# CHAPTER 2

## LITERATURE SURVEY

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2. LITERATURE SURVEY

Since this work embodies preparation and studies on the crystal forms of Amlodipine besylate, Entacapone & Lomefloxacin hydrochloride, it is in order to review literature on polymorphs and its implications in pharmaceuticals.

2.1. Effect of temperature and humidity on polymorphs

In which polymorphic compounds are accelerated at higher temperatures according to the activation theory of Arrhenius; humidity acting as a catalyst on the solid surface. Therefore, temperature and humidity are very important factors for the formulation scientist to consider.

Miyazaki et al [18] described the hygroscopic behavior of polymorphic forms of chlortetracycline hydrochloride. The α form was stable up to 82% relative humidity (RH), while the β form was hygroscopic; the α form converted into the β form at high humidity (84-95% RH).

Matsunaga et al [19] studied the polymorphic transformation of phenylbutazone, determined by differential scanning calorimetry (DSC); polymorphic transformation occurred after heating.

Awata et al [20] investigated the polymorphic transformation of acebutolol hydrochloride at high humidity and temperature. The amorphous form transformed into form I through forms II and III at 91% RH. The forms II and III again transformed into form I as a stable at 91% relative humidity. Finally the obtained forms II and III transformed into form I at 130 and 138°C respectively, and the amorphous form acebutolol converted into form III at 80°C.

Saito et al [21] reported the hygroscopic properties of polymorphs of tulobuterol hydrochloride (forms I, II and III, monohydrate and amorphous) at various levels of humidity. These forms II and III transformed into the monohydrate above 75% RH and the amorphous form above 59% RH, but form I became
the monohydrate above 91% RH, indicating that the order of hygroscopicity was amorphous > form II > form III > form I.

Kaneniwa et al [22] examined the hygroscopicity of carbamazepine crystalline powders. The Form I was stable to moisture, but form II was relatively hygroscopic and transformed into the dihydrate under conditions of high humidity. This form IV (dihydrate) was stable at high humidity, but was described under less than 32% RH conditions.

Matsuda et al [23] found in a kinetic study, that the α and β forms of phenylbutazone transformed into the stable δ form at various RH levels and temperatures. The transformation of α form was not affected by humidity, but that of the β form was affected. The transformation rate of the α form was not affected by humidity, but that of the β form increased according to rise in humidity. The temperature dependence of the transformation rate constant was remarkable. These results suggest that the α form was more stable than the β form under all storage conditions.

Matsuda et al [24] investigated the solid-state stability of the amorphous form of oxyphenbutazone under various temperature and humidity conditions. At low humidity the amorphous form transformed into the anhydride while, at moderate or high humidity it transformed into the hemihydrates or the monohydrate forms. The hemihydrates and monohydrate transformed into the amorphous form at 0% RH and 40°C.

Otsuka et al [25] reported the physicochemical stability of nitrofurantoin anhydride and monohydrates under various temperature and humidity conditions, and suggested that the decreasing bioavailability might be caused by polymorphic transformations. The monohydrate was stable at 32-100% RH at 40°C and at 0-100% RH at 25°C whereas, the anhydride was stable at 0-82% RH at 40°C and at 0-89% RH at 25°C after four months. These results indicate that the crystallographic phase change occurs during storage at relatively high or low humidities. Commercial
drug preparations exhibit side effects caused by fluctuations of the dissolution rate which affect bioavailability. It therefore appears that the crystallographic stability of nitrofurantoin bulk powder may be one of the most important factors for controlling its bioavailability.

Umeda et al [26] reported the isothermal transformation of acetazolamide polymorphs at high temperature. The transformation of form A to B followed random nucleation with first order kinetics, and the activation energy was estimated to be 246 KJ/mol (58.7Kcal/mol).

Ashizawa et al [27, 28] found that the phase transition of the crystalline $\gamma$ form of a new parenteral cephalosporin antibiotic (E1040) showed by water content on dehydration. During dehydration, the hydrated $\alpha$-form (decahydrate) and $\beta$ form (pentahydrate) became the anhydride $\gamma$ form with the x-ray studies. Diffraction angle shifted from hydrate to the anhydride form and contraction of the crystal lattice at low humidity conditions. In a preformulation study, they investigated the solid state chemical stability of the crystalline $\gamma$ form and amorphous forms of the same drug. The degradation rate of the crystalline form was much lower than that of the amorphous form.

