World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Review Article

Pharmaceutical polymorphism: The phenomenon affecting the performance of drug and an approach to enhance drug solubility, stability and bioavailability

Priyanka Maurya[1]*, Ruchi Tiwari[2], Gaurav Tiwari[3], Pooja Yadav[1], Priyanka Shukla[1]

[1]Research Scholar, [2]Assistant Professor and [3]Associate Professor, Department of Pharmacy, Pranveer Singh Institute of Technology, Kanpur, India

Received: 25-07-2016 / Revised: 18-08-2016 / Accepted: 21-08-2016 / Published: 27-08-2016

ABSTRACT

Pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist two or more crystalline phases that have different arrangements and conformations of the molecules in the crystal lattice. In past decades, there have been significant efforts on the discovery, selection and control of the solid forms of active pharmaceutical ingredients and bulk drugs. Polymorphs and solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapour pressure, and density. Polymorphism must be controlled to prevent possible ineffective therapy and improper dosage. Drugs with low water solubility are predisposed to poor and variable oral bioavailability and, therefore, to variability in clinical response, that might be overcome through an appropriate formulation of the drug. Polymorphs (anhydrous and solvate/hydrate forms) may resolve these bioavailability problems Number of strategies exists for enhancing the bioavailability of those drugs, these strategies are greatly dependent on the physical and chemical nature of the molecules being developed. This review will discuss the applied nature of polymorphism starting from their preparation, characterization and pharmaceutical importance with a special emphasis on drug.

Key Words: Polymorphism; Active pharmaceutical Ingredients; Crystal Form; Solid State; Poorly Soluble Drugs; Pharmaceutical Application.

INTRODUCTION

Many active pharmaceutical ingredients can exist in different physical and morphological forms. Polymorphism is often characterized as the ability of active pharmaceutical ingredient to exist in two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice. Polymorphism refers to the occurrence of different crystalline forms of the same drug substance. Polymorphs and solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapour pressure, and density. These properties have a direct impact on the processability of drug substances and the performance of drug products, such as stability, dissolution, and bioavailability [1].

Physical Forms of Pharmaceutical Solids: Most pharmaceuticals are fundamentally organic compounds, and organic compounds can often exist in a variety of solid forms. This means that although a drug will remain as the same chemical entity and have the same chemical properties of stability, reactivity, etc., it may not always act in the same way in the solid state. These differences may or may not cause a difference in pharmacological effect (i.e., how the drug may work in the human body such as inhibiting proteases or reducing blood pressure). In the Norvir example, the change in solid form had a great effect on solubility, which in turn reduced bioavailability [2].

Definition: 'Polymorphism' comes from the Greek word, Polus = manyand and morph=shape. Thus it is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice. It is essentially means that the different polymorphs, the same molecule exist in the same ways.[3] A variety of polymorphs of a drug

***Corresponding Author Address:** **Priyanka Maurya,** Department of Pharmacy, Pranveer Singh Institute Of Technology, Kanpur, India; E- mail: priyankamauryapharma@gmail.com.*

molecule may have different physical and chemical properties such as stability, solubility, melting point, bioavailability ,etc.[4] In pharmaceutical science, however, the term is used to designate several solid state forms of drugs and excipients, including amorphous forms, solvates, hydrates, salts and co-crystals.[5,6]

Methods of polymorphs preparation: The most effective and common method for preparing drug polymorphs is crystallization from solutions or melts [7,8].The typical methods for preparing drug polymorphs and solvates are Equilibrium and non-equilibrium crystallization[7-10].which are given in table 1. Equilibrium crystallization Methods from solution are depended on isothermal or constant concentration solvent evaporation from a solution in equilibrium with crystals of a given polymorph. Methods of Non-equilibrium crystallization are carried out at significant supersaturation conditions in a method owing to rapid variable-temperature crystallization, solvent exchange, and drying by spraying or sublimation.[11]

Table-1: Equilibrium and Non-equilibrium crystallization Methods for Producing Drug Polymorphs

Polymorphism-Equilibrium Crystallization Methods			
Method	Principle	Examples	Reference
By Equilibrium crystallization	Slow isothermal crystallization of drug	Pramocaine Chloramphenicol-palmitate	[12,13]
Isothermal evaporation of solvent	Slow isothermal evaporation of solvent from a solution in equilibrium with crystals of drug	Prednisolone-acetate Phenobarbital Efavirenz Tolbutamide Acyclovir	[14-18]
Non-equilibrium Crystallization Methods			
Non equilibrium crystallization From the melt	Moderately fast crystallization	Paracetamol	[19]
Polythermal crystallization	Preparation of preliminary hot saturated solution of drug followed by rapid decrease of drug solubility in solution by cooling	Diflunisal	[20]
Exchange of Solvent	Depended on rapid isothermal reduction of drug solubility in solution by addition of solvent that diminishes the solubility of the drug in the resulting solution	sulfamethoxydiazine, diflunisal histidine Ibuprofen Sodium	[20-22]
Spray drying	BASED ongenerating the vital degree of drug supersaturation in a solution dispersed in a gas heat transfer stream because of solvent evaporation	Phenobarbita	[23]
Spraying from supercritical solvents	It involves generating the required degree of drug supersaturation in a supercritical solution upon dispersion because of solvent evaporation	Tolbutamide, Barbital	[17,24]
Sublimation drying	Based on solvent sublimation from a preliminarilyfrozen drug solution	Pyrazinamide Phenobarbital	[15,25]
Crystallization	A saturated solution or melt in drops placed on various surfaces and films leads to crystallization	Sulfathiazole	[26]

