra of Nateglinide.

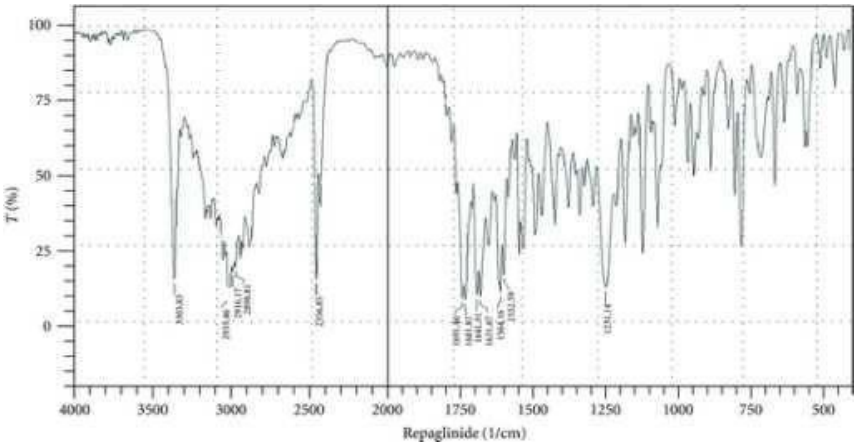

Fig. 14: IR Spectra of Solid dispersion 1:1.

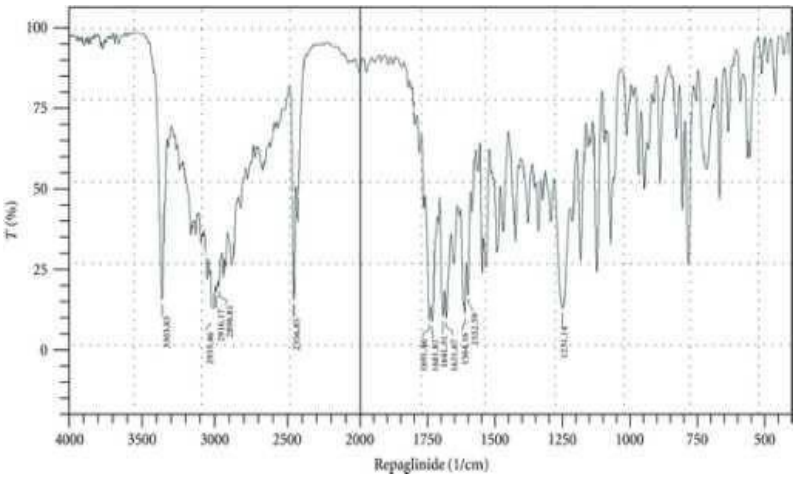

Fig. 15: IR Spectra of Physical mixture 1:1.

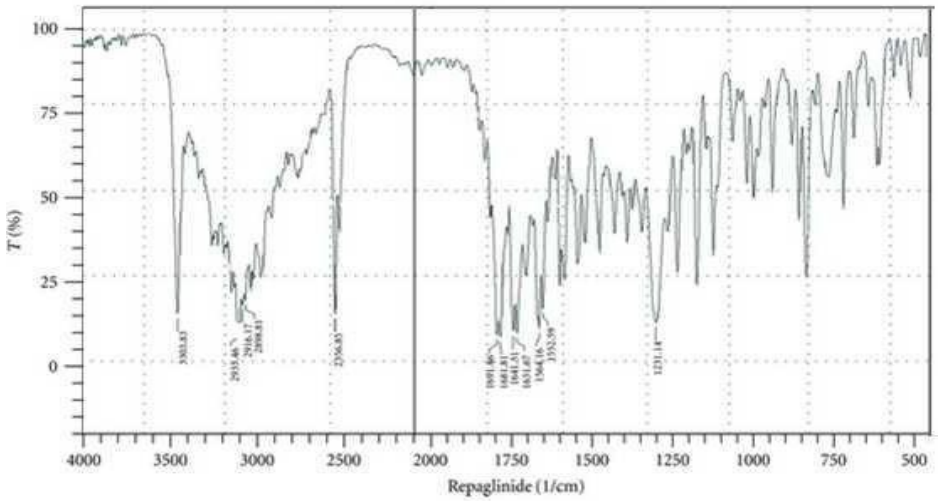

Fig. 16: IR Spectra of Solid dispersion 1:3.

