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Original Article

EXPLORING STRUCTURAL ASPECTS OF NATEGLINIDE POLYMORPHS USING POWDER X-RAY DIFFRACTION

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ABSTRACT

Objective: The present manuscript highlights the structural aspects of some polymorphic forms of nateglinide using powder x-ray diffraction (PXRD) pattern.

Methods: All the polymorphic forms were isolated as microcrystalline powder, therefore, powder diffraction patterns was used as a tool to determine the crystal structure. For this, Reflux Plus module of BIOVIA Material Studio software was used. Polymorph prediction (PP) and crystal morphology analysis were performed to estimate the global minimum in lattice energy landscape and morphologically important (M. I.) facets, respectively. Besides this, to investigate the behavior of polymorphs in solution phase, *in vitro* studies (enthalpy of solution, solubility, intrinsic dissolution rate) were also performed.

Results: A new form MS was prepared and characterized. The Form H, B, MS and S were found to exist in space group P-1, C2, P-4 and P-42C, respectively. These crystal structures were found to lie on local minima in crystal energy landscape. The stability ranking of nateglinide polymorphs follows the order: Form MS<Form B<Form H<Form S.

Conclusion: This research work demonstrates that PXRD is a valuable alternative for determining the structure of microcrystalline powders.

Keywords: Nateglinide, Powder diffraction pattern, Crystal structure, Polymorph prediction, Crystal energy landscape, Crystal morphology

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INTRODUCTION

The issue of polymorphism is of immense consideration as not only electronic, thermal but also physicochemical [1] (solubility, stability and bioavailability) properties are influenced by this phenomenon. The arrangement of atoms in the crystal lattice is the root cause for molecules to exhibit polymorphism. The identical molecules moiety can be packed into different periodic crystal structure [2] leading to distinct packing arrangement. To understand this arrangement the structure determination is of utmost importance. Single crystal X-rays diffraction (SCXRD) analysis, without any doubt, is the most powerful technique for elucidating the structure of the molecule. But an intrinsic limitation of this technique is the requirement to prepare a crystal of sufficient size, quality and stability. When appropriate single crystals cannot be obtained, PXRD becomes the vital tool to tackle the problem of structure determination [4]. For these reasons, from the past decade, the emphasis was laid on the development, implementation and optimization of new techniques for structure solution from powder diffraction data. Hence, opening up many new opportunities in structural science for microcrystalline powders [4, 5].

The objective of the present manuscript is to use PXRD for studying the structural aspects of polymorphs of nateglinide, a poorly water-soluble oral hypoglycemic agent [6]. Nateglinide has potential to exhibit polymorphism because of the complexity of its structure. The presence of two strong hydrogen bond donors (NH and OH) and two strong acceptors (C=O) are responsible for the existence of a variety of intermolecular hydrogen bonding pattern leading to different polymorphic modifications [7]. Many research groups have tried to isolate the polymorphs of nateglinide. The first patent appeared in 1995, explicating the methods for preparing two forms i.e., Form B and H [8]. Later, a patent unfolded 26 modifications (polymorphs and solvates) of nateglinide, using different solvents, anti-solvents and their mixtures, along with their characterization [9]. Gang Li, *et al.* with the assistance of PXRD and scanning electronic microscopy (SEM), have reported the existence of new crystal form *i.e.* Form S [10]. Subsequently, publications by Bruni, *et al.* reported a new but unstable anhydrous polymorphic modification melting at 102 °C (form X), which gradually transformed to form H. These researchers have also proposed the method for evaluating the purity of H polymorph in the binary mixture of B and H using diffraction scanning calorimetry (DSC) [11-13]. The monotropic relationship between Form B and H and stability co-relation between these two had been established by Upadhyay, *et al.*, using configurational free energy phase diagrams [14]. Recently, Pasha, *et al.* have evaluated few crystal forms by recrystallizing nateglinide from solvents as well as aqueous solution of surfactants without proper characterization, interpretation and structure determination [15].

The major lacuna in the literature is the unavailability of the structure of either the nateglinide or its reported forms except for the one crystallographic report of its cocrystal with dilute HCl [8]. Gang Li, *et al.* has attempted to solve the structure of two polymorphs (Form H and S) from PXRD pattern using Jade software [16]. However, the arrangement of atoms as well as the hydrogen bond pattern prevailing in different polymorphs was not described. Besides this, Jain, *et al.* has performed *ab initio* calculations and semi-empirical calculation on this molecule, reporting few important conformations and concluded that polymorphism in nateglinide might have originated from the dimerization of the molecule [17].

The main focus of the present work is to determine the crystal structure of experimentally crystallized polymorphs using PXRD pattern by BIOVIA Material Studio software. As isolating the perfect crystal for SCXRD is always a tough and skillful task, so was the case with nateglinide. All the forms of nateglinde were isolated only as microcrystalline powder, so powder diffraction patterns were used as a tool to determine the crystal structure.