CRYSTALLINE FORM

In order to form a solid, a compound must have internal attraction between molecules that is sufficient to restrict the free movement that exists in liquids and gases, but how strong the internal attractions are can vary. There are multiple well-known solid forms that have been identified in pharmaceuticals. A crystalline solid form or crystal exists when the molecules of the drug are arranged in the solid in a three-dimensional repeating pattern or unit cell. Crystalline solids are usually highly stable and have a well-established

solubility and dissolution rate. Most drugs are used in the crystalline form.[27]

Mechanism to prepare crystal form: Operating conditions of crystallization can affect in the final crystalline forms. Consequently, a full understanding of the nucleation, crystal growth and phase transformation in the crystallization sequence is vital for the control of the polymorphic form. It is recognized that the nucleation process is the principal step in the control of polymorphic crystallization.[28]

The Amorphous Solids: A second type of solid form that is non-crystalline is referred to as the amorphous form. This type of solid is randomly arranged with a high degree of disorder in the molecular arrangement. The amorphous state is usually much faster dissolving than the crystalline state, and has a variable solubility that is usually higher than the crystalline form. The amorphous form is often less stable than the crystalline form and is usually hygroscopic (i.e., the amorphous form will absorb water from the atmosphere under ambient humidity conditions).[27] In amorphous and crystalline forms, a solid drug may be anhydrous or a solvate/hydrate. When a solid form contains a solvent, it is known as a solvate. When the solvent is water, it is termed a hydrate.[30]

TYPES OF POLYMORPHISM

Phase transition: the process of transformation of one polymorph into another. Which may also occur on storage or during processing is called Phase transition.

ENANTIOTROPIC

In some cases one polymorphic form can change into another at a definite temperature when the two forms have a common vapour pressure. This temperature is known as the transition temperature. One form is stable above this temperature and the other form below it. When the change of one form to the other at the transition temperature is reversible, the phenomenon is called Enantiotropy and the polymorphic forms enantiotropes. For example, rhombic sulphur (α-sulphur) on heating changes to monoclinic sulphur (β-sulphur) at 95.6ºc (transition temperature). Also monoclinic sulphur, on cooling, again changes to rhombic sulphur at 95.6°c.[32]

MONOTROPHS

It occur when one form is stable and the other meta stable. The meta stable changes to the stable form at all temperature and the change is not reversible. Thus there is no transition temperature as the vapour pressures are never equal. This type of polymorphism is exhibited by phosphorus.

White phosphorus → red phosphorus

Another example is graphite and diamond, graphite being stable and diamond meta-stable, although the change is infinitely slow.[32]

POLYMORPH PROPERTIES DIFFERENCES

Packing properties
- Molar volume and density
- Refractive index, optical properties
- Conductivity, electrical and thermal
- Hygroscopicity

Thermodynamic properties
- Melting and sublimation temperatures
- Internal energy
- Enthalpy
- Heat capacity
- Entropy
- Free energy and chemical potential
- Thermodynamic activity
- Vapour pressure
- Solubility

Spectroscopic properties
- Electronic transitions, ultraviolet-visible spectra
- Vibrational transitions, infrared and Raman spectra
- Rotational transitions
- Nuclear magnetic resonance chemical shifts

Kinetic properties
- Dissolution rate
- Rates of solid state reactions
- Stability

Surface properties
- Surface free energy
- Interfacial tensions
- Habit

Mechanical properties
- Hardness
- Tensile strength
- Compactibility, tabletability
- Handling, flow and blending[33]

Characterization and Quantification
- X-ray powder diffraction (XRPD)
- Microscopy,
- Thermal analysis (e.g. differential scanning calorimetry (DSC),
- Thermal gravimetric analysis (TGA),
- Hot-stage microscopy,
- Spectroscopy (e.g. IR, Raman, solid-state NMR)

X-RAY POWDER DIFFRACTION

Single crystal and powder X-ray diffraction techniques are the most suitable and more utilized tools to study and characterize polymorphs in pharmaceutical solids because they provide unequivocal proof of either polymorphism existence or polymorphism occurrence[28]. Powder

X-ray diffraction is feasible for application in the quality control of polymorphism in capsules, tablets, and pastes, among others. For this purpose, the API must be crystalline and be present at a concentration greater than 5% (w/w) in the formulation, which is the commonly adopted detection limit for phase quantification using PXRD techniques. The pharmaceutical formulation can be analyzed after minimal or no pretreatment of the sample without a requirement to separate the API from the excipients because most excipients are not detected by X-rays. Moreover, it is possible to simultaneously identify more than one API in the formulation[34].