Matsuda and Tatsumi et al [29] reported the physicochemical characterization of frusemide modifications at various temperatures. In this, forms I, II and III were transformed into form IV after heating to 180°C. They demonstrated the chemical potential of polymorphisms by kinetic means.

Vadas et al [30] examined the solid state phase transitions initiated by water-vapour adsorption of crystalline L-660,711, a leukotriene D$_4$ receptor antagonist.
2.2. Photo stability of polymorphic drug

Light-sensitive drugs are usually protected from photolytic degradation by packaging in light-resistant containers. However, bulk powders of stable crystalline forms resist photochemical degradation and do not require a light-resistant system. There are fewer reports concerning the photostability of solid dosage forms, since the mechanism is too complex for basic studies.

Yoneda et al [31] investigated the polymorphism of acemetacin. The color changes of six polymorphs in tablet form exposed to ultraviolet light suggested that the α and β forms were stable, whereas the γ form was not.

Akimoto et al [32] reported the photostability of several crystal forms of cianidanol. In these, form I, monohydrate II was stable to UV irradiation at 20 °C and 0-96% RH, whereas the other forms (tetrahydrate I, anhydride II and anhydride IV) were affected by humidity, and degraded rapidly.

2.3. Effect of grinding on polymorphs

Since the physicochemical properties of some drug polymorphs are affected by mechanical energy, the characterization of ground products is critical to the development of pharmaceutical preparations.

Florence et al [33] found that grinding increases the solubility of digoxin three to four times. The x-ray diffraction, differential thermal analysis, infrared spectrometry, and solubility studies confirm the transformation from crystalline solid to the amorphous form during grinding.

Nakagawa et al [34] investigated grinding of prasterone sulfate dihydrate; with increased grinding time and water content the compound became unstable. A study of the thermal behavior of the water of crystallization suggested that the bonding crystal was weakened by grinding, and water molecules
participated more easily in the hydrolysis of the drug. They concluded that the dihydrate was more stable than the anhydride under high humidity.

Takahashi et al [35] laid down impact of milling and drying on the solid-state stability of ampicillin trihydrate. The stability of the ground sample decreased with increasing the grinding time. The ground sample was stable when stored at high humidity. This effect was interpreted in terms of a reduction of the amount of water available to move within the crystal.

Kaneniwa and Otsuka et al [36] investigated the effect of grinding on polymorphs of the antibiotic chloramphenicol palmitate with less than 10% of the stable form A, according to the USP XX (1980) and the British Pharmacopoeia 1980. The metastable forms B and C were transformed to the stable polymorphic form A after grinding at room temperature for 140 min, and the solubility decreased due to the transformation of forms B and C into form A. However, the ground form A was more stable than bulk chloramphenicol palmitate, since part of form A was converted into a non-crystalline solid.

Huttenrauch et al [37] reported the chemical stability of ergocalciferol (vitamin D2) after grinding in a porcelain mortar. Degradation followed first-order kinetics, and the rates increased with increasing grinding time. They described the extent of activation of the ground product for the degradation induced by relevant process.

Forni et al [38] found that chloramphenicol stearate changed from form III into form I during grinding, and then tended to become amorphous. Therefore, the grinding of both forms produced a “physically activated” form with a low degree of crystallinity and a high chloramphenicol content.

Otsuka et al [39] demonstrated the effect of temperature on the polymorphic transformation of indomethacin (IMC) during grinding. The α and γ forms were transformed into a noncrystalline solid at 4° C. These findings suggested that the
conversion was irreversible at 4°C, and that the solid was unstable at 30°C. The solid had crystallized to the α form reaching an equilibrium state where the rate of crystallization was equal to the rate of its destruction by grinding.

