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The effect of polymorphism on active pharmaceutical ingredients: A review

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Abstract

Active pharmaceutical ingredients (API) are the main components in the production process of pharmaceutical products. If the API has a good quality, then it will lead to good pharmaceutical products. API consists of more than one different crystal form which, then forms a polymorph through the process of polymorphism. Until now, API polymorphism is still a big challenge in the pharmaceutical industry. That is because the nature of polymorphism is difficult to predict. One of them is by crystallizing molecules in one or many crystalline forms or combining with other molecules to form stable co-crystal. This process will lead to several polymorph forms of one certain API. Sometimes, these forms will have characteristics that differ one to another. Each polymorph has different mechanical, physical, thermal, and chemical properties that will affect the solubility, dissolution, bioavailability, stability, bioequivalence, and manufacturing of the API. Therefore to know the nature of an API, it is necessary to characterize the polymorphic form of the API before. If the form is not incompatible with the formulation, it can cause a failure in the production process. This review will discuss the effect of polymorphism on the physicochemical properties of API. It is hoped that this review can become the basis for improving the stability and effectiveness of pharmaceutical products.

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INTRODUCTION

Active pharmaceutical ingredients or so-called 'API' are organic chemicals, which are generally synthetic. These materials are chemicals used in the final pharmaceutical dosage form (Stauffer *et al.*, 2018). Pharmaceutical manufacturers are branches of chemical manufacturers for the manufacture of chemicals whose end use is in the form of pharmaceutical preparations, which referred to as active pharmaceutical ingredients ("API") (Muris and Nuechterlein, 2019). Active pharmaceutical ingredients (API) in the form of solid preparations containing single crystalline forms.

API is a crystalline solid that tends to be more stable and can be reproduced in the context of purification and processing when compared to other types of solid forms such as amorphous solids and soluble solids (Ainurofiq *et al.*, 2018a).

The choice of crystal shape during the development of API included polymorph, salt, solvent/hydrate, and cocrystal forms (Ainurofiq *et al.*, 2018b; Brittain, 2009).

Recently, many studies have been carried out regarding polymorphisms in active pharmaceutical ingredients (API) because of their importance in the pharmaceutical industry technology (Garnero *et al.*, 2016). Polymorphism is still a big challenge in the

pharmaceutical industry. That is because the nature of polymorphism is challenging to predict. One of them is by crystallizing molecules in one or many crystalline forms or combining with other molecules to form stable cocrystal (Aitipamula *et al.*, 2012).

Most of the API development consists of the same molecule. However, it can also be molecules which have different arrangement or conformation, and if they have different polymorphs, then the crystal structure is also different. Because polymorphs have different physicochemical properties, such as solubility, dissolution rate, and crystal shape, they have a significant effect on bioavailability and stability. Practical methods for controlling the desired polymorphs, namely the dissolution of metastable crystals, forming stable crystal nucleation, and solvent-mediated phase transformations. This technique is used to form stable crystals continuously (An *et al.*, 2016).

Polymorph is a solid crystalline phase given by compounds resulting from the possibility of at least two or more different molecular arrangements in the solid-state so that the compound can be in one or several crystalline forms (Grillo *et al.*, 2012). Polymorphism is a phenomenon wherein one molecule several different crystal phases can form, which can affect the physicochemical properties of compounds such as melting point, density, morphology, solubility and colour. It impacts on stability (physical and chemical), bioavailability and bioequivalence (Aitipamula *et al.*, 2012). Drug polymorphism can have a significant effect on therapeutic efficacy, especially when the dissolution rate is the stage for determining the rate of absorption in the digestive tract. In each variation of solubility, dissolution, density, flow properties, and shape of crystals can affect the absorption and, ultimately, the bioavailability of the drug (Brittain, 2009).