THERMAL ANALYSIS

Thermal properties of polymorphs are an important aspect and are generally fetched by DSC and TGA [35-37]

Differential Thermal Analysis (DTA)

The advantage is that the sample size required is only 2-5mg. DTA measures the temperature difference between sample and reference as a function of temperature or time when heating at constant rate. A DTA consist of a sample holder comprising thermocouples, sample containers and a ceramic or metallic block; a furnace; a temperature programmer; and a recording system. The key feature is the existence of two thermocouples connected to a voltmeter. One thermocouple is placed in an inert material such as Al_2O_3, while the other is placed in a sample of the material under study. As the temperature is increased, there will be a brief deflection of the voltmeter if the sample is undergoing a phase transition.[35-37]

Differential Scanning Calorimetric (DSC)

DSC is also like DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference, it measures the enthalpy of transition. When no physical or chemical changes is occurring within the sample then there is neither a temperature change nor the need to input energy to maintain an isotherm. Samples that may be studied by DSC or DTA are: Powder, single crystals, polymer films, semi-solids. DSC measures endothermic ad exothermic transition as a function of temperature. Endothermic heat flow into a sample, Exothermic heat flow out of the sample.[35-37]

Thermal Gravimetric Analysis (TGA)

TGA is a type of testing that performed on sample to determine change in weight in relation to change in temperature. Such analysis relies on a high degree of precision in measurements: weight and temperature change. As many weight loss curve look similar, the weight loss curve may require transformation before results may be interpreted.

TGA is commonly employed in research and testing to determine characteristics of material such as polymers, to determine degradation temperature, absorbed moisture content of materials, the level of inorganic and organic components in materials, decomposition points of explosives, and solvent residues. It is also often used to estimate the corrosion kinetics in high temperature oxidation.[35-37]

Hot Stage Microscopy

Hot stage microscopy part of light microscopy is one of the oldest and powerful techniques to characterize the phase transitions of crystals as well as the optical properties. Temperature variations induced while microscopic view assists in the formation as well as detection of another crystal form(s). Nicotinamide and many more other crystal forms have been successfully studied employing hot stage microscopy[38].

Application

- In the study of solid state active pharmaceutical ingredients, excipients, and pharmaceutically relevant polymers and lipids.
- By observing melting behaviour in silicon oil using hot stage microscopy.
- Here in this technique pseudopolymorph evolve the gas causing bubbling of the oil.[38]

SPECTROSCOPY

FT-IR

FT-IR helps to identify the polymorphs by indicating changes in frequencies, relative intensities, band contours and the number of bands. Difference in spectra gives an inference to the internal arrangement of crystals. [39,40]

RAMAN SPECTROSCOPY

Raman spectroscopy is analogous to FT-IR spectroscopy and is considered an ideal non destructive tool for polymorphic studies. As far as distinction of various polymorphs and amorphous forms is considered, Raman spectroscopy offers better spectral selectivity. [41,42]

NMR

Solid state NMR is a relatively newer, tough powerful tool to study crystalline polymorphs, relative crystallinity and amorphous content of pharmaceutical mixtures. This technique provides information about the local structure of selected atoms nuclei.[43,44]

APPLICATION OF POLYMORPHISM

PURIFIATION OF DRUGS

Crystallization is used as a purification process. It is used f or removing impurities from pharmaceutical products, i.e., recrystallization technique.[45]

Better Processing Characteristics

Crystallization technique is used to change the micromeritics of drugs such as compressibility and wet ability.[45]

SUSPENSION

AQUEOUS VEHICALES

Transitions produce drug particles having different solubilities. Caking, producing suspensions that cannot be uniformly resuspended by shaking. A good Due to use of a wrong polymorph of a drug, a phase conversion from the metastable to stable polymorph may occur. This produces: Crystal growth, resulting in undesirable particle size distribution. This can produce serious problems with parenteral suspensions where syringeability of the product can become difficult if significant particle growth occurs. Biological availabilities of the drug also can be altered because phase example of suspensions in aqueous vehicle is the cortisone acetate suspension. Cortisone acetate was one of the most difficult polymorphic problems to solve. Macek obtained the first patent on stable noncaking aqueous suspension of cortisone acetate.