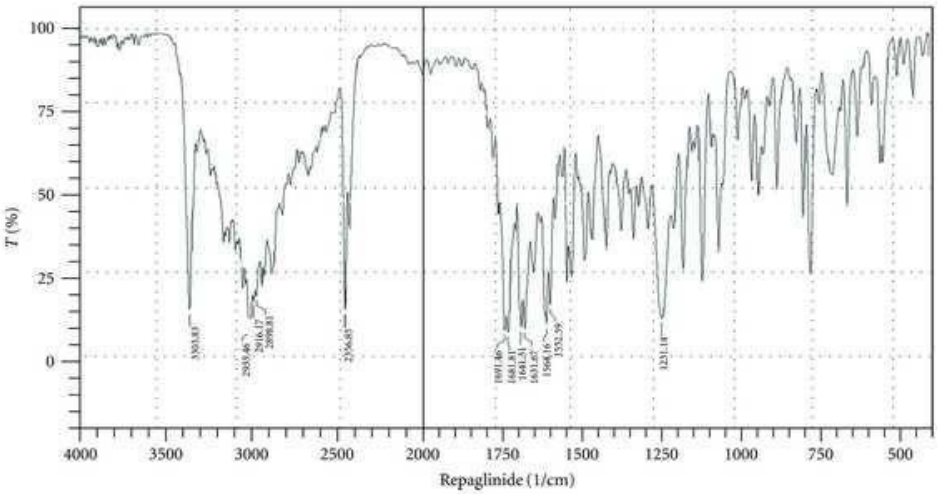

Fig. 17: IR Spectra of Physical mixture 1:3.

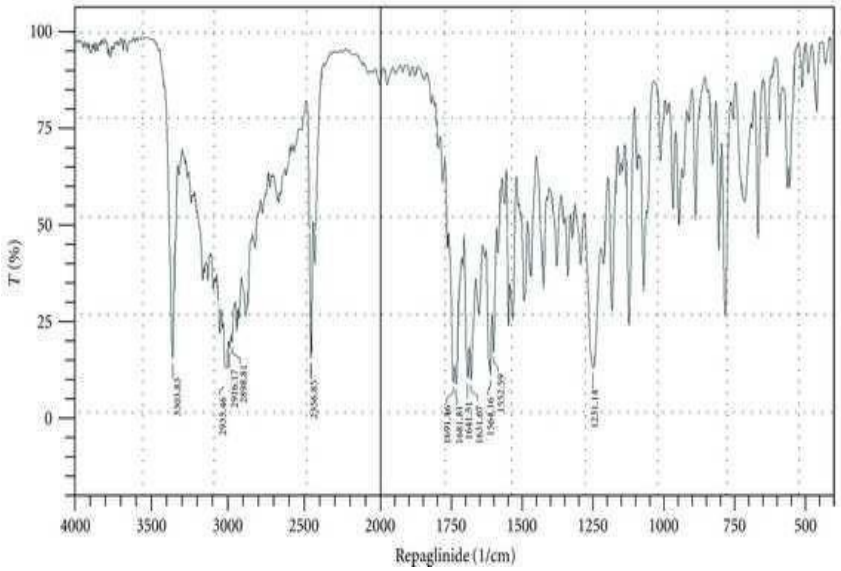

Fig. 18: IR Spectra of Solid dispersion 1:5.