Experimental hunting of potential polymorphs may be expensive, tedious and time-consuming. Alternate to it or rather an assisting hand to experimental screening is polymorph prediction (PP). All the possible polymorphic forms can be identified by computational crystal structure prediction (CSP), which further calculates their lattice energies. This will aid in spotting polymorphic structure with minimum energy (the global minimum) [18]. The lower energy

regions in crystal energy landscape grab attention to locate the thermodynamically viable polymorph [19]. All the plausible polymorphs that appear at local minima show different packing arrangement, which subsequently determines its properties. The understanding of crystal structure and the intermolecular forces in crystals are the integral quests to predict, understand or modify the physicochemical properties. These properties are also influenced by the crystal morphology, [20] which is the critical parameter for the quality assessment of the crystalline material [21]. Thus, screening of all the plausible crystal structures and their morphology takes us one step ahead for better understanding and controlling polymorphism [22]. Selection of polymorph with optimum properties is an integral part of formulation and development for crystalline products. Thus this work also deals with *in silico* prediction of all the possible polymorphs in respective space groups obtained from crystal structure determination along with a simulation of their morphology and thus estimating the M. I. facets. The experimentally prepared polymorphs were also evaluated for their physicochemical properties like solubility, intrinsic dissolution rate (IDR) and enthalpy of solution.

MATERIALS AND METHODS

Materials

Nateglinide was obtained as a gift sample from Glenmark Pharmaceuticals Ltd. (Baddi, India). Analytical grade solvents (Sigma Aldrich) were used in this work.

Preparation of polymorphs

Different polymorphic forms of nateglinide were precipitated out by slow evaporation of solvent-anti-solvent mixture. Form B was obtained by dissolving Form H (marketed form) in hot ethyl acetate and was subjected to slow evaporation. Apart from this, the same polymorph, Form B was also generated on dissolving Form H in dioxane (solvent), followed by adding anti-solvent i.e. hexane, heptane and cyclohexane in 1:1 ratio, respectively. Slow evaporation of Form H from ethanol (solvent): hexane (anti-solvent) (1:3) produced Form MS.

Preparation of Form S was done in two steps. Firstly, Form H was added to heptane (anti-solvent) followed by addition of ethyl acetate (solvent) in ratio 1:1, to solubilize it completely and kept for slow evaporation for 30 d. Then the recrystallized product was heated up to 150 °C for 30 min under nitrogen and dried in a desiccator.

Thermal methods of analysis

DSC thermograms were obtained on Q20, TA Instruments-Waters LLC, USA. The instrument was calibrated for temperature and heat flow accuracy using the melting of pure indium (mp 156.6 °C and ΔH of 28.45 Jg-1). A mass between 2-4 mg was taken into the aluminium pan, covered with lid and sealed. DSC curves were obtained under a nitrogen purge of 50 ml per minute at a heating rate of 10 °C per minute with the temperature range from 50-250 °C.

Powder x-ray diffraction analysis

The powder diffraction patterns were observed on x-ray diffractometer (XPERT-PRO, PANalytical, Netherlands) using Cu tube anode. The diffractograms were recorded under following conditions: voltage 40 kV, 35 mA and fixed divergence slit using the configuration; 2θ range: 2 ° to 50 °, 0.01 step size, 10 s dwell time. Approximately 200 mg of samples were loaded into the sample holder.

Solid state stability studies

The physical stability of polymorphs is dependent on atmospheric conditions. It is an important aspect for quality, safety and efficacy of a drug product [23]. To monitor the stability of polymorphs of nateglinide accelerated stability were performed at 40 °C/75% RH for 6 mo. Samples were withdrawn after 0, 3 and 6 mo and were analyzed with the assistance of DSC and PXRD.

Crystal structure determination from PXRD

The PXRD pattern was used to solve the crystal structure of polymorphs of nateglinide using the Reflex Plus module of BIOVIA Material Studio software. This process was carried out using Dmol3, X-Cell, Pawley Refinement, Powder Solve and Rietveld Refinement modules [24]. Geometry optimization was done with the gradient-corrected generalized gradient approximation (GGA) and PBE functional in density functional theory (DFT) Dmol3 with double numeric plus polarization (DNP) basis set. It was followed by indexing using X-Cell on 20-35 peaks ranging from 2 °-30 ° 2θ. The unit cell from X-Cell was used as input for Pawley refinement. The weighted rietveld parameter (Rwp) value obtained after the refinement was used to establish the relation between simulated and experimental powder patterns. The optimized structure of the drug molecule and the above-generated unit cell were subjected to Reflex Powder Solve that involved simulated annealing algorithm (10 cycles with 2000100 steps each). Further, rietveld refinement of the structure was performed to obtain a final structure solution.