SOLUTIONS

One of the first considerations in for mulating a solution is to determine the solubility of the drug in its vehicle. If the solubility determination is con-ducted using a metastable form of the drug and the concentration of the drug in the system exceeds the equilibrium solubility of a less soluble form of the drug, a thermodynamically unstable formulation results. In a sense, this is akin to emulsions which are also thermodynamically unstable systems. Some solutions that are supersaturated with respect to the stable form of the drug may remain in this state for relatively long periods of time. Chance nucleation of the stable form, however, quickly results in crystallization until equilibrium is reached with respect to this form. This is a frequent problem with sparingly water-soluble drugs, such as the steroids, and this phenomenon has been frequently encountered in these laboratories.[46]

SUSTAINED RELEASE

Drug substances with different sizes of crystals can be used in the production of sustained release dosage forms. For example protamines zinc insulin in crystalline form slowly and continuously release insulin from the site of injection for prolonged periods.[45]

IMPROVEMENT OF THERAPEUTIC ACTIVITY OF DRUG

Polymorphism also improve the therapeutic activity of drug because a polymorphic form drug also exist more than one form, that is affect on bioavailability so improve the therapeutic activity of drug.[46]

POLYMORPHISM IMPACT ON STABILITY, SOLUBILITY AND BIOAVAILABILITY

Impact on stability: Polymorphs of a pharmaceutical solid may have different physical and solid-state chemical reactivity) properties. These differences arise based upon differences in thermodynamic ability and also upon differences in molecular mobility, particularly in the case of an amorphous form. For this reason, the most stable form of the drug substance is often chosen during development, based upon its minimal potential for conversion to another form and upon its greater chemical stability[47].

Impact on solubility: Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.[48]

Impact on bioavailability: A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes being the important ones[49]. To reach an expected therapeutic aim, it is imperative that pharmaceuticals exist at the expected concentration. Considering solid formulations, the medications must release the appropriate amount of active pharmaceutical ingredient at a suitable rate for the desired therapeutic effect and be bioequivalent to the reference product. Moreover, these formulations must exhibit physicochemical stability within their shelf life.[50]

Drug Substance: Chloramphenicol palmitat

Polymorphism Aspects: Chloramphenicol palmitate is a prodrug of chloramphenicol with antibiotic properties [51]. Chloramphenicol palmitate exist in three polymorphic forms: (A, B, C)[52,53], the stable form A (biologically inactive modification), the meta stable form B (active modification) and unstable form C[54-56]. The three crystalline forms were also called α, β and γ. The α form is unstable at room temperature and gradually transforms to β on storage [57,58].

Bioavailability Issues: Form B (β) dissolves faster than Form A (α), and has a much higher solubility[59-61]. Low serum levels for the stable polymorph A were observed[62].

Drug Substance: Oxytetracycline

Polymorphism Aspects: Oxytetracycline is a broad spectrum antibiotic. It exists in two different polymorphs[63]

Bioavailability Issues: Oxytetracycline showed differences in patients' blood levels[64] or differences in vitro dissolution of tablets [65] because of differences in polymorphic forms.

Drug Substance: Carbamazepine

Polymorphism Aspects: Carbamazepine is used in the treatment of epilepsy and trigeminal neuralgia. Different polymorphic forms were described [66–78]. Four anhydrous polymorphs were characterized: I, II, III, and IV, respectively identified as triclinic, trigonal, monoclinic, and monoclinic[64].

Bioavailability Issues: In spite different studies demonstrated similar pharmacokinetics in humans of anhydrous and dihydrate forms of carbamazepine[79] and nodifferences in bioavailability between a generic carbamazepine product and an innovator product[80], several clinical failures were reported concerning carbamazepine[81,82], in particular with generic carbamazepine tablets[83]. More recently, it was confirmed that the initial dissolution rate of carbamazepine was in the order of form III > form I > dihydrate, while the order of AUC values was form I > form III > dihydrate. This discrepancy may be attributed to the rapid transformation from form III to dihydrate in GI fluids[84].

Drug Substance: Ritonavir

Polymorphism Aspects: Ritonavir is an antiretroviral drug belonging to protease inhibitor class and used to treat HIV-1 infection. Ritonavir exhibits conformational polymorphism[85] and a total of five forms were described[86]. The forms I and II were more extensively characterized[85].

Bioavailability Issues: 2 years after the launch of the first ritonavir product, several batches failed dissolution specifications because the presence of a different polymorphic form having ~50% lower intrinsic solubility of reference form[87].

Drug Substance: Atorvastatin calcium

Polymorphism Aspects: Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, with strong ability to lowering blood cholesterol. At least 60 polymorphic forms/solvates/hydrates have been patented[88-90]. It is not unusual to verify the presence of polymorphic impurities in the marketed atorvastatin calcium (API) with consequences on drug bioavailability and stability[91].

Bioavailability Issues: Atorvastatin is unstable and the hydroxy acid form is converted to lactone form that is 15 times less soluble than the hydroxyl acid form[92,93]. This instability of atorvastatin calcium leading to poor solubility (0.1 mg/mL) is the main cause for low bioavailability of the drug after oral administration as the absolute bioavailability of atorvastatin calcium is only 14% [94].

Drug Substance: Axitinib

Polymorphism Aspects: Axitinib is a tyrosine kinase inhibitor of endothelial growth factor interrupting tumor angiogenesis and thus, preventing the growth of cancer cells. 60 solvates, polymorphs of solvates, and five anhydrous forms were discovered[95-98].