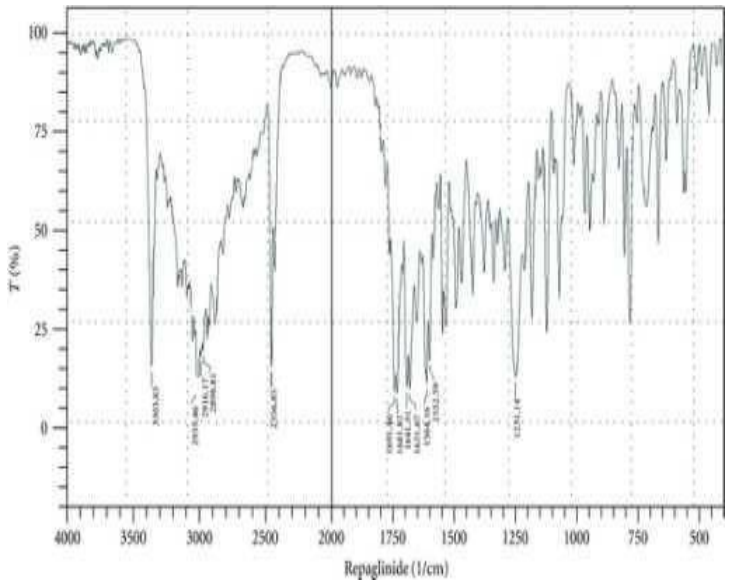

Fig. 19: IR Spectra of physical mixture 1:5

The IR spectra of SDs and PMs were compared with the standard spectrum of Nateglinide. IR spectrum of Nateglinide was characterized by the absorption of carbonyl (C-O) group at 1108.83cm^{-1}. In spectra of SDs and PMs, this band was shifted towards higher frequencies at 3005.14 and 2,825.87cm−1 respectively. Also the O-H group which is located at 3,103.54 cm−1 from the IR spectrum of Nateglinide, N-H group at 1599.09, C=C group at 3005.90, C-N group at 2825.87 It was concluded that there was no well defined chemical interaction between Nateglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

Preparation And Evaluation Of Natural Superdisintegrants

Table 21: Preliminary evaluation of natural superdisintegrants.

Parameters	Mucilage	Seed Powder	Husk Powder
Bulk Density (gm/cm^3)	0.96	0.50	1.17
Tapped Density (gm/Cm^3)	1.08	0.91	1.35
Hausners Ratio	1.083	1.14	1.11
Compressibility index (%)	6.58	15.37	14.66
Angle of Repose (°)	25.20	40.36	33.15

Evaluation of Immediate Release Tablets

Table 23: Evaluation Chart of Tablet.

S. No	Para meter	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Weight Variation Test	198.66 ±0.23	199.66 ±0.25	197.66 ±0.39	200.66 ±0.43	198.66 ±0.23	196.66 ±0.49	198.66 ±0.39	197.66 ±0.35	199.66 ±0.23	198.66 ±0.23	199.66 ±0.27	199.66 ±0.23
2	% Friability	0.26	0.20	0.21	0.30	0.28	0.20	0.23	0.21	0.24	0.32	0.25	0.23
3	Thickness (mm)	2.58± 0.01	2.59± 0.03	2.35± 0.05	2.30± 0.02	2.41± 0.05	2.42± 0.06	2.42± 0.02	2.48 ± 0.06	2.44 ± 0.04	2.43± 0.05	2.41± 0.04	2.35± 0.06
4	Hardness (Kg / cm^2)	2.06 ±0.10	2.06 ±0.09	2.84 ±0.41	3.17 ±0.15	2.91 ±0.18	2.95 ±0.14	2.74 ±0.14	2.79 ±0.31	2.84 ±0.36	2.90 ±0.37	2.91 ±0.39	2.96 ±0.40
5	DisintegrationTime(sec)	23.36 ±2.6	21.05 ±1.5	27.39 ±2.5	23.69 ±2.8	25.63 ±2.4	26.05 ±3.5	22.00 ±2.8	22.05 ±2.5	28.05 ±2.6	26.63 ±3.7	34.68 ±2.9	34.69 ±2.5

6	Wetting time (sec)	50.69 ±1.6	47.69 ±1.9	63.04 ±2.9	66.33 9 ±2.9	63.36 ±2.6	57.63 ±2.6	54.36 ±1.6	52.69 ±2.7	52.05 ±2.6	53.36 ±2.9	65.39 ±2.5	63.06 ±2.6
7	Uniformity ofDispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	W.A.Ratio (%)	65.46	65.36	73.85	74.07	66.07	67.35	65.34	65.39	66.15	66.93	74.19	73.69
9	Assay (%)	99.48	100.5	98.34	99.82	99.10	101.4 1	100.0 6	100.1 5	101.2 1	101.0 2	100.9	100.4