Polymorphism is the formation of crystals for one molecule. There are several different crystal shapes for the same molecule with different crystal structures and different physical properties, such as melting points. Thus, this polymorph is a different form of solid with the molecular formula of the same compound from the crystals that are made, having different physical properties. So it can have a direct effect on the process and produce medicinal substances, such as the stability of drug products, dissolution, and bioavailability (Egusa *et al.*, 2017).

So it is necessary to study the nature and characteristics of polymorphs, which can affect differences in physical properties, solubility, dissolution profiles, BABE, chemical stability, as well as for additives and manufacturing. This difference can have a direct effect on the ability of active pharmaceutical ingredients (API), which will later give different pharmaceutical product performance (Brittain, 2009).

Generally, the polymorphism process occurs through the crystallization process of substances from a single or mixed solvent and then the process of crystal cooling, evaporation, or antisolvent crystallization. Solvents are grouped based on solvent parameters such as hydrogen acceptor bonds/donor tendencies, polarity / dipolarity, dipole moments, and dielectric constants. Also, the polymorph will form by the level of heating and cooling, temperature crystallization, the rate of evaporation, the level of saturation, the level of agitation, the pH of the media are variables that can influence the crystallization process.

In enantiotropic systems, polymorphs in the metastable form at room temperature can be obtained by heating the stable form above the transition temperature. In a monotropic system, a stable form at room temperature can be obtained by heating a metastable form at any temperature.

Observing transition events during DSC measurements can estimate Transition temperatures. By calculating Gibbs, free energy differences between polymorph temperature range through direct heat capacity measurement, by van Hoff plots that measuring polymorph solubility at a specific temperature range, or by stirring polymorph mixes over a specific temperature.

Polymorphism in acetaminophen. Acetaminophen consists of three polymorph forms, namely polymorphs I, II, and III. Polymorphic forms I and II are known to show the same molecular conformational polymorphism but have different crystalline forms. The commercial form of the acetaminophen is polymorph I. Crystallizing solids can obtain the polymorph II form in benzyl alcohol at high temperatures, then cooling the melt, by adding carboxylic acid additives, or by using an evaporation method. Polymorph III is known as a precarious polymorph form, obtained by a melt cooling process, but can undergo a solid-state polymorphic transformation to form II within a few hours, and polymorph form III acetaminophen can quickly crystallize in nanostructures with pore sizes ranging from 10 to 103 nm (Lee, 2014).

Solubility

The solubility nature of active pharmaceutical ingredients in each solvent is essential in the manufacture and development of drugs. Each active pharmaceutical ingredient consists of different polymorphs. Moreover, every polymorph in active pharmaceuti-

cal ingredients has a different structure. Therefore each polymorph has different properties, including its solubility. The heat of fusion, which is the energy released during the melting process, influence polymorph solubility.

In a study of polymorphs, it knows that polymorph systems are based on heat-of-fusion rules, i.e., polymorphs that have higher melting points will have stronger lattices. So that will require higher heat to dissolve polymorph crystals. Therefore crystals with lower lattice will be more natural to dissolve (Rajamma *et al.*, 2015).

The polymorph shape influences its solubility. For example, in the metastable form, when compared with the stable form, the stability of this form is less durable but has better solubility. The solvent used in the recrystallization process dramatically affects solubility. Polymorphs of a drug substance can have high solubility and different dissolution rates. Dissolution testing can detect polymorphic differences and transformations that result in different solubility and dissolution rates. If there are differences in the solubility of various polymorphs, it will affect the effectiveness of the drug product, bioavailability, bioequivalent, gastrointestinal motility and intestinal permeability. If a drug has permeability limits, the solubility of the polymorphic form shows a smaller effect on bioavailability and bioequivalence (Prasanthi *et al.*, 2016).

The solubility of the polymorph can show the thermodynamic properties of the compound that are needed to determine how the crystallization process can occur, distribution polymorph crystals. It can find out the nature of a phase that is in a multi-phase system.