In silico studies

a) Polymorph prediction

All the possible polymorphs of nateglinide in space groups (P-1, C2, P-4, P-42C) were predicted using Polymorph Predictor module of BIOVIA Material studio software. The molecule of nateglinide was geometrically optimized with COMPASS forcefield. The high-level *ab initio* calculation on these optimized molecules leads to the generation of electrostatic potential (ESP) charges. These were then used as input for polymorph prediction. The same forcefield with Ewald summation for the Van der Waals and electrostatic interactions was used for the calculation and minimization of energy.

The prediction of polymorphs took place in four steps *i.e.*, packing (Monte Carlo simulation), pre-clustering, optimization, and clustering. This results in the generation of the potential crystal structures for the molecule in the selected space group(s). This is followed by grouping the crystals into clusters of similar structures, optimization of generated structures. The optimized structures were then rechecked if any of them converge to the same energy minima. Energy vs density graph (crystal energy landscape) was plotted to search for global minima.

b) Morphology simulation

Morphology of the polymorphs was simulated using Donnay-Harker rules in the Morphology module of BIOVIA Material Studio, employing COMPASS forcefield. The growth morphology algorithm generates growth faces and their attachment energy (**E**att). This is based on the assumption that the crystal face growth rate is proportional to its attachment energy (AE) [25-27]. The maximum value for the Miller indices and number of growing faces were set to 3 and 200, respectively and inter-planar spacing minima was set to 1.3 A °.

Enthalpy of solution

Enthalpy of the solution was determined by isoperibol solution calorimetry (ISC) (Calorimetry Science Corporation, UTAH, USA) model 4300 in phosphate buffer at pH 7.4 at 37 °C. The procedure followed was same as in our earlier work [28].

Solubility studies

The solubility studies were done by shaking an excess amount of drug (approx.5 mg) in 3 ml phosphate buffer pH 7.4, in water bath shaker (MSW-275 Macroscientific works, Delhi) at 37 °C for 24 h at 200 rpm. The resulting slurry was filtered through a 0.45µm membrane filter. The absorbance was measured at 200 nm with Lambda 25 UV/VIS spectrometer to determine the concentration of nateglinide.

Intrinsic dissolution studies

Intrinsic dissolution studies were performed on dissolution test apparatus, DS 8000 (Lab India Analyticals) in phosphate buffer pH 7.4 at 37 °C with 100 rpm for 3 h. The concentration of nateglinide was determined by measuring absorbance at 200 nm with Lambda 25 UV/VIS spectrometer.

RESULTS

Thermal method of analysis

DSC pattern of a form produced from recrystallization of commercial sample (form H, melting endotherm at 140.98 °C, enthalpy of fusion: 53.88 J/g) from ethyl acetate, dioxane: heptane (1:1), dioxane:

hexane (1:1), dioxane: cyclohexane (1:1), showed the appearance of single sharp melting endothermic peak at 129.25 °C (enthalpy of fusion: 23.75 J/g) as shown in fig. 1(a)). The position of the melting endotherm suggested it to be Form B, which has already been reported in the literature. However, these authors have used different solvents to prepare Form B [8, 29].

A new polymorphically pure form (Form MS) has been isolated by recrystallization from ethanol: hexane (1:3). Its DSC thermogram showed sharp endotherm at 105.12 °C (enthalpy of fusion: 4.34 J/g) (fig. 1(a)). Recrystallization of Form H from ethyl acetate: heptane (1:1), showed interesting DSC pattern comprising of two endotherms at 129.57 °C and 174.79 °C, separated by an exotherm at 147.32 °C, (fig. 1(b)).

The thermogram of pure Form S, obtained after heating up to 150 °C, showed a single sharp melting endotherm at 172.36 °C (enthalpy of fusion: 103.50 J/g) (fig. 1(b)).