Table 36: Comparative dissolution study F 1 – F 12.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	78.45	78.72	79.82	80.37	81.47	84.75	82.58	80.37	83.23	84.76	83.85	83.81
10	80.92	81.45	82.02	82.30	84.50	86.69	85.05	82.15	86.17	86.70	86.05	87.17
15	84.76	84.50	85.03	85.85	86.14	89.15	87.24	85.46	88.55	89.19	89.24	88.65
20	89.15	90.00	90.52	91.90	90.10	93.25	90.53	89.11	92.70	93.29	91.55	92.60
25	93.82	94.37	94.91	94.35	94.15	97.39	95.73	94.15	96.05	96.40	95.75	96.15
30	97.92	99.50	98.75	98.23	98.05	98.87	99.35	99.65	98.41	97.50	98.35	98.99

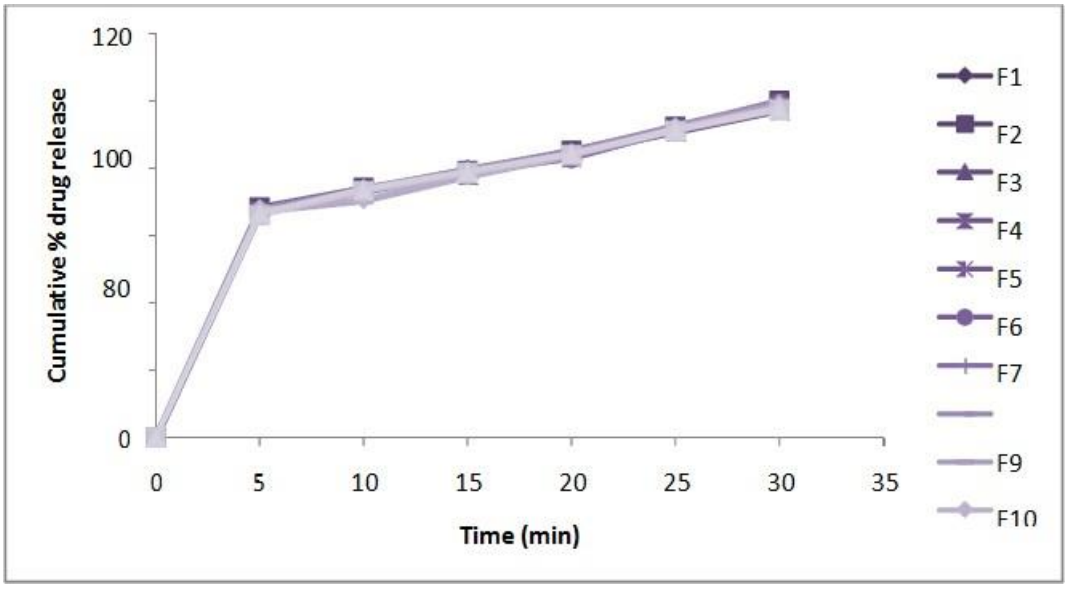

Fig. 32: Comparison of *In-vitro* dissolution profile of formulation F1-F12.

Kinetic Study of Optimized Formulation

In-vitro release data was flatted in different kinetic model and given in table 37 and figure 33 to 36.

Table 37: Kinetic data of Optimized Fomulation F2.