Otsuka and Kaneniwa et al [40] studied the crystallization process of noncrystalline indomethacin obtained by grinding, and analyzed the fusion method kinetically at various temperatures. The noncrystalline solid obtained from α form crystallized to both the α and γ forms simultaneously. The noncrystalline solids obtained from the γ form by grinding and by fusion crystallized into the γ form. These results suggested several forms of noncrystalline solids.

Matsumota et al [41] investigated the transformation behaviour of phenylbutazone polymorphs during grinding at 4 and 35°C. The, β and σ forms were transformed into a new polymorphic ζ form. The α form was transformed into the σ form by way of the ζ form. The β form was apparently transformed directly into the σ form. The solubility of all the ground products were higher than that of the bulk form. The stability of the ground products was estimated based upon solid-state kinetic model equations.

Ojala and Etter et al [42] found that the polymorphic form III of anthranilic acid reverted to form I upon grinding. This III → I transition also occurred when an authentic sample of form III was vigorously ground. Crystals of form II transformed into form I upon thorough grinding and also spontaneously.

Kitamura et al [43] reported the chemical stability of cefixime trihydrate after grinding. The degradation and the discoloration rates increased with increased grinding time, since the crystalline compound was transformed into a noncrystalline solid.

Otsuk and Kaneniwa et al [44] examined the effect of grinding on the crystallinity and chemical stability of solid cephalothin sodium. The decomposition points and the critical relative humidity of the ground products decreased with
increased grinding time. The noncrystalline hygroscopic solid was unstable at high temperatures.

Dugue et al [45] reported that the dehydration point of carbamazepine dihydrate decreased with increased grinding time at room temperature, and that part of the dihydrate was transformed into the β anhydride.

Otsuka et al [46] studied the isomerization of solid lactose by mechanical stress during grinding. The crystalline monohydrate, as well as the α and β anhydrides were transformed into a noncrystalline solid which absorbed water. Noncrystalline α and β lactose were transformed into their counterparts (β and α, respectively) by the mechanical effect of grinding.

The content of moisture on the physicochemical properties of nitrofurantoin anhydride and monohydrates were reported during grinding in a humidity-controlled system, using several methods. The anhydride & non stable hydrate became a solid amorphous on milling under closed system. Other side, grinding began an open system in which the humidity of the air was controlled (5, 50, and 75% RH), the anhydride absorbed moisture from the air, which increased to 75% RH. Thereafter, it was transformed into the monohydrate II. The single hydrate I lost water during grinding at 5% RH and transformed into a noncrystalline solid. However, it was transformed into monohydrate II at 50 and 75% RH. These results suggest that the solid state transformation of nitrofurantoin modifications during grinding depend upon the environmental humidity [47].

2.4. Crystal growth in suspension and its inhibition

Temperature fluctuations, polymorphic transformation and ostwald ripening destabilize the suspensions owing to particle aggregation and particle growth during storage [48]. When solubility of a drug is strongly dependent on temperature, crystals of drug may dissolve and form supersaturated solutions at raised temperature, which favours crystal growth [49]. The difference in the solubility of polymorphs also provide a driving force for crystal growth in suspension and the process is accelerated
if the drug used contains a mixture of polymorphs[50]. Dissolved impurities may affect the rate of crystallization and even change the crystal habit, provided that these impurities are surface active and become adsorbed on the nuclei or growing crystals [51].

Ziller et al [52] Polysorbate 80 (0.005%) significantly inhibits the growth of methyl prednisolone crystals in aqueous media. Gelatin, polyvinylpyrrolidone (PVP) at concentration < 0.10% retard the crystal growth of sulphathiazole in the water. Inhibition of crystal growth by PVP in acetaminophen suspensions has also been reported. The study states that some of the segments of the polymer PVP attach to the free spaces on the drug crystal lattice and a hydration shell surrounds the polymer. The adsorbed segments form a barrier that resist the approach of the drug molecules from the solution to the crystal surface and inhibit crystal growth.

Lucks et al [53] suggested that the physical stability of the suspension might be enhanced due to the repulsion of the like charged particles induced by a cationic surfactant.

Tiwari and his colleague [54] worked on the choice of crystal habit and improved suspension stability and bioavailability.