In a study conducted by (Fang *et al.*, 2015) notes that the two polymorphs in the clopidogrel studied were experiencing an increase in solubility along with an increase in temperature. Also, in this study, polymorph solubility is influenced by the type of solvent. The solubility of the two polymorphs generally increases with an increase in isopropanol in a mixture of solvents (ethyl acetate and isopropanol), and it can indicate that the polymorph solubility of the clopidogrel compounds in isopropanol is better than in ethyl acetate. In the temperature 278.15K; 283.15K; 288.15K; 293.15K; 298.15K; 303.15K; 308.15K; 313.15K; 318.15K with 0 N ispropanol in a mix solvent the solubility of polymorphs I of clopidogrel is 0.0868; 0.1393; 0.2252; 0.3336; 0.5143; 0.7691; 1.1376; 1.6779; 2.4339 g solvent $^{-1}$. At same temperature with 0.2 N ispropanol can found that solubility of polymorphs I of clopidogrel is 0.8025; 1.1521; 1.2831; 1.6863; 1.9563; 2.5569; 2.9171; 3.6895; 4.4532 g solvent $^{-1}$. At same temperature with 0.4 N isopropanol can found that solubility of polymorphs I of clopidogrel is 2.4995; 2.6631; 3.1677; 3.7983; 4.3018; 4.8981; 5.5754; 6.3684; 7.5816 g solvent $^{-1}$. At same temperature with 0.6 N isopropanol solubility of polymorphs I of clopidogrel is 3.4971; 2.6631; 3.1677; 3.7983; 4.3018; 4.8981; 5.5754; 6.3684; 7.5816 g solvent $^{-1}$. At same temperature with 0.8 N isopropanol solubility of polymorphs I of clopidogrel is 4.3285; 5.3631; 5.8772; 7.1563; 7.9225; 9.6696; 10.7247; 12.6854; 14.4365 g solvent $^{-1}$. At same temperature with 1 N isopropanol solubility of polymorphs I of clopidogrel is 4.6436; 5.5453; 6.7813; 8.0223; 9.7539; 12.4419; 14.0831; 16.3312; 16.3312; 19.2761 g solvent $^{-1}$. Whereas at Polimorf II of clopidogrel in the sampe temperature at polimorf I of clopidogrel with 0 N isopropanol solubility of polymorphs II is 0.0578; 0.0953; 0.1551; 0.2356; 0.3716; 0.5696; 0.8716; 1.3025; and 1.9659 g solvent $^{-1}$. With 0.2 N isopropanol solubility of polymorphs II is 0.5561; 0.8063; 0.9154; 1.2304; 1.5034; 1.9876; 2.4193; 3.1025; and 3.8303 g solvent $^{-1}$. With 0.4 N isopropanol solubility of polymorphs II is 1.7278; 2.0156; 2.5073; 3.0968; 3.5639; 4.2632; 4.9659; 5.6987; and 6.8542 g solvent $^{-1}$. With 0.6 N isopropanol solubility of polymorphs II is 2.8702; 3.6984; 4.1187; 5.2987; 5.9039; 6.7698; 7.9938; 8.9875; and 10.3871 g solvent $^{-1}$. With 0.8 N isopropanol solubility of polymorphs II is 3.6915; 4.6589; 5.2015; 6.2863; 7.1075; 8.6325; 9.9651; 11.6367; and 13.9904 g solvent $^{-1}$. With 1 N isopropanol solubility of polymorphs II is 4.1209; 4.9863; 6.1013; 7.2369; 8.9252; 11.3698; 13.0811; 15.2863; and 18.0211 g solvent $^{-1}$.