Bioavailability Issues: The commercial formulation under trade name Inlyta®contains the stable anhydrous form[96].

Drug Substance: Phanylbutazone

Polymorphism Aspects: Phenylbutazone is a potent anti-rheumatic drug existing in different polymorphic and solvated forms[99-102]. Anhydrous forms I and II were more extensively described and form II resulted more soluble than form I. The Form III is a highly unstable form[99].

Bioavailability Issues: Anhydrous forms I and II polymorphic forms exhibited different solubilities, dissolution rates and oral absorption[97-103].

FACTORS AFFECTING POLYMORPHISM

Different types of factors which are affect the polymorphism, Which are given below

Temperature and humidity: Storage conditions affect physicochemical reaction which are accelerated at higher temperature. One of the predominant and generally considered as operational factors is Temperature that affect nucleation, growth and transformation of polymorphs. The effect of temperature on nucleation has both thermodynamic and kinetic inferences, predominantly for enantiotropic polymorphs.[104]

Photo stability: Generally light sensitive drugs are protected from the photolytic degradation by packing them suitable in light resistant container. Stable crystalline form resist photochemical degradation and does not require light resistant system.

Other Factors: Other factors which are also affect the polymorphism and the factors are agitation, supersaturation and growth rate dispersion[104].

CONCLUSION

Polymorph screening, selections, and controls play parts in determining the success of new drug discovery and development. The existence of polymorphs may potentially be an important source of variation in pharmaceutical properties, which

can cause problems concerning the stability, solubility and, consequently, efficacy and bioavailability of drug products. Dissolution of the drug is the rate determining step for oral absorption of poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs because drug bioavailability is depends on drug solubility. Such technique (polymorphism, crystallization, etc.) prove to be a milestone for poorly soluble drugs.