Crystal habit can also be of great importance in suspension re dispersibility, sedimentation, physical stability and appearance. Agglomerate of crystals of sulfisoxazole on caking in a suspension system may exhibit little tendency to re-disperse because of the tenacity of the clumps. These clumps may exhibit retarded dissolution and thus retarded bioavailability rates.

2.5. Spherical crystallization and its importance

More recently, a modified crystalline technique has been adopted for the development of directly compressible drugs. This technique is known as spherical crystallization. It can transform crystals directly into a compact spherical form, which is found to have good flow ability, compressibility, packability and also good
solubility in some cases. So it was a new approach, by which crystallization and agglomeration can be carried out simultaneously in simple procedure [55].

There are four methods of spherical crystallization, viz: Simple spherical crystallization method, Emulsion solvent diffusion method, Ammonia diffusion system method and Neutralization method.

Martino et al [56] produced spherical propylphenazone crystals by an agglomeration technique using a three solvent system. Those are tri-phase system of ethanol-water-isopropyl acetate. The proportions of solvents estimated by phase of ternary diagram and flow measurements was investigated and compared to that of unagglomerated crystals.

Sano et al [57] prepared tolbutamide spherical agglomerates using emulsion solvent diffusion method. The micromeritic properties and the dissolution rate of the prepared spherical agglomerates were evaluated by comparison with agglomerates prepared by the solvent change method. The agglomerates were nearly spherical in shape, had great mechanical strength and showed excellent flowability due to their spherical shape.

Kawashima et al [58] Enoxacin crystals of were prepared by a spherical crystallization technique using the ammonia diffusion system. In which enoxacin containing ammonia-water solution added to an acetone-dichloromethane with agitation, a trace amount of ammonia was released.

Sano et al [59] the spherical crystallization of anti-diabetic drug tolbutamide was prepared by neutralization method. The drug was dissolved in sodium hydroxide solution. Aqueous solution of hydroxyl propyl methylcellulose and hydrochloric acid was added to neutralize sodium hydroxide solution of tolbutamide.

Deshpande et al [60] Aspirin spherical crystals revealed that the angle of repose value 31.13° while that of unagglomerated particles was 47.12°. This
improvement taken place due to their spherical shape and a lower static electric charge and improved packability has been suggested for the agglomerates prepared by spherical crystallization. The friction angle, shear indices and stress are lower than those of single crystals, which can explain the improved packability of the agglomerates.

Kawashima et al [61] prepared spherical agglomerates with a two solvent system and made comparison with those of the original powder of the drug. It was found that the arrangement was improved compared with those of the original crystals and that the agglomerated crystals were adaptable to direct tableting.

Morishima et al [62] investigated properties of bucillamine agglomerates which are prepared by different spherical crystallization techniques and made comparison studies between the compacted agglomerates and conventional crystals using a suitable compaction apparatus equipped with flat surfaced punches.

Kawashima et al [63] it has been elucidated that when the apparent specific surface area increases, the agglomerates dissolution gets increased. Hence the desirable surface areas of crystal agglomerates depend on method of spherical crystallization.

The spherical crystallization technique can enable subsequent processes such as separation, filtration and drying to be carried out more efficiently. It exhibits high flow ability, compressibility and wettability of the materials. The studies on spherically agglomerated salicylic acid revealed that, the agglomerated crystal were in the size range of 460 to 1210 µm (average, 930 µm). Micromeritic properties of agglomerated crystals were significantly improved compared with those of the crystals, which were not agglomerated.

Chourasia et al [64] converted conventional drug crystals of flurbiprofen into spherical crystal agglomerates via the spherical crystallization technique using
acetone-water-hexane solvent system. These were characterized for micromeritic properties (particle size, shape and flow ability), packability (bulk density), wettability (contact angle) and compressibility. Agglomerated crystal angle was 31.7°, while that for the crystals that were not agglomerated was 46.7°. Due to improved flow properties and packing ability of the agglomerated crystals they were directly compressible.