Whereas in the research conducted by (Zhai *et al.*, 2017) related to the solubility of rivaroxaban polymorphs, which have solubility data in seven solvents determined by the dynamic dissolution method at atmospheric pressure. The results show that the solubility of the two rivaroxaban polymorphs increases along with the increasing temperature and form II has a higher solubility than form I, which shows that form II is a metastable form. In 7 different solvents, it is known that the solubility of rivaroxaban form 1 and form 2 is 1,4-dioxane> Acetonitrile, acetone> 2-butanone> methyl acetate> 3 pententone> 2-hexanone. In other words, the solubility of two forms of rivaroxaban at a certain temperature decreases by increasing the amount of carbon ketone. The ability of a substance to dissolve in the solvent is related to the polarity and hydrogen bonding between the solute and the solvent. In this study, the solubility sequence roughly follows the order

of the polarity of the solvent and the possibility of forming hydrogen bonds between the rivaroxaban molecule and the molecules in the solvent.

In research conducted by (Gong *et al.*, 2019) on polymorph podophyllotoxin (PPT), it is known that polymorph solubility base on the shape of the crystal. Amorphous polymorphs PPT can dissolve faster than polymorphs I and II, which are anhydrous. Amorphous polymorphs have higher energy so they can easily reach equilibrium. When form I compare with form II, form II has a higher solubility than form I, which can also increase its original bioavailability and other desired characteristics. Based on stability testing and results from the *intrinsic dissolution rate*, form II is the best form of PPT crystal.

Dissolution

Dissolution is the dissolving process of pharmaceutical products into a particular medium, or briefly defined as the process of chemicals (drugs) dissolved in a solvent. A pharmaceutical preparation is said to have a good dissolution profile if it can be dispersed in body fluids after consumption, releases active substances in certain concentrations so that they can be dissolved in biological media, then the active substances will be absorbed into the systemic circulation, and finally show clinical response (Wagne, 1970; Shargel *et al.*, 2004).

Active pharmaceutical ingredients (API) can form crystals. Various forms of crystals consist of molecules arranged in three-dimensional structures with regular patterns that repeat periodically. Under ideal conditions, the resulting conformation can be a single crystal (all the atoms in its solids are in the same crystal structure). However, crystals are generally formed simultaneously and produce polymorphs, which are crystals that are in different phases and conformations (Larkin *et al.*, 2014). This is what can affect the characteristics and properties of crystals, one of which is the rate of dissolution (Khankari and Grant, 1995).

The form of API must be highly considered because it can affect the dissolution rate and ultimately affect its bioavailability in the patient's body. Chlorthalidone (2-chloro-5- (1-hydroxy-3-oxo-1-isoindoline) benzenesulfonamide, CTD) is a diuretic antihypertensive drug that inhibits sodium ion transport in the distal tubule (Sica, 2006; Supuran, 2008). There are four known CTD crystal forms, namely form I, form II, form III, and form IV. Form I is a solid form of CTD that is usually used in drug production (Martins *et al.*, 2009). Form II is a mixture of two crystal structure types, namely (R) -enantiomer and (S) -enantiomer (Martins *et al.*, 2013). Form III has a racemic crystal structure (Martins *et al.*, 2009). While the IV form has a racemic structure and is described as a non-stochometric chloroform solvent from CTD containing 0.25 moles of chloroform in each mole of CTD (Martins *et al.*, 2012).

From the results of research conducted by (Bonfilio *et al.*, 2014)on CTD tablets form I, form II, and a combination of forms I and II, it was proven that polymorphisms that affect the dissolution rate and ultimately can affect the therapeutic effect of CTD. Form II has a higher dissolution rate (14-49%) than form I. However, the form I has higher acceptability for making tablets. Therefore, it is recommended that the pharmaceutical industry conduct polymorphic quality control on raw materials and CTD tablets using X-ray diffraction analysis, infrared spectroscopy and dissolution profiles.