Time	Logtime	*Time*	Cumulative % drugrelease	Log cumulative % drugrelease	Cumulative % drug remained	Log cumulative % drug remained
0	0	0	0	0	100	2.00
5	0.698	2.23	78.72	1.89	21.28	1.32
10	1.0	3.16	81.45	1.91	18.55	1.26
15	1.176	3.87	84.50	1.92	15.50	1.19
20	1.301	4.47	90.00	1.95	10.00	1.00
25	1.397	5.0	94.37	1.97	5.63	0.75
30	1.477	5.477	99.50	1.99	0.50	0.30

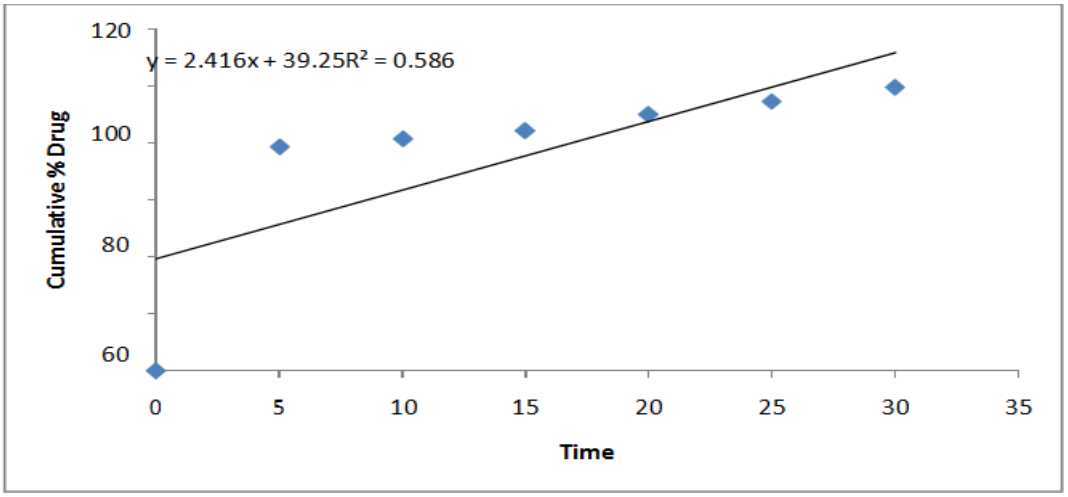

Fig. 33: Zero Order.

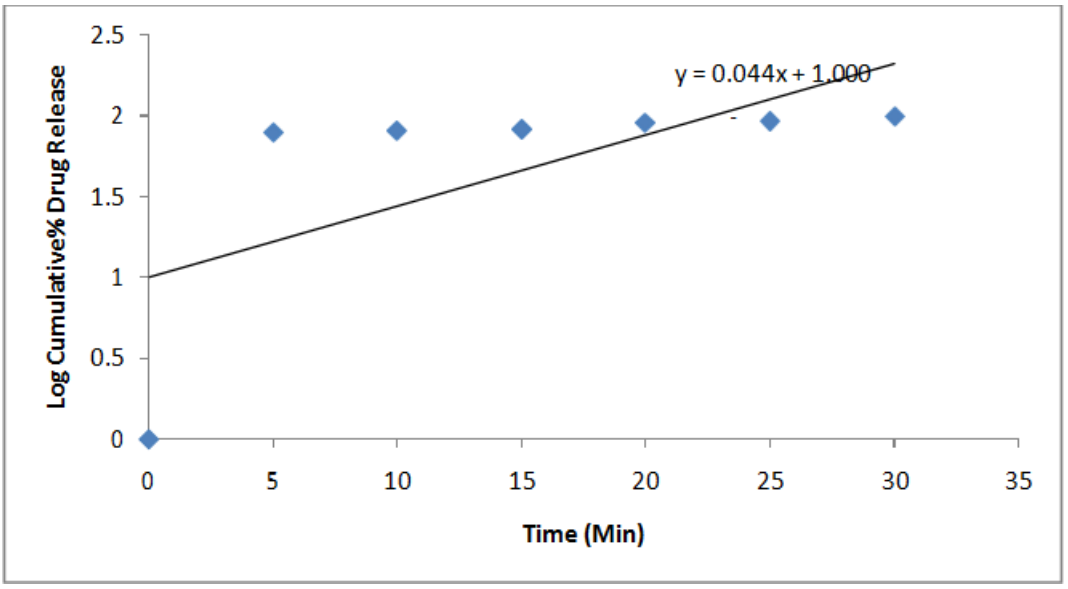

Fig. 34: FIRST ORDER.