Jbilou at al [65] Due to the poor compressibility and dissolution of ibuprofen, there are many processes to optimize these properties through conventional formulations. Spherical crystallization more satisfactory to obtain agglomerated crystals directly during the crystallization step that can be compacted directly. Ibuprofens spherical were raised using a very simple method based on the difference miscibility of core substance in ethanol-water phase. A study of the physical properties of ibuprofen agglomerates was carried out using x-ray diffraction. Finally better improvement in compression and dissolution properties of the spherical agglomerates was observed.

Adhesive and cohesive properties of chlorpromazine hydrochloride crystals were modified by agglomeration to improve their powder processing. Moreover, sustained–released gelling microcapsules of chlorpromazine hydrochloride were devised to prolong the pharmacological effect.

Kawashima et al [66] Spherical crystallization technique is utilized for crystal modification. Spherical crystallization of phenytoin incorporating water soluble polymer, polyethylene glycol (PEG). Incorporation of PEG into agglomerates of poorly soluble crystals improved dissolution rate and bioavailability of phenytoin. It also increased mechanical strength of the agglomerates. Addition of PEG reduced cohesive force of the bridging liquid allowing the elemental crystals in the agglomerates to be easily compacted by external stress. The bridging liquid would be forced to move to the outer surface from the interstices in the agglomerates by the compaction promoting further agglomeration. Therefore, the compaction of agglomerates was responsible for increasing the agglomeration rate leading to
increase in the size of the agglomerates. After critical concentration of the PEG, the increased kinematic viscosity of the medium reduced the collision frequency of the agglomerates causing further decrease in agglomeration force of the bridging liquid. These two factors cause subsequent decrease in size of agglomerates.

Therefore, spherical crystallization is a novel particle engineering technique aimed at modifying the secondary micromeritic properties like flow ability, packability, compressibility and wettability. The technique can also be used to modify drug release characteristics to provide novel drug delivery systems like micro balloons and micro sponges besides having application in the field of the taste masking. Also, the spherical crystallization process can be scaled up to the manufacturing level as this technique is economical and efficient [67].

2.6. Density measurement and its importance

Density measurements have been correlated to a number of physical properties. The crystalline and purity of powders have been investigated using a variety of density measurements [68]. Particle shape has been shown to influence bulk and tapped densities [69], and the calculation of the shape coefficient was found to correlate linearly with bulk density [70-73]. Therefore, a number of NDDS are used to determined the desirable density as well as porosity of microspheres of analgesic action of Ibuprofen and CNS stimulant of theophylline[74-76].

2.7. Effect of tableting compression on pharmaceutical properties of polymorphs

Tableting is an important process necessary for making the most common dosage form of pharmaceuticals. Although there have been many studies on the tableting process, where attempts have been made to clarify the underlying physical and intrinsic inter particle bonding mechanisms, the process remains unclear. Since the physicochemical state of a drug controls its dissolution rate and affects its bioavailability, according to the FDA guidelines, polymorphism of pharmaceutical drugs in the crystalline form has recently attracted the interest of many investigators. Many drugs are manufactured in tablet form, and the mechanochemical stability and compaction behavior of the polymorphic form of a drug during tableting are very
important in practice. There are few quantitative studies of the physico chemical changes in polymorphs caused by mechano chemical effects during tableting even though, the bioavailability of the drug could be seriously affected [77].

The crystal habit may be altered due to interference with the uniform approach of crystallizing molecules to the different faces of a crystal, resulting in anhedral (irregular) or euhedral (regular) crystals [78]. Polymorphism is known to influence dissolution rates that directly affect absorption and bioavailability of drugs [79]. When the estrogen, ethinylestradiol is crystallized from solvents like acetonitrile, methanol, chloroform and water. Four crystalline solvates are formed [80]. Crystallization of sulphamerazine has been studied from selected solvents to understand the preferential formation of polymorphs.

Consolidative behavior of a particular drug material can be influenced by crystal habit under appreciable applied force [81]. Substances possessing rhombohedra lattice arrangements were noticed to be tableted with difficulty than those with a cubic lattice. Solids undergo some elastic deformation when subjected to some external compressional forces. Armstrong and his colleague reported that lamination of tablet structure resulted from considerable elastic recovery on decompression. Ibuprofen exhibits poor compression ability due to excessive elastic recovery, making its tableting by direct compression problematic [82].