Nicergoline is a semisynthetic derivative of ergot, which is hydrophobic but has the potential as an α1-adrenoreceptors blocker. There are two crystalline forms of nicergoline that show a monotropic relationship. Form I is triclinic, while form II is orthorhombic, which is less thermodynamically stable (Foresti *et al.*, 1988; Husak *et al.*, 1994; Malaj *et al.*, 2011). In the production of pharmaceutical preparations that use nicergoline, it is necessary to reduce particle size in order to increase the dissolution of nicergoline. This is based on Noyes and Whitney's law, which states that the dissolution rate increases with the increase in the surface area of the substance caused by the reduction in the particle size of the substance (Khadka *et al.*, 2014; Liversidge and Cundy, 1995). Research conducted by (Censi *et al.*, 2019) stated that reducing the particle size of nicergoline by the grinding method can increase the rate of dissolution. However, supervision must still be carried out on the physicochemical properties of the material to avoid the transition of solids, which can ultimately reduce the dissolution rate.

Stability

Polymorphisms are very important for active pharmaceutical ingredients (API) because of their different physicochemical and bioactivity properties in many cases such as crystal habits, intermolecular forces, particle density, thermodynamic activity, physical-chemical stability, solubility, dissolution rate and bioavailability (Yang *et al.*, 2013). The stability relationship between polymorphs and pharmaceutical active ingredients (API) is an important step for the development of drug formulations. This relationship makes it possible to identify polymorphic forms that are suitable for normal conditions (Pandey and Dalvi, 2019). Polymorphs are compounds that exhibit thermodynamic physical properties that have differences such as solubil-

ity, free energy and melting point which are key to developing the right dose of all active pharmaceutical ingredients (API) (Garnero *et al.*, 2016).

In drug development, a stable form of active pharmaceutical ingredients (API) is always considered. A thermodynamically stable polymorphic form is usually highly selected for drug development because there is little phase change. An understanding of the behavior of polymorphisms and ensuring thermodynamic stability in their polymorphs is necessary. There are 2 relationships in polymorphs, namely monotropic and enantiotropic. Enantiotropic can be said if one polymorph is stable at a certain temperature and pressure range while the other is stable at different temperatures and pressure ranges. However, if only one polymer is stable at all temperatures while the other is unstable, then it can be said that the relationship is monotropic (Pandey and Dalvi, 2019).

The polymorph thermodynamic stability is determined by changes in free energy Gibbs (ΔG). In diagram ΔG versus temperature can provide information about polymorph stability. Based on research conducted by (Yang *et al.*, 2013), there are two polymorphic crystalline forms of m-nisoldipine (1,4-dihydro-2,6-dimethyl-4- (3-nitrophenyl) -3,5-pyridine carboxylic acid methyl 2- methyl propyl ester) in which the two polymorph forms are marked with polymorph A and Polymorph B. polymorph A is a crystal produced by acetone/ethanol (1: 1) solution with slow evaporation whereas polymorph B is obtained from ethyl acetate/hexane (1: 1) solution. Both m-nisoldipine polymorphs indicate that both forms are enantiotropic. Enantiotropic is a polymorph that is stable at different temperatures and pressure ranges (enthalpy of fusion). Enthalpy of fusion polymorphs A and B, respectively 88.88$\pm$1.55 and 90.28$\pm$1.09. This can be seen in the DSC data, where there are differences in enthalpy of fusion, although not very clear (Yang *et al.*, 2013).

The temperature in the polymorphic transition phase is 47^{0}C. The temperature in the polymorphic transition phase is obtained from the graph of the relationship between ln c (solubility) versus 1 / T (temperature). The values of $\Delta H^{\theta}{}_{A}$ and $\Delta H^{\theta}{}_{B}$ obtained from the slope of the two curves on the graph are 54.35 kJ mol^{-1} and 18.34 kJ mol^{-1}, respectively. At the intersection of two curves, it is a transition temperature (Yang *et al.*, 2013).

Research conducted by (Yang *et al.*, 2013), it can be concluded that crystal A is more thermodynamically stable under transition temperatures and has low solubility at room temperature. While crystal B has higher solubility at room temperature compared to crystal A. So that in crystal A m-nisoldipine is preferred for pharmaceutical preparation.