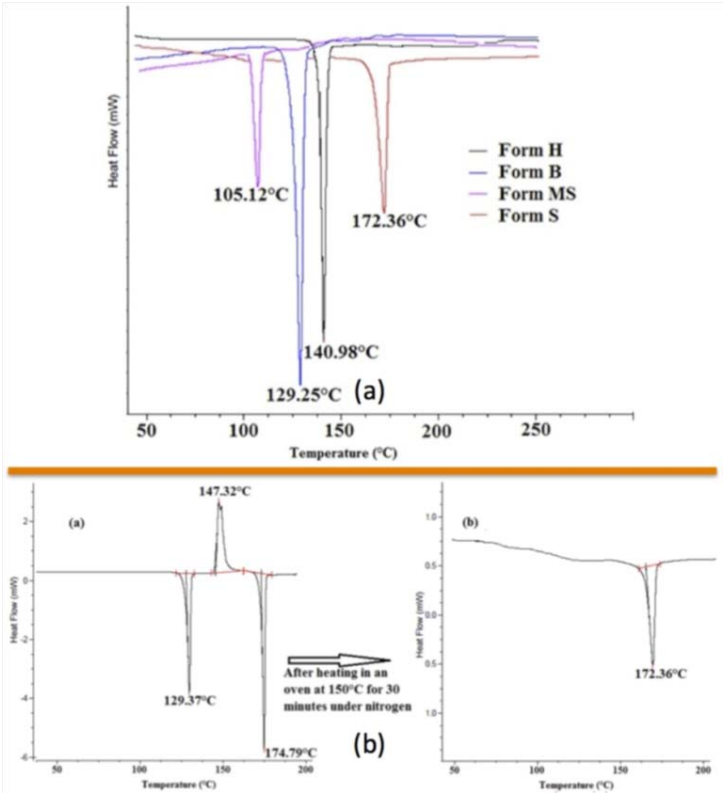


Fig. 1: (a) DSC thermograms of nateglinide polymorphs, (b) DSC thermogram showing isolation of pure Form S

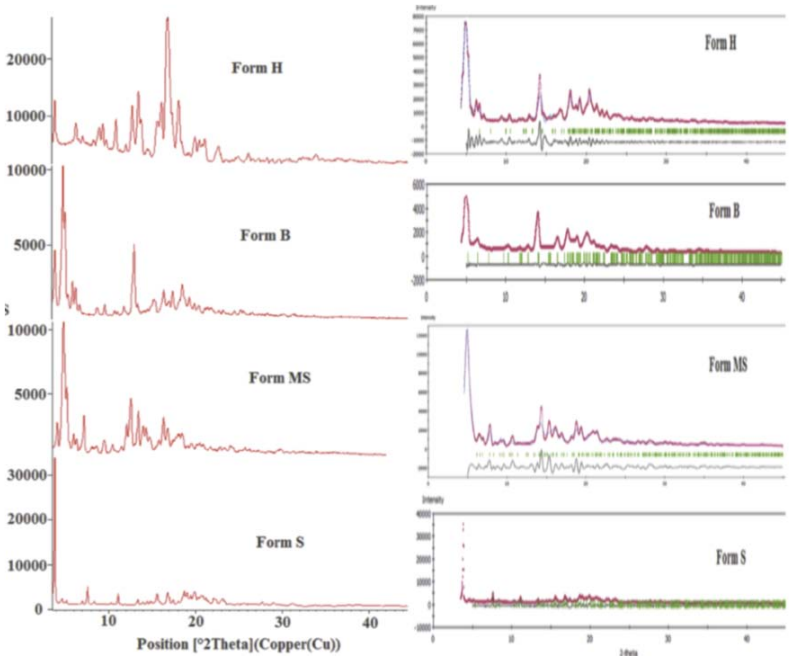


Fig. 2: PXRD pattern of polymorphs of nateglinide and their comparison with the respective simulated pattern (black line indicates the difference between the experimental and simulated PXRD pattern

Powder x-ray diffraction analysis

Powder diffraction pattern of prepared polymorphs are given in fig. 2. The diffraction patterns are different from each other and from the marketed form (Form H) as well. The quality of diffraction pattern was adequately good for solving the crystal structure.

Solid state stability studies

For a drug substance with a number of polymorphs, it is significant to comprehend their relative stability and their inter-conversions. During the stability studies, a consistency in DSC and PXRD pattern of the form H, B and S were observed. The DSC and PXRD pattern of all these aged polymorphic forms were found to be same as that of initial samples.

Crystal structure determination

PXRD was used to understand the arrangement of atoms in the crystal lattice, utilizing Reflux Plus module of BIOVIA Material studio. The results obtained were interesting and are unique as shown in fig. 3-6. These results demonstrate the packing arrangement of these polymorphs in the crystal lattice along with their hydrogen bonding pattern. The crystallographic parameters of all the polymorphs are given in table 1. The crystallographic files are deposited to CCDC with reference number 1401735-1401738. The reliability of determined crystal structures was estimated by the similarity between their experimental and simulated PXRD patterns (comparison shown in fig. 2).