Nogami et al [83] reported that a metastable barbital form II was transformed to the stable form I during tableting compression at more than 3000kg/cm².

Summers et al [84] investigated the compression characteristics of the polymorphic forms of barbitone and sulfathiazole. The results were explained in terms of the degree of plastic flow and crushing that occurred with each material, and the degree to which the final compact under elastic compression.
Matsunaga et al [85] examined the polymorphic transformation of phenylbutazone. From these form III was transformed into form II by compression above 2000 kg/cm$^2$ or by grinding in a mortar.

Ibrahim et al [86] reported that the metastable form of phenylbutazone is transformed to the stable form during mechanical stress.

Summers et al [87] commented on the influence of the crystal form on the tensile strength of sulfathiazole, aspirin, and barbital tablets. The results suggested that the polymorphic forms affected the mechanical strength of compressed tablets.

Yamaoka et al [88] investigated the impact of polymorphism in cracking in the tablet of carbochromen hydrochloride. This transformation of form II into the dihydrate at high humidity resulted in capping–like cracking of the tablet, although the form I tablet did not crack under the same conditions.

Reports [89, 90] indicated that the polymorphic changes in fostedil increased with increasing mechanical energy. Grinding for 2 h transformed form II into form I and 80% of form I reverted back to form II on compression at 1000 kg/cm$^2$ pressure.

Kaneniwa et al [91] studied the changes in the degree of crystallinity and in the dehydration and decomposition points of cephalexin (CEX) during compression. The degree of crystallinity of the compressed products decreased with increasing values of maximum compression stress and loss of energy. The dehydration and decomposition points fell with the decreasing degree of crystallinity. The value of energy loss estimated by extrapolating the plot of log energy loss versus crystalline to zero crystallinity was 58.6 kJ/mol (14.0 kcal/mol).

Ueda et al [92] examined the dissolution behavior of chlorpromazine (CPM) polymorphs by the stationary disk method. The dissolution rate of the metastable form C is higher than that of the stable form A. Since the polymorphs of the
drug were transformed by compression, the dissolution rate of CPM may be affected by tableting compression.

Swarbrick et al [93] the effect of temperature was reported by x-ray diffractometry on the polymorphic transformation and compression of chlorpromazine forms A and C during tableting. A single-punch eccentric tableting machine equipped with two loads of cells (upper and lower punches) and a noncontact displacement transducer was used to measure the compression stress, pressure and gap between the dies. A heater and liquid nitrogen pool were mounted on the punch of the tableting machine, temperature was controlled with a thermo controller. They studied two types of compression, multi tableting at room temperature and single tableting at 0-45°C. In the first method, the stable form A or metastable form C was loaded into the die and compressed with a force of 196 MPa up to 30 times. The form C was greater at 45°C than at 0°C which obtained from A. This indicates that the chemical stability of form A was affected by compression temperature, whereas that of form C was independent. The crushing strength was more in form A when same porosity was applied.

2.8. Dissolution behavior of polymorphs

The dissolution behavior of different polymorphic forms of a drug and their relationship to drug bioavailability and absorption are generally in agreement; the lower the thermodynamic activity of a polymorph, the lower is its apparent solubility and consequently its absorption[94].

Because the intrinsic dissolution rate in the gastrointestinal is controlled by the solubility and the surface area of the solid phase, the Noyes-Whitney equation holds as given below:
Where, \( k \) = the rate constant per unit area,
\( C_s \) = the solubility
\( S \) = the available surface area,
\( C \) = the solute concentration
\( V \) = the solvent volume

Shefter and Higuchi et al. [95] reported the dissolution behaviors of pseudo polymorphic forms of several drugs. They suggested that the anhydride forms of theophylline, cholesterol, caffeine, glutethimide and succinyl sulfathiazole (the metastable form) apparently had higher solubility than the hydrates, which are stable in water. They concluded that the thermodynamic parameters of the anhydrates were much higher than those of hydrates.

Wurster et al. [96] studied the dissolution kinetics of three kinds of prednisolone polymorphs. Determination of their relative dissolution rates under different rotations, the dissolution could be described by consecutive processes involving a mechanism at the boundaries and transport away from the interface. The data suggest that these processes pose a double barrier to dissolution under the experimental conditions.