Based on research (He *et al.*, 2016), different polymorphs from the same active pharmaceutical ingredient may exhibit different physicochemical properties. In this study investigating the effects of polymorphism on the thermodynamic properties of cefamandole nafate. Two new polymorphs of cefamandole nafate, namely form IV and form V, have been characterized. From the DSC data, it was found that the IV form is more stable because it has a high melting point compared to V (He *et al.*, 2016). The IV form of the DSC curve shows a single endothermic peak with an onset temperature of 442.5 K and a fusion enthalpy of 18.88 kJ mol-1, whereas the V shape DSC curve shows a single endothermic peak with an onset temperature of 437 K and a fusion enthalpy of 13.93 kJ. So that from this study, it can be concluded the thermodynamic properties of the two properties are different wherein the IV form is more stable because it has a higher melting point and enthalpy of fusion. The relationship between the two polymorph forms is monotropic and IV form can be obtained from the transformation of V.

Bioavailability

Drug polymorphism is related to the effects of drugs and the performance of solubility, dissolution, and bioavailability. Thermodynamically stable polymorphs are more widely used because there are no changes during storage, and thus have the potential to change in bioavailability. However, the most stable and least soluble form can produce bioavailability that is too low. Thus, a metastable form might be desirable to achieve better therapeutic benefits (Deng *et al.*, 2017).

Bioavailability or biological availability is the amount of drug concentration that is released at the site of action. Bioavailability is highly influenced and is a component of solubility. Bioavailability with low solubility in question is having low water solubility (Censi and Martino, 2015).

Carvedilol (CVD) is a drug used to treat hypertension, mild to severe heart failure, myocardial infractions and treatment of angina pectoris. This drug is a non-selective β-blocker class. CVD is classified as a class II BCS drug, which means it has low solubility and high permeability (Censi and Martino, 2015). The solubility of CVD drugs in water is poor and depends on pH. The solubility at pH around 9 is less than 1 μg / mL; pH 7 is 23 μg / mL and pH 5 100 μg / mL at room temperature (Hamed *et al.*, 2016). As a result of poor solubility in water, the maximum

bioavailability in the body is 30% or less (Kukec *et al.*, 2012). So to improve the bioavailability of active ingredients, CVD salts are formed with high water solubility and good stability. Experiments were carried out using a Buffer pH 6.8 solution at 37^{o}C for 24 hours. The result of CVD salt formation is an increase in the solubility value compared to CVD. With the increase in the value of solubility, bioavailability is further increased (Hiendrawan *et al.*, 2017).

Thalidomide (TLD) is a drug used for the treatment of erythema nodosum leprosum (ENL), multiple myeloma, Crohn's disease and wasting syndrome in HIV patients (Vargesson, 2015). The active ingredient of TLD is crystalline and lipophilic solids which have low water solubility. This drug can be found in 3 forms of polymorphism, namely α, β and β*. Polymorphs α and β have melting points respectively 272.3^{o}C and 275.7^{o}C and energies of -349.2 kcal and -416.9 kcal, as seen from melting points and their energy polymorphs form β are more stable than those of the polymorph α. Then the test was carried out with SI and q values using a sink condition with a 500 mL surfactant medium (Oliveira *et al.*, 2019).

According to the f2 factor and DE% values, the two profiles are not comparable, and also α-TLD shows the fastest and highest dissolution extension and pharmacokinetics, which are more advantageous compared to active ingredients in the form of polymorph β-TLD. The α-TLD has a fast onset with a higher concentration than β-TLD. The α-TLD is smaller (152.1 μm vs. 210 μm) compared to β-TLD, so for α-TLD with a higher area, this causes α-TLD to have a faster onset. But in α-TLD, bioavailability in the body is faster, too, whereas for β-TLD, bioavailability in the body is long with a more stable concentration compared to α-TLD. So after the experiment, it was concluded that β-TLD has thermodynamics that is more stable than α-TLD. However, the speed and high extension of the dissolution test on α-TLD illustrates good pharmacokinetics and bioavailability. It is recommended that the pharmaceutical industry use polymorph α-TLD as an active ingredient (Oliveira *et al.*, 2019).