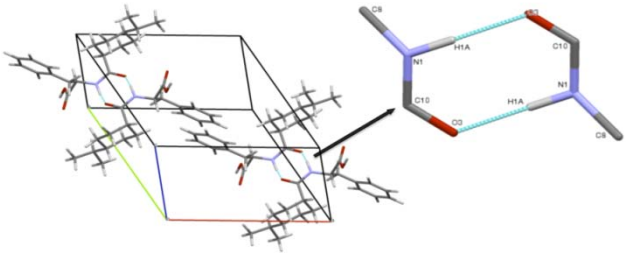


Fig. 3: Packing arrangement along c axis and homomeric synthon of form H

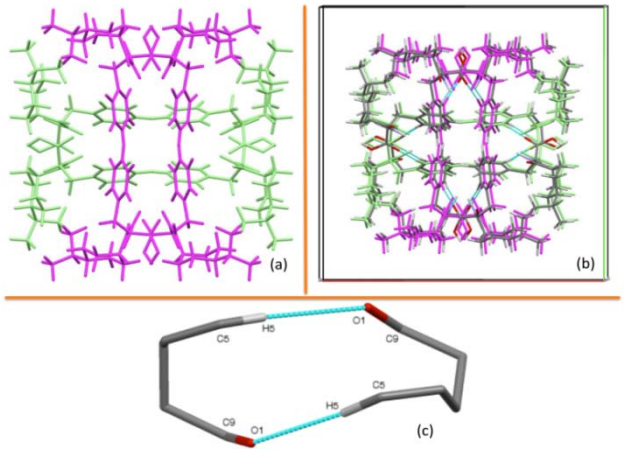


Fig. 4: Form S (a) I-shaped intersecting top view along c axis, (b) packing arrangement, (c) homomeric synthon

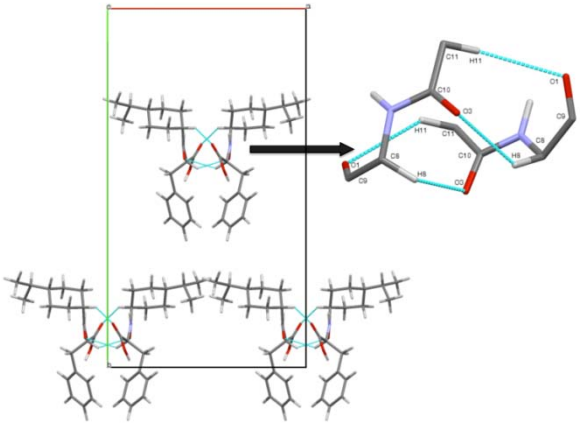


Fig. 5: Packing arrangement along c axis and homomeric synthon of Form B

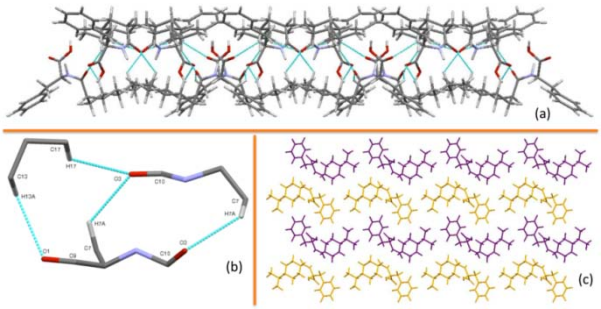


Fig. 6: Form MS (a) sandwiched bilayer along a axis, (b) homomeric synthon, (c) top view along c axis

Table 1: Crystallographic parameters of nateglinide polymorphs

Polymorph	Form H	Form B	Form MS	Form S
Space group(s)	P-1	C2	P-4	P-42C
Crystal Lattice	Triclinic	Monoclinic	Tetragonal	Tetragonal
a (Å)	12.27	16.13	13.47	23.70
b (Å)	11.44	27.54	13.47	23.70
c (Å)	8.84	18.24	41.93	12.45
α (deg)	66.46	90	90	90
β (deg)	104.33	108.99	90	90
γ (deg)	116.42	90	90	90
Z	2	4	4	8
Cell Volume (Å^3)	1014.93	7659.06	7610.04	6992.19
Rwp (%)	14.37	5.14	17.77	16.16

***In silico* studies**

Indexing of the powder diffraction pattern of experimentally prepared polymorphs (Form H, B, MS and S) revealed that the forms exists in P-1, C2, P-4 and P-42C, respectively, therefore, the possible crystal structures were explored in these space groups using Polymorph Predictor, employing COMPASS force field.

The search produced more than 2100 distinct hypothetical crystal structures within 30 KJ/mol of global energy minimum.

These energy-optimized polymorphs were used as input for CSP calculations, and the resulting crystal energy landscape, comprising energetically feasible crystal structures are shown in fig. 7. The structures corresponding to forms H, B, MS and S were successfully found in the search at local minimum of-55.28,-52.69,-52.28 and-55.40 KJ/mol, respectively.