Higuchi et al. [97] investigated the dissolution kinetics of two polymorphs each of methyl prednisolone and sulfur derivative compound. A relation between the conversions of metastable to stable form was found. This data obtained in a number of solvents showed that growth of stable phase was slow, when solubilization takes place.

Lin et al. [98] examined the dissolution kinetics of an experimental antihypertensive drug by the dispersed amount and rotating disk methods in 0.1 N hydrochloride solutions at various temperatures. From this experimental data polymorph I was obtained, by re-crystallization from methanol, water or
hydrochloride solution. The polymorph II was harvested from iso-propanol, di-ethyl formamide or di-methyl acetamide. The release rates of polymorph II are 3-4 times greater than I. The dissolution rate of polymorph II is exceeded by the aggregation of particles and an apparent first order release in the drug concentration is observed.

Kanke and Sekiguchiet al [99] investigated the dissolution kinetics of the α and β forms of sulfathiazole polymorphs by the stationary disk method. The solubility of the metastable β form and of the stable α form were estimated and the ratios of dissolution rates of both forms at various temperatures were also determined. By comparing the solubility data obtained by dissolution ratio, and solubility equilibrium methods, gave good agreement between the two results, so obtained.

2.9. Bioavailability of pharmaceutical preparation containing polymorphic drugs

If the absorption rate of the active ingredient in an oral preparation in gastrointestinal tract is dissolution-rate dependent, the use of a compound exhibiting polymorphism may have good or bad consequences. The successful utilization of a polymorph having significantly greater thermodynamic activity than the stable modification may provide in some instances therapeutic blood levels from otherwise inactive drugs.

Mullins and Macek et al [100] while investigating the pharmaceutical properties of novobiocin, it was identified two forms, one crystalline insoluble and the other one soluble amorphous. By giving oral administration of soluble novobiocin, which is active orally but unstable chemically in the gastro intestinal tract, whereas the insoluble forms of novobiocin are chemically stable.

Hamlin et al [101] methyl prednisolone pellets were prepared from two polymorphic forms (forms I and II) and determined their dissolution rates by suitable four different in vitro methods and the obtained results were compared with in vivo studies by implanting pellets in rats. From the above studies the rate
of dissolution methyl prednisolone form II was 1.2 times > form I and it was concluded that thermodynamically more stable.

Aguiar et al [102] investigated the bioavailability of Chloramphenicol palmitate form A and B estimated the effect by using concentrations. In these obtained two forms of chloramphenicol administrated orally, then collected blood samples after the study period. After oral ingestion above the suspension of form B maintained the greater mean blood plasma level comparatively form A.

Kato and Kohketsu et al [103] reported the polymorphic form of amobarbital on its bioavailability. The dissolution rate of form II was higher than that of form I. In absorption experiments in rabbits, two crystal forms were administered orally and the resulting plasma concentration levels were compared with the percentage drug release. It appeared that the polymorphic forms drug well appreciably influence the absorption process from the digestive tract.

Kojima et al [104] investigated the bioavailability of polymorphs of α–bromo isovaleryl urea in rabbits. The area under the blood concentration curves and the mean dissolution times of polymorphic forms I, II, and III were calculated to determine the rate and extent of bioavailability. The results indicated that the polymorphic states of the drug did not show significantly different bioavailability.

Kokubo et al [105] studied the bioavailability and inhibitory effect on ulcers of cimetidine polymorphs in rats. The forms A, B, C, and D (monohydrate) were characterized by X-ray diffraction and other methods. In these Peak plasma levels were reached within 30min after oral administration with each form, and absorption was very rapid. The plasma concentration curves of forms A and B were similar. The areas under the curves of form C were 1.5 and 1.4 times larger than those of form A and B, respectively.
The inhibitory effect of form C, especially at the lower dose (12.5mg/kg), was significantly higher than those of forms A, B, and D. Therefore, it was concluded that, among the four cimetidine crystalline forms, form C had the highest bioavailability and inhibitory effect on stress ulceration.