REFERENCES

1. Thirupathi Ajimera et al. Solid State Characterization of the Polymorphic Changes in Candesartan Cilexetil Solid Dispersion with Poly Ethylene Glycol 8000, J. Pharm. Sci. & Res. 2014;6(1):27 – 32.
2. J bauer john , Polymorphism—A Critical Consideration in Pharmaceutical Development, Manufacturing and Stability, Journal of Validation technology [Autumn 2008],15-23.
3. Purohit rahul and Venugopalan p, Polymorphism: AnOverview, RESONANCE September 2009;882-893.
4. Doherty C and York P. Frusemide crystalforms—solid-state and physicochemical analyses. Int J Pharm., 1988;47:141–155.
5. AALTONEN, J. et al, J. Solid form screening – a review. Eur. J. Pharm. Biopharm.,2009; 71(1): 23-37.
6. Gandhi Saurabh and Kaushal Chandrul, Pharmaceutical Solid Polymorphism in Abbreviated New Drug Application (ANDA) – A Regulatory Perspective, Journal of Chemical and Pharmaceutical Research, J. Chem. Pharm. Res., 2011; 3(3): 6-17.
7. Swarbrick J., Encyclopedia of Pharmaceutical Technology, Informa Healthcare USA, NewYork.2007; 6: 834–858.
8. Augustijns P and Brewster ME. Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics, Springer, New York 2007; 53–109.
9. Khamskii EV. Supersaturated Solutions [in Russian], Nauka, Leningrad. 1975; 99.
10. Leonidov NB et al Khim. Zh., 1997; 16(5): 37–39.
11. Miller JM et al, Pharm. Dev. Technol., 2005; 10(2): 291–297.
12. Schmidt AC et al, J.Therm. Anal. Calorim., 2003; 73: 397–404.
13. Csakurda Z and Thege IK.J.Therm.Anal.,1997; 50: 867–871
14. Callow RK and Kennard O.J. Pharm.Pharmacol.,1961; 13(2): 723–728.
15. Otsuka M et al, Drug.Dev. Ind. Pharm., 1994; 20(8):1453–1456.
16. Sudarshan Mahapatra et al, New Solid State Forms of the Anti-HIV Drug Efavirenz.Conformational Flexibility and High Z′Issues. Cryst. GrowthDes.Crystal.,2010; 10(7):3191-3202.
17. Thirunahari S et al Conformational polymorphism of tolbutamide: A structural, spectroscopic,and thermodynamic characterization of Burger's forms I-IV, J Pharm Sci.,2010; 99(7): 2975-90.
18. Sohn YT and Kim SH. Arch. Pharm. Res.2008; 31(2): 231–234.
19. Perlovich GL et al, J.Therm.Anal. Calorim., 2007; 89(3): 767–774.
20. Brittain HG et al Pharm. Res.,2005; 22(6): 999–1006.
21. Roelands CPM et al, Cryst. Growth Des.,2006; 6: 955–963.
22. Angel Martın et al Production of Polymorphs of Ibuprofen Sodium by Supercritical Antisolvent (SAS)Precipitation, Cryst.GrowthDes.,2009; 9(5): 2504-2511.
23. Otsuka M et al, Pharm. Res.,1993; 10(4): 577–782.
24. Shinozakei H et al, Drug. Dev. Indust. Pharm.,2006; 32: 877–891.
25. Ricardo AE.Castro et al, A New Insight into Pyrazinamide Polymorphic Forms and their Thermodynamic Relationships, Cryst.GrowthDes.,2010; 10: 274-282.
26. Lee T et al, Pharm.Res.,2006; 23: 2542–2555.
27. j bauer john , Polymorphism—A Critical Consideration in Pharmaceutical Development, Manufacturing and Stability, Journal of Validation technology Autumn 2008;15-23.
28. Jie LU et al, Polymorphism of pharmaceutical molecules: perspectives on nucleation. Front. Chem. Eng. China., 2010; 4(1):37–44.
29. Stieger Nicole and Liebenberg Wilna,Recrystallization of Active Pharmaceutical Ingredients,North-West University, Unit for Drug Research & Development South Africa,183-204.
30. EUROPEAN Pharmapoeia. 6.ed. Strasbourg: Council of Europe, 2008; 1: 649.
31. S. Raw et al, Regulatory considerations of pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAs), Advanced Drug Delivery Reviews 2004 ;56 : 397–414.
32. B.S. Bahl et al, Essential of physical chemistry; twenty-fourth, Edition-1997;565.
33. Datta Sharmistha and J.W.Grant David , CRYSTAL STRUCTURES OF DRUGS: ADVANCES IN DETERMINATION, PREDICTION AND ENGINEERING, JANUARY 2004; 3: 42-57.
34. PHADNIS N.V. et al, Identification of drugs in pharmaceutical dosage forms by X-ray powder diffractometry. J. Pharm. Biomed. Anal., 1997; 15(7) : 929-943.
35. Yu L. Inferring thermodynamic stability relationship of polymorphs from melting data. J Pharm Sci. 1995; 84(8):966-74.
36. Jayaraman S1 and Maginn EJ. Computing the melting point and thermodynamic stability of the orthorhombic and monoclinic crystalline polymorphs of the ionic liquid 1-n-butyl-3-methylimidazolium chloride. J Chem Phys. 2007; 127(21): 214504.
37. Chadha R et al, An insight into thermodynamic relationship between polymorphic forms of efavirenz. J Pharm Pharm Sci. 2012; 15(2): 234–51.
38. Berry DJ et al, Applying hot-stage microscopy to co-crystal screening: a study of nicotinamide with seven active pharmaceutical ingredients. Crystal Growth and Design. 2008; 8(5): 1697-1712.
39. Brittain HG et al, Solidstate NMR and IR for the analysis of pharmaceutical solids: polymorphs of fosinopril sodium. J Pharm Biomed Anal. 1993; 11(11-12): 1063-9.
40. Aboul-Enein HY et al, Analysis of mebendazole polymorphs by Fourier transform IR spectrometry using chemometric methods. Biopolymers. 2002; 67(1): 56-60.
41. Croker D M et al, A comparative study of the use of power x-ray diffraction, raman, and near infrared spectroscopy for quantification of binary polymorphic mixtures of piracetam. J Pharm Biomed Anal. 2012; 63: 80-86.
42. Láng P et al, Polymorph screening of an active material. J Pharm Biomed Anal. 2013; 84: 177-83. doi: 10.1016/j.jpba.2013.06.002.
43. Brittain HG et al, Solid-State Fluorescence Studies of Some Polymorphs of Diflunisal. Pharm Res. 2005; 22(6): 999–1006.