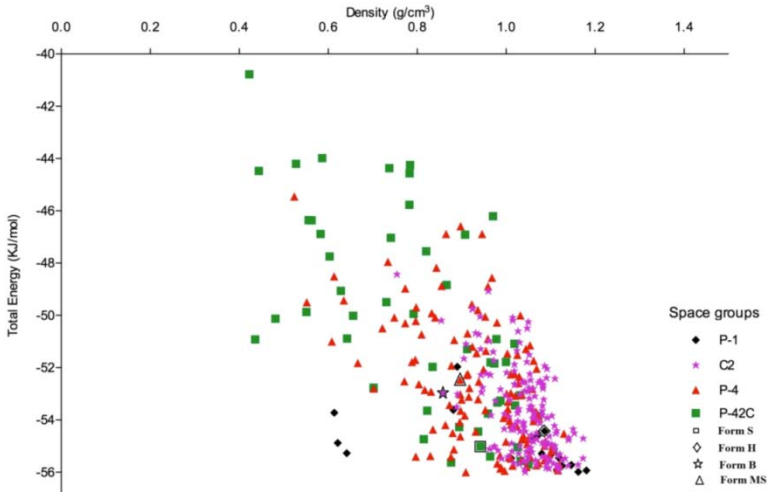
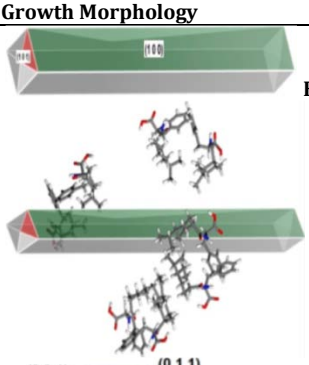
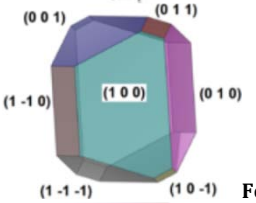
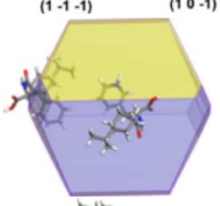
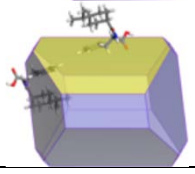
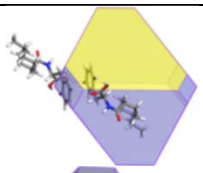
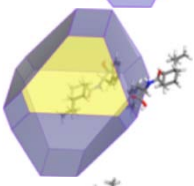
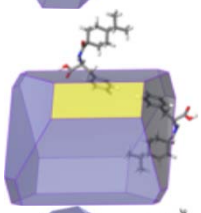
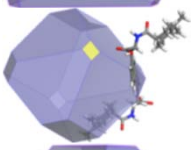
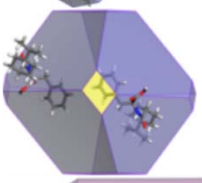
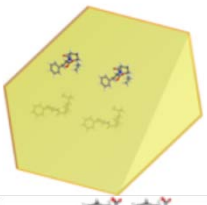
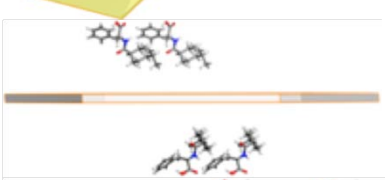
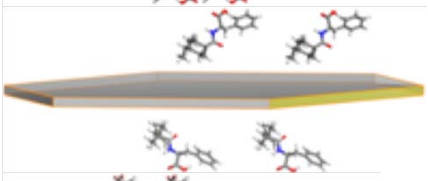
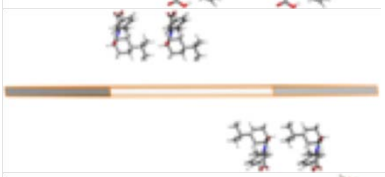
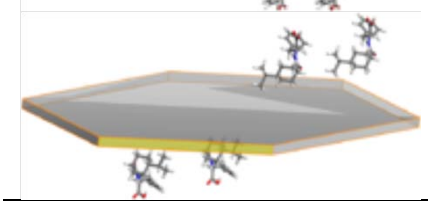


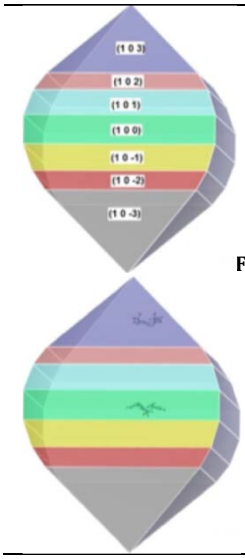
Fig. 7: Crystal energy landscape within 16KJ/mol of global energy minimum. The lattice energy minima corresponding to the experimental crystal structure are also shown

Morphology is an important parameter to distinguish various polymorphs, which are in turn affected by the experimental conditions and thus the morphology of nateglinide polymorphs were simulated. The crystal habits along with their M. I. facets (slowest growing faces) of the all forms (H, B, MS and S) are represented in table 2. As the growth rate of a crystal face is relative to its attachment energy, [24] keeping this in mind, morphologies of all the forms were assessed.