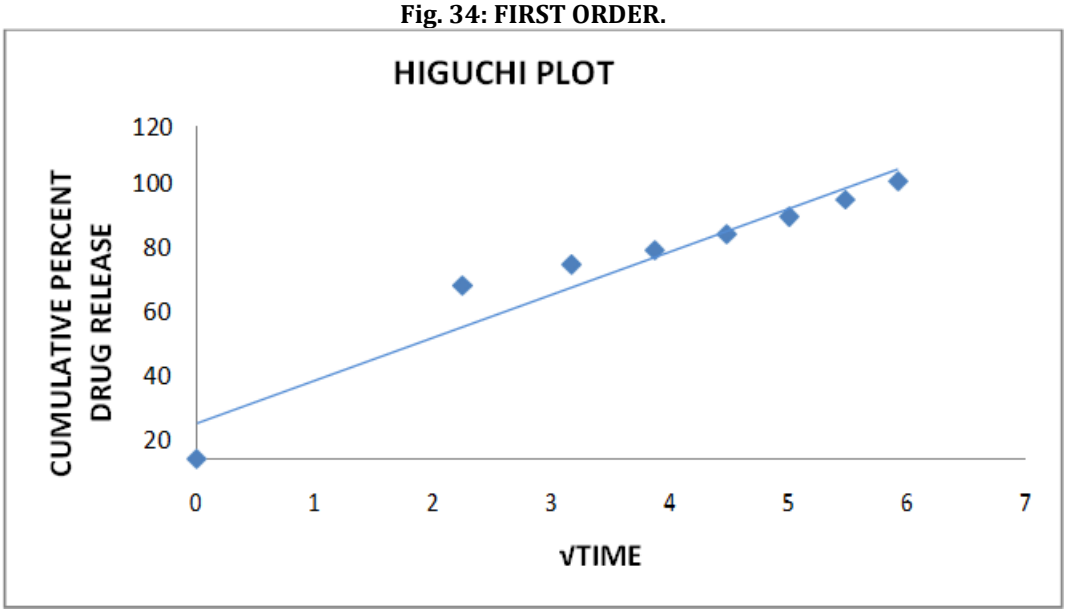

Fig. 35: HIGUCHI.

The above studies showed that the drug release follows first order kinetics.

Stability Studies

Optimized formulation (F2) was subjected to stability studies at 40°c± 2°c/75% RH ±5 % for 90 days. The product was evaluated for appearance and hardness, friability, disintegration. Drug release studies were conducted as per the planned scheduled as above.

Descriptions

Table 38: Description.

Storage condition	Test	Observation	Inference
RT	Descriptions	No change of color in allstrengths	Complies with stabilitycondition
40°C + 2°C/75% RH	Descriptions	No change of color in allstrengths	Complies with stabilitycondition

Stability parameters of formulation F2 stored at 40°C+ 2°C/ 75% RH

The results were illustrated in following table no. 39.

Table 39

Sr. No.	Parameters	Initial	30 days	60 days	90 days
1	% Friability	0.20	0.27	0.270	0.273
2	Hardness (kg / cm^2)	2.6	2.5	3.1	3.2
3	Drug Content (%)	100.01	99.10	98.51	98.21
4	*In-Vitro Disin.Time(Sec)*	21.05	21.15	23.24	24.11

All results complies with the stability condition

In-vitro Dissolution study

It was done as per procedure given in material and method part. The results wereillustrated in following table no. 45.

Storage Condition at 40°C + 2°C

Table 40: In-vitro dissolution study.

Formulation(F2)	Percentage Drug Release After 30 minutes			
	Initial (0Days)	30 Days	60 Days	90 Days
	99.50	99.60	98.54	98.60

The results showed that there was no significant change in physical andchemical parameter of the tablet, hence the formulation was found to be stable.