44. Harris RK. Applications of solid-state NMR to pharmaceutical polymorphism and related matters. J Pharm Pharmacol. 2007; 59(2): 225-39.
45. Cesur S. and Gokbel S. Crystallization of mefenamic acid and polymorphs. Crystal Research Technology 2008; 43(7): 720-8.
46. HALEBLIAN JOHN and McCRONE WALTER, Pharmaceutical Applications of Polymorphism, Journal of Pharmaceutical Sciences, AUGUST 1969; 58(8): 911-929.
47. Gandhi Saurabh and Kaushal Chandrul, Pharmaceutical Solid Polymorphism in Abbreviated New Drug Application (ANDA) – A Regulatory Perspective, Journal of Chemical and Pharmaceutical Research, J. Chem. Pharm. Res., 2011; 3(3): 6-17.
48. Aulton M.E., Pharmaceutics, (2002) The science of dosage form design, 2nd edition,ChurchillLivingstone,London,,P.P.-113–138,234–252.
49. Yu L.X. et al, Predicting oral drug absorption. In: Amidon, G. L.,Lee P. I., Topp E. M. editors. Transport Processes in Pharmaceutical Systems. New York: MarcelDekker, Inc.;p.377-409.
50. AULTON, M.E. Delineamento de formas farmacêuticas. 2.ed. Rio de Janeiro: Artmed. 2005; 678 .
51. Edgerton, W.H. Chloramphenicol Esters and Method for Obtaining Same. U.S. Patent 2,662,906, 15 December 1953.
52. Borka, L. And Backe-Hansen, K. IR spectroscopy of chloramphenicol palmitate. Polymorph alteration caused by the KBr disc technique. Acta Pharm. Suec. 1968; 5: 271–278.
53. Kanenewa, N. And Otsuka, M. Effect of grinding on the transformation of polymorphs of chloramphenicol palmitate. Chem. Pharm. Bull. 1985; 33: 1660–1668.
54. Burger, A. Neue untersuchungergebnisse von chloramphenicolpalmitat. Sci. Pharm. 1977; 45:269–281.
55. Gamberini, M.C. et al Solid state characterization of chloramphenicol palmitate. Raman spectroscopy applied to pharmaceutical polymorphs. J. Mol. Struct. 2006; 785: 216–224.
56. Mishra, R. et al Structural, electronic, thermodynamical and charge transfer properties of chloramphenicol palmitate using vibrational spectroscopy and DFT calculations. Spectrochim. Acta Part A Mol. Biomol. Spectr.2013; 101: 335–342.
57. Eguchi, Y. and Iitaka, Y. The β-form of chloramphenicol palmitate. Acta Cryst. 1974; B30: 2781–2783.
58. Szulzewsky K. et al, The structure of the b modification of chloramphenicol palmitate. A redetermination. Acta Cryst. 1981; B37: 1673–1676.
59. Aguiar, A.J. et al, J.C.Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate. J. Pharm. Sci. 1967; 56: 847–853.
60. Aguiar, A.J.and Zelmer, J.E. Dissolution behavior of polymorphs of chloramphenicol palmitate and mefanamic acid. J. Pharm. Sci. 1969:58: 983–987.
61. Glazko, A.J. et al, W.R. Chloromycetin palmitate—A synthetic ester of chloromycetin. Antibiot. Chemother. 1952; 2: 234–242.
62. Maeda, T. et al, Use of rabbits for absorption studies on polymorphs of chloramphenicol palmitate. Chem. Pharm. Bull. 1980; 28: 431–436.
63. Liebenberg, W. et al, The effect of polymorphism on powder compaction and dissolution properties of chemically equivalent oxytetracycline hydrochloride powders. Drug Dev. Ind. Pharm. 1999; 25: 1027–1033.
64. Brice, G.W. and Hammer, H.F. Therapeutic nonequivalence of oxytetracycline capsules. J. Am. Med. Assoc. 1969; 208: 1189–1190.
65. Groves, M.J. Solution tests on generic brands of oxytetracycline tablets. Pharm. J. 1973 ;210 : 318–319.
66. Reboul, J.P. et al, 5H-5-Dibenzyl[b,f]azepinecarboxamide (carbamazepine). Acta Crystallogr. Sect. B Struct. Commun. 1981; 37: 1844–1848.
67. Himes, V.L. et al, Structure of carbamazepine-5H dibenz[b,f]azepine-5-carboxamide. Acta Crystallogr. Sect. B Struct. Commun. 1981; 37: 2242–2245. Molecules 2015,20 18774
68. Chang, C.H. et al, The crystal structures of (S) and (R) baclofen and carbamazepine. Acta Crystallogr.1981;A37.
69. Reck, G.and Dietz, G. The order-disorderstructure of carbamazepine dihydrate: 5H-Dibenz[b,f] azepine-5-carboxamide dihydrate, C15H12N2O···2 H2O. Cryst. Res. Technol. 1986; 21: 1463–1468.
70. Lowes, M.M.J. et al Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepine. J. Pharm. Sci. 1987; 76: 744–752.
71. Lisgarten, J.N. et al. Crystal and molecular structure of 5-carbamyl-5H-dibenzo[b,f]azepine. Crystallogr. Spectrosc. Res. 1989; 19: 641–649.
72. Ceolin, R. et al, X-ray characterization of the triclinic polymorph of carbamazepine. J. Pharm. Sci. 1997; 86: 1062–1065.
73. Rustichelli, C. et al, Solid-state study of polymorphic drugs: carbamazepine. J. Pharm. Biomed. Anal. 2000; 23: 41–54.
74. Lang, M.D. et al, Form IV of carbamazepine. J. Pharm. Sci. 2002; 91: 1186–1190.
75. Lang, M.D. et al, The use of polymer heteronuclei for crystalline polymorph selection. J. Am. Chem. Soc. 2002; 124: 14834–14835.
76. Grzesiak, A.L. et al, Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J. Pharm. Sci. 2003; 92: 2260–2271.
77. Fleischman, S.G.et al, Crystal engineering of the composition of pharmaceutical phases: Multiple-component crystalline solids involving carbamazepine. Cryst. Growth Des. 2003; 3: 909–919.
78. Young, W.W.L. and Suryanarayanan, R. Kinetics oftransition of anhydrous carbamazepine to carbamazepine dihydrate in aqueous suspensions. J. Pharm. Sci. 1991; 80: 496–500.
79. Kahela, P. et al Pharmacokinetics and dissolution of two crystalline forms of carbamazepine. Int. J. Pharm. 1983;14:103–112.
80. Jumao-as, A. et al, Comparison of steady-state blood levels of two carbamazepine formulations. Epilepsia 1989 ; 30: 67–70.
81. Koch, G. and Allan, J. Untoward effects of generic carbamazepine therapy. Arch. Neurol. 1987; 44: 578–579.
82. Sachdeo, R. et al Risk of switching from brand-name to generic drugs in seizure disorder. Epilepsia 1987; 28: 581.
83. Meyer, M.C. et al, The bioinequivalence of carbamazepine tablets with a history of clinical failures. Pharm. Res. 1992; 9: 1612–1616.
84. Kobayashi, Y. et al, Physicochemical properties and bioavailability of carbamazepine polymorphs and dihydrate. Int. J. Pharm. 2000; 193: 137–146.
85. Bauer, J.et al, Ritonavir: An extraordinary example of conformational polymorphism. Pharm. Res. 2001; 18: 859–866.
86. Morissette, S.L. et al, Elucidation of crystal form diversity of the HIV protease inhibitor ritonavir by high-throughput crystallization. Proc. Natl. Acad. Sci. USA 2003; 100: 2180–2184.
87. Borka, L. and Haleblian, J.K. Crystal polymorphism of pharmaceuticals. Acta Pharm. Jugosl. 1990 ;40 :71–94.
88. Mckenzie, A.T. Applicant: Warner-Lambert Company. Form III crystalline (R-(R*,R*)-2-(4-fluorophenyl)-beta,delta-dihyxory-5-(1-methyl-ethyl)-3-phenyl-4phenylamino)carbonyl) -1H-pyreol- 1-heptanoic acid hemi calcium salt (Atorvastatin). WO97/03958, 6 February 1997. Molecules 2015 ;20 :18775.
89. Jin, Y.S. and Ulrich, J. New crystalline solvates of atorvastatin calcium. Chem. Eng. Technol. 2010 ;33 :839–844.
90. Chadha, R. et al, Characterisation and evaluation of pharmaceutical solvates of atorvastatin calcium by thermoanalytical and spectroscopic studies. Chem. Cent. J. 2012 ;6 :114–129.