Table 2: Crystal morphology prediction

Growth Morphology		Total % area	E_{att} (KJ/mol)
	**Form S, Aspect ratio: 3.6, MI facets: 2**		
	{1 0 0}	98.46	-1.60
	{1 0 1}	1.54	-5.03
			
	**Form H, Aspect ratio: 2.8, MI facets: 7**		
	{0 1 0}	28.89	-2.62
			
	{1 0 0}	25.92	-6.43

	{0 0 1}	18.25	-7.27
	{1-1-1}	16.42	-7.43
	{1-1 0}	7.99	-8.51
	{1 0-1}	0.82	-9.04
	{0 1 1}	1.71	-12.23
	**Form B, Aspect ratio: 1.8, MI facets: 5**		
	{0 0 1}	94.98	-3.65
	{2 2-1}	1.80	-4.71
	{2-2-1}	1.80	-4.71
	{0 2 0}	0.71	-5.27
	{0-2 0}	0.71	-5.27



Form MS, Aspect ratio: 1.4, MI facets: 7

{1 0 2}	9.07	-16.43
{1 0-2}	9.07	-16.43
{1 0 3}	20.83	-16.43
{1 0-3}	20.83	-16.43
{1 0 1}	12.80	-16.43
{1 0-1}	12.80	-16.43
{1 0 0}	14.59	-16.43

Enthalpy of solution

The molar enthalpy of solution (ΔH_{sol}) is an important parameter, which is closely related with the lattice energy and can be used to distinguish different polymorphs. The molar enthalpy of solution (ΔH_{sol}) of polymorphs was determined in phosphate buffer pH 7.4 at 37 °C. All the polymorphs showed endothermic behaviour in phosphate buffer and the molar enthalpy of solution have been found to be of order: MS form (1.2 KJ/mol)<Form B (1.9 KJ/mol)<Form H (2.2 KJ/mol)<Form S (4.7 KJ/mol).

Equilibrium solubility and intrinsic dissolution studies

Equilibrium solubility and IDR of all the polymorphs were determined in phosphate buffer pH 7.4. The studies suggested that Form MS (89.7 mg/100 ml; 0.496 mg/min/cm^2) and Form B (87.1 mg/100 ml; 0.479 mg/min/cm^2) have high solubility and IDR whereas Form S (71.3 mg/100 ml; 0.263 mg/min/cm^2) has low solubility and IDR, respectively, as compared to the drug (Form H, 86.5 mg/100 ml; 0.317 mg/min/cm^2).

DISCUSSION

The DSC pattern of Form B shows single endotherm suggesting it to be polymorphically pure. The presence of endotherm at 105.12 °C indicates the formation of new polymorph, i.e. Form MS. DSC pattern of Form S demonstrates the presence of two endothermic and one exothermic peak. This suggested the conversion of one solid form to another through the molten state. The first endotherm indicates melting of Form B followed by its liquid-solid transition to a stable form, which melts at 174.79 °C and was similar to the earlier reported Form S. Thermal analysis shows that the Form MS have lowest melting point along with the lowest heat of fusion followed by form B, H and S (highest melting point and heat of fusion). So, according to Burger's rule all the forms are monotropically related.

The different diffraction patterns of the prepared polymorphs showed the formation of distinct crystalline phase. The solid state stability studies of polymorphs were carried out. As the thermograms and diffraction patterns of aged samples were similar to that of initial samples, therefore, these samples are found to be stable even after 6 mo. On the other hand, Form MS showed time-mediated conversion to Form B after 6 mo. DSC and PXRD pattern of Form MS after 6 mo were found to be similar to that of the Form B, thereby, confirming its conversion to Form B.

The primary objective of this study was to explore the structural aspects of nateglinde polymorphs. To achieve this, the crystal structures of these crystalline polymorphs were determined using PXRD by BIOVIA Material Studio software. Form H was found to exist in triclinic crystal system, (P-1 space group), which is in concordance with the results reported by Gang *et al.* [16]. However, the cell parameters are not same. The reason for this may be attributed to the difference in the indexing algorithm. Moreover, they have not described the space group and the packing arrangement. Form H consists of two molecules in the unit cell (fig. 3). Homomeric synthon between-NH and-CO of an amide group (N1-H1···O3) of different molecules is formed. It appears as a dimer (amide-amide dimer), showing hydrogen bonded wavy arrangement of molecules along c axis in the crystal lattice lying parallel to one another.