Carbamazepine (CBZ) is a drug used in the treatment of epilepsy, neuropathy, and psychiatric disorders. CBZ is a derivate of iminodibenzyl whose structure is similar to tricyclic antidepressants (Ambrósio *et al.*, 2002). CBZ is classified in the BCS II class, which means it has low solubility and high permeability. Two forms of CBZ anhydrous are better absorbed than dihydrate because of their higher solubility and faster dissolution rate. However, the difference between solubility and bioavailability for these two forms of anhydrous can be attributed to the different levels of transformation, as identified in the intrinsic dissolution test. The transformation of form I to dihydrate is faster than form III, which affects the dissolution kinetics and decreases available dissolved drugs for absorption, which could be the main reason for having lower bioavailability than in vivo forms (Deng *et al.*, 2017).

Biphasic dissolution tests are used to investigate differences in formulations with BCS II drugs. The relationship between in vitro dissolution and in vivo absorption is likely to be obtained for BCS II drugs when in vitro dissolution can reflect the in vivo rate-limiting process. For polymorphic drugs, the interaction between dissolution and solution-mediated phase transformation can dominate the overall release kinetics. In this study, three forms of carbamazepine crystals were successfully differentiated through the biphasic system and correlated well with their in vivo performance (Censi and Martino, 2015).

The form of carbamazepine anhydrous undergoes phase transformation to dihydrate under aqueous conditions, so the solubility of the anhydrous form is estimated based on the intrinsic dissolution rate using the dissolution rate constant equation must be the same for these three crystal shapes, because hydrodynamic conditions and a constant surface area are maintained. The solubility of carbamazepine form I, form III and form of dihydrate were 503.9, 462.0 and 216.3 μg / ml, respectively (Deng *et al.*, 2017).

The order of solubility ranking of the three polymorph forms of carbamazepine corresponds to the intrinsic dissolution rate. It can be concluded that the polymorph I form has higher bioavailability compared to the polymorph III form and the dihydrate form (Deng *et al.*, 2017).

Bioequivalence

A pharmaceutical industry that has made product innovations and is going to apply for a distribution permit must have a bioequivalence test. This test is carried out as a condition where the results must be bioequivalent. This requirement does not apply to all types of drugs but only for certain drugs included in the biopharmaceutics classification system. The bioequivalence of a drug to its innovator product can be used to assess the drug, whether it has the quality, safety, and efficacy that is equivalent to the innovator drug. Bioequivalence test is a test that compares the bioavailability of a drug with the bioavailability of the innovator drug. This research was conducted using drugs made in dosage form, dosage,

route of administration and the same experimental conditions (Shargel *et al.*, 2004).

Polymorphisms can cause differences in physical terms. The chemical properties of the active ingredients and the variations in these properties can cause the drug product to not show bioequivalence, and hence in the product is not equivalent to therapeutic brand innovators (Raw A S, Furness, M.S, Gill, D.S, Adams, R.C, Holcombe, F.O, Yu L.X. , 2004). Polymorphisms of pharmaceutical solids can modify the physicochemical properties when pharmaceutical solids exist in more than one crystal form or structure, significant differences in drug solubility can be detected, especially for drugs that are not soluble in water and are classified as class II and IV according to BCS (FDA, 2014; Bonfilio *et al.*, 2014). In this case, the dissolution step is a limiting step for drug absorption, and the lack of bioequivalence between different formulations may be related to polymorphism (Resende *et al.*, 2016).