91. Shete, G.; et al, Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. AAPS Pharm. Sci. Technol. 2010 ;11 :598–609.
92. Kerc, J. et al, Atorvastatin Calcium in a Pharmaceutical formComposition Thereof and Pharmaceutical Formulation Comprising Atorvastatin Calcium. U.S. Patent ,18 April 2006; 18: 7030.
93. Kerc, J. Stable Pharmaceutical Formulation Comprising a HMGCoAreductase Inhibitor. U.S. Patent Application US 2009/0264497 A1, 22 October 2009.
94. Khan, F.N.; Dehghan, M.H.G. Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. AAPS Pharm. Sci. Technol. 2011;12 :1077–1086.
95. Chekal, B.P. et al,The challenges of developing an API crystallization process for a complex polymorphic and highly solvating system. Part I. Org. Process. Res. Dev. 2009; 13: 1327–1337.
96. Campeta, A.M. et al, Development of a targeted polymorph screening approach for a complex polymorphic and highly solvating API. J. Pharm. Sci. 2010 ; 99: 3874–3886.
97. Abramov, Y.A. QTAIM application in drug development: prediction of relative stability of drug polymorphs from experimental crystal structures. J. Phys. Chem. A 2011; 115: 12809–12817.
98. Vasileiadis, M. et al, Prediction of the crystal structures of axitinib, a polymorphic pharmaceutical molecule. Chem. Eng. Sci. 2015; 121: 60–76.
99. Matsunaga, J. et al, Physicochemical approach to biopharmaceutical phenomena. XXX. Polymorphism of phenylbutazone. Chem. Pharm. Bull. 1976; 24: 1169–1172.
100. Ibrahim, H.G. et al, Polymorphism of phenylbutazone: Properties and comparisonal behaviour of crystals. J. Pharm. Sci. 1977; 66: 669–673.
101. Matsuda, Y. et al, Polymorphism of phenylbutazone by spray dried methods. J. Pharm. Pharmacol. 1980; 32: 579–580.
102. Hosokawa, T. et al, Relationships between crystal structures and thermodynamic properties of phenylbutazone solvates. Cryst. Eng. Commun. 2004; 6: 243–249.
103. Pandit, J.K. et al, Effect of crystal form on the oral absorption of phenylbutazone. Int. J. Pharm. 1984; 21: 129–132.
104. Shekunov BY and York P. Crystallization processes in pharmaceutical technology and drug delivery design. J Cryst Growth.,2000; 211:122–136.