The crystal structure of Form S as determined in the present study is tetragonal (P-42C) and the packing arrangement (fig. 4) shows two I-shaped intersecting perpendicular layers consisting of four molecules in each layer. Homomeric synthon (C5-H5···O1) between two molecules involving-CH of the benzene ring and CO of carboxylic group is formed. They are arranged in such a manner that four molecules appear on anterior and four on posterior face alternatively. The crystal structure of Form S as determined in the preset study is not in agreement with the literature [16]. The comparative profile for both the structures cannot be analyzed, as the procedural details concerning the structural determination from PXRD pattern using Jade software are not provided

The structural aspects of From B and MS have not been explored till date. Form B exists in monoclinic crystal system with C2 space group (fig. 5). Nateglinide molecule is present in in L-shaped conformation forming two homomeric synthons. One homosynthon (O3···H8-C8) is formed between–CO of amide group and methine–CH (attached to carboxylic group) of different molecules. The other homosynthon formed (O1···H11-C11), shows the hydrogen bonding between CO of carboxylic group and–CH of cyclohexyl ring. The packing arrangement is in such a fashion that the benzene ring (head) of two center molecules faces each other whereas the cyclic ring and hydrocarbon chain (tail) are opposite to each other. Other two molecules are present at the corners, with the head emerging out of the unit cell while the tail is approaching each other in the unit cell.

Form MS exists in tetragonal crystal system with P-4 space group (fig. 6). Carbonyl oxygen of amide group bifurcates to form hydrogen bond with methine–CH (attached to cyclohexyl ring) and methylene–CH (attached to benzene ring) to generate C17-H17···O3 and C7-H7A···O3. Another homosynthon (C13-H13A···O1) is formed by the involvement of–CO of amide group and–CH of cyclohexyl ring. The molecules are oriented like a rippled bilayer in which all the hydrogen bonds are sandwiched (along a axis). When viewed from c axis, the molecules seem to form zigzag antiparallel layers.

The lattice energy of the polymorphs was estimated by CSP calculations. The crystal energy landscape shows the presence of global minima at-40.78 KJ/mol. The crystal energy landscape gives explicit account of the packing arrangement rather than the space

group. The aforesaid landscape was cluttered, indicating the strong tendency to form polymorphs having different motifs, henceforth, packing problem (close packing). The experimental crystal structures lie on local minimum energy rather than global minimum. The reason for this may be attributed to the kinetic inaccessibility of the polymorphs that lie on global minima.

To move one step closer for understanding polymorphism in nategilnide, its morphology was simulated. This demonstrated the M. I. facets along with their attachment energies. The faces with the lowest attachment energies (in terms of magnitude) are the slowest growing and are of more importance [26, 27]. The appearance probability of the observed forms in lattice energy landscape (Form MS> Form B> Form H> Form S) can be explained easily on the basis of attachment energy [30-32]. Table 2 clearly shows that the magnitude of attachment energy of form MS is-16.43 which is highest of all the forms, and is responsible for its early appearance. The growth rate and attachment energy are inversely related to aspect ratio. Slower the growth rate of M. I. facet, higher will be its aspect ratio implying plate-like or needle morphology. The attachment energy and the aspect ratio, in a way, are also related to the stability of the polymorphs. Thus, stability ranking of nateglinide polymorphs follows the order (Form MS<Form B<Form H<Form S). The high aspect ratio may also be the reason for the nonexistence of the predicted polymorphs.

The physico-chemical parameters of all the polymorphs were evaluated in phosphate buffer pH 7.4. The ΔH_{sol} of polymorphs showed endothermic behavior with values different from that reported by Gang Li *et al.* It is worth mentioning that these authors have used Van't Hoff's equation to calculate the heat of solution from solubility data [33]. The more the magnitude, the higher is the lattice energy, i.e., atoms are held more strongly in crystal lattice. The highest magnitude of ΔH_{sol} of Form S is indicates that it is associated with the strongest lattice as compared to other forms. Low solubility and low IDR of Form MS implies its strong crystal lattice, which is in concordance with the enthalpy of solution and thermal analysis data.

CONCLUSION

To understand the arrangement of atoms in crystal lattice, structure determination is of utmost importance. Driven by this objective, the determination of crystal structure from powder diffraction pattern was carried out. This research work demonstrated that PXRD is a valuable alternative for determining the structure of microcrystalline powders. Crystal structures of polymorphs were determined using Reflux Plus module of BIOVIA Material Studio software. The Form H, B, MS and S were found to exist in triclinic, monoclinic, tetragonal and tetragonal, correspondingly. This Form MS is a new isolated polymorphic from. All the possible polymorphs in the respective space groups were explored using Polymorph Predictor. The crystal energy landscape concluded that the experimentally isolated polymorphs lie on local minima. For moving one step ahead in understanding the crystal habit, morphology of these polymorphs was studied. The calculations of attachment energy and aspect ratio from morphological prediction were useful to establish the stability of the polymorphs.

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AUTHOR CONTRIBUTION

These authors contributed equally to this work.

CONFLICT OF INTERESTS

Declared none

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