Summary

In the present study immediate release drug delivery system of Nateglinide were successfully developed in the form of mouth dissolving tablets with improved dissolution characteristic by forming solid dispersion with PEG 6000, which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Immediate release tablets of Nateglinide were prepared by using natural superintegrants like microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate and their combination as superdisintegrants. Superdisintegrants work as an auxiliary or as a facilitator of the flowability and compressibility of the mixture and contribute to the immediate release of the tablet, due to its high solubility in water. For the Nateglinide formulation, batch No. 2 was chosen as it has disintegration time around 5-35 seconds and hardness3.5 Kg/Cm^2. IR spectra of drug with other excipients has not shown any interaction and also selected formulation was stable after stability studies.

CONCLUSION

The solubility and dissolution rate of Nateglinide can be enhanced by formulating SDs of Nateglinide with PEG 6000.The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wetability and dispersibility, and alteration of the surface properties of the drug particles might be

responsible for the enhanced solubility and dissolution rate of Nateglinide from its SD and to some extent in PMs. No endothermic peak of Nateglinide was present in of SDs with PEG 6000 suggesting the absence of crystalline Nateglinide. From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between Nateglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed. The identical composition of Superdisintegrants showed that a substantialshorter time require for disintegration can be obtained and immediate release tablet were prepared. The Nateglinide immediate release tablet (F2) showed 78.72% drug release within first 5 min. and 99.50% drug release with in 30 min. The results showed that the formulation satisfied the objective of fast disintegration, dissolution, % friability, hardness, wetting time, water absorption ratio, ease of administration and safety. Success of the present study recommends a detailed investigation in to *in-vivo* studies for its effective use in clinical practice.

REFERENCES

1. Leon Lachmann, Herbert A, Liberman, Joseph L.Kaing, The theory and practice of dustrial Pharmacy, 293-303.
2. Ansel`s Pharmaceutical dosage forms & drug delivery systems, eighth edition, 227- 260.
3. Aulton`s Pharmaceutics, The design & manufacture of medicines, Biopharmaceutics and pharmacokinetics, A Treatise, second edition, Valabh Prakashan, 315-384.
4. Debjit Bhowmik, Chiranjib.B, Krishnakanth, Pankaj, R.Margret Chandira, Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research, 2009; 1(1): 163-177.
5. Dali Shukla, Subhashis Chakraborty, Sanjay Singh, Brahmeshwar Mishra, Mouth Dissolving Tablets II:An Overview of Evaluation Techniques, www.scipharm.at.
6. Susijit Sahoo, B. Mishra, P.IK. Biswal, Omprakash Panda, Satosh Kumar Mahapatra, Goutam Kumar Jana, Fast Disslving Tablet: As A Potential Drug Delivery System, Drug Invention Today, 2010; (2): 130-133.
7. S. Ullas Kumar, B. Ramu, G. Srikanth et al (2016). Formulation and evaluation of sustained release verapamil hydrochloride using natural polymers. Int J Appl Pharm Sci Res. 1(2):76-87. Doi: 10.21477/ijapsr.v1i2.10179.
8. B Ramu, N. Ramakrishna, Meruva Sathish, D. Anoosha (2015). Formulation of tellmisartan Hcl Fast Disintegrating Tablets by Sublimation Technique. International Journal of Pharm Tech Research. 8(3), 330-339..
9. Reddy.L.H et al., "Fast dissolving drug delivery systems: A review of the literature, IJPS., July 2002; 331-336.
10. Jon Gabrielsson, Nils-Olof Lindberg and Torbjorn Lundstedt, Multivariate Methods in Pharmaceutical Applications, J.Chemom, 2002; 16: 141-160.
11. Dedhiya et al, "Lercanidipine immediate release compositions" United States Patent Application, 2006; 0134212.
12. Eriksson et al, "New oral immediate release dosage form" United States Patent Application, 2006; 0034: 911.
13. Nyol S, Gupta M.M: Immediate drug release dosage form: A Review. Journal ofdrug delivery and therapeutics, 2013; 3(2): 155-161.
14. B. Ramu, Chandrul KK, Pandiyan PS, BioAnalytical Method Development of Repaglinide Drug Delivery Systems, Journal of Drug Delivery and Therapeutics. 2019;9(6):140-142 http://dx.doi.org/10.22270/jddt.v9i6.3718.