Spironolactone (SPR) is a steroid drug given as a potassium-saving diuretic for high blood pressure treatment. According to the research of (Resende *et al.*, 2016) solid-state formulations made with the same excipients and processes, the SPR polymorphism effect in drug solubilityand dissolution rate can change in vivo pharmacokinetics of this drug, which results in a lack of bioequivalence among medicinal products. The dissolution profile of tablets from batch A and B was shown where the amount of drug dissolved in 60 minutes was 89.32 $\pm$ 3.43% for batch A, and 79.55 $\pm$ 9.72% for batch B. However, the dissolution profile comparison used a factor f2 shows the value of 19.00. According to these results, the dissolution profile of the tablets produced was different, which might be related to the solubility of the API (SPR-L1 and SPR-L2). The dissolution rate of tablets in batch A is higher than that of batch B, and maybe because tablets in batch A are produced with a more soluble API (SPR-L1). Considering that, this solid-state formulation is made by the same excipient and process, the effect of SPR polymorphisms in drug solubility and dissolution rate can change the in vivo pharmacokinetics of this drug, which results in a lack of bioequivalence among drug products. These results indicate a lack of pharmaceutical equality among the evaluated solid-state formulations. Therefore, formulation scientists must carefully explore the design of SPR formulations to optimize their performance and improve pharmaceutical equivalence and bioequivalence among drug products (Resende *et al.*, 2016).

The Food and Drug Administration (FDA) announced the availability of a draft guideline for the industry entitled "Bioavailability and Bioequivalence Studies Submitted in NDA or IND - General Considerations" (draft BA and BE guidelines for NDA). The draft guidelines provide recommendations for sponsors and/or applicants who plan to include bioavailability (BA) and bioequivalence information (BE) for drug products in the investigation of new drug applications (IND), new drug applications (NDA), and NDA supplements. This draft guideline revises portions of the March 2003 guideline titled "Study of Bioavailability and Bioequivalence for Oral-Given Medicinal Products - General Considerations" related to BA and BE studies for IND, NDA supplements, and NDA supplements. Based on these regulations, the polymorphism required bioavailability and bioequivalence tests to compare the quality is almost the same as the innovator products.

Manufacturing

Drug manufacturing is the process of making a type of pharmaceutical preparation. In this process, extensive knowledge is needed in every aspect and mechanical properties possessed by API and other excipients. This aims to simplify the manufacturing process so that products with good quality can be produced (Khomane and Bansal, 2014).

In the pharmaceutical field, polymorphism is one of the phenomena to study the effects of molecular-level material properties on the mechanical properties of pharmaceutical material. This is due to the consistency of the chemical composition, which eliminates the complexity caused by different molecular structures (Khomane and Bansal, 2014). Some examples of the influence of polymorph molecular properties on the manufacturing process are the density of crystal packaging, differential molecular packaging, and thermodynamics. The results of the study stated that the molecular properties affect the powder preparation process (Khomane *et al.*, 2012; Khomane and Bansal, 2013).

A study conducted by (Upadhyay *et al.*, 2013) states that polymorph ranitidine hydrochloride form I (does not have an active slip-plane system) has poor compressibility and deformation properties, but has greater tablet ability properties. Meanwhile, shape II has a relatively open crystal structure so that it shows an increase in compressibility and a lower average melting point. Thus, polymorphism plays an important role in the compressibility and also compactness of the material.

CONCLUSIONS

Polymorph is a solid crystalline phase given by compounds produced from the possibility of at least two or more different molecular arrangements in the solid-state so that the compound can be in one or several crystalline forms. Based on the review that has been done, polymorphism has been shown to affect the physicochemical properties of an API, namely solubility, dissolution, stability, bioavailability, and bioequivalence, as well as the manufacturing process. Therefore, in the manufacturing process of pharmaceutical preparations, it is necessary to analyze the crystalline form of the raw material so that the most stable, acceptable and effective crystal form is known.

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