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A Review: Solubility and Dissolution of Drug Products

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ABSTRACT

Solubility, which is one that relates with the dissolution is a very important factors that relates with the pharmacological action of a drug. This is because it is to achieve the minimal or desired concentration in the blood circulation for a drug to give its pharmacological effects. More than 40% new chemical entities are found to be insoluble in water. The solubility of the active ingredients of the drugs is then be the main problems for the researchers these days. Therefore, there are a few techniques which we can use to improve the solubility of the drugs such as particle size reduction. Dissolution is also important for drugs to be absorbed into the blood circulation. Therefore, for oral taken drugs, usually dissolution testing is needed to have a better control of the product's activity throughout its life cycle.

Introduction

Solubility defines as one or more liquid, solid or also gaseous known as dissolving solute in a particular solvent of liquid, solid or gaseous. This then lead the formation of a solution that is homogeneous. Solvent used, temperature and pressure will affect the solubility of a substance. At one point, adding solute not affect the solution's concentration to increase (Lachman*et al.,* 1986). This is known as saturation concentration. In general, solvent refers to a liquid either contain only one substance or admixture of two liquids. Low or very low soluble compounds refer to insoluble compounds (Clugston and Fleming, 2000). Equilibrium of solubility happens when two processes continue at a steady rate (Myrdal &Yalkowsky, 2011). Solubility may be stated in units of milligrams per litre. Solubility is commonly termed as a concentration, molarity, molality and also mole fraction (Martin, 2011).

Descriptive term	Part of the solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Table 1: Solubility criteria of USP and BP

Physical constants like enthalpy of fusion can be used to predict solubility. The difference of solubility within a compound in solvent that is hydrophobic such as octanol and water which is hydrophilic solvent can be measure using partition coefficient (Log P). These two logarithm values allow to rank compounds in terms of lipophilicity or lipophobicity. Solubility criteria of USP and BP in Table 1 categorize the solubility of solvent only in terms of quantification (Aulton, 2002). These two logarithm values allow to rank compounds in terms of lipophilicity or lipophobicity. Solubility criteria of USP and BP in Table 1 categorize the solubility of solvent only in terms of quantification (Aulton, 2002). The Biopharmaceutics Classification System

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(BCS) is a standard to determine absorption of drug in the intestinal. The prediction using solubility parameters and permeability of intestinal is restricts by this system. Solubility depends on the greatest strength of dose for an immediate release product. When the greatest strength of dose soluble in 250 mL or less within the ranging of pH 1 to 7.5 is considered as a highly soluble drug (USP, 2007). The categorization permeability of intestinal depends on comparison to the intravenously injection. These factors are crucial because a lot of drugs that sold in the USA and Europe are administered orally. There are four classes of drugs which are high permeable and high soluble (class I), high permeable and low soluble (class II), low soluble and high permeable (class III) and lastly low soluble and low permeable (class IV).

Dissolution defines as a process where a solute in gaseous, liquid or solid phase dissolves in a solvent to form a solution. There are methods to improve dissolution of drug products. This to make sure that the oral bioavailability can be achieve in high concentration. The methods are micronization which the surface area for dissolution process can be increase. Besides that, formation of salt of the active ingredient, the co-solvents and micelle solutions usage which help to aid solubilisation.Complexation with use of cyclodextrins also one of the methods.Lastly the lipidic systems usage especially for lipophilic drugs. Dissolution is important in drug products. Drugs must be in solution so that the drugs can be absorbed and produce therapeutic effect in the human body. The rate of dissolution for solid preparations such as tablets, capsules and suppositories affect time taken for a drug to be absorbed in the body.

IMPORTANCE OF SOLUBILITY

The route of administration through orally is the most convenient route to take a drug. This is because of the easy administration, less of cost and also high in patience compliance. By that, most of the drug companies that produce the generic drugs are more inclined to produce oral drugs which are bioequivalent (Lachman*et al.*, 1986). To design an oral dosage form, the most important thing that needs to be seriously measured is their bioavailibility. The bioavailability of an oral dosage form drugs actually depending on a few factors which including the dissolution rate, aqueous solubility, permeability of drug, first pass metabolism and others. However, the major causes which effects the bioavailibility are because of the low permeability and also poor solubility of the drug. Drugs which is given parenterally also has connections with the solubility of the drugs (Clugston and Fleming, 2000).

For drugs to gives out its pharmacological action, it must reach the blood circulation with the minimum or desired concentration. Thus, the solubility of drug is very important for the drugs to reach the systemic circulation (Myrdal &Yalkowsky, 2011). For drugs which has low water solubility, to reach the minimum concentration into the plasma, high doses is needed after the oral drug administration. One of the challenges in new development and discovery of drugs is the low of aqueous solubility. This is because, for drugs to be absorbed to the circulation, it needs to be in an aqueous solution form. And also, majority of the drugs are having a poor aqueous solubility because it is either from a weak acid or a weak base.

Throughout the new developments of drugs these days, more than 40% new chemical entities are found to be insoluble in water. This will then effect to makes the absorption of drugs become slower, and then leads to a variable bioavailability and also toxicity at the gastrointestinal lining. Drug solubility is one of the important things to be measured in oral drugs, because it needs to reach the minimal and desired concentration in the blood to produce its pharmacological effects.

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Therefore, this problem with the solubility of the newly found chemical entities is causing problem with the researchers to form a new drug (Martin, 2011).

ADVANTAGE AND DISADVANTAGE OF SOLUBILITY

The solubility of a drug is depending crucially on its potential of chemical reaction since it is present in the undissolved solute. The composition and state of the undissolved solute when the ASD is equilibrated with water is the factor where the solubility of a pharmaceutical amorphous solid dispersion (ASD) depends on. One of the advantages of solubility is that the drug candidates with characteristic of poorly water-soluble becomes more prevalent with increasing of solubility. Rough estimation has been done where around 60% to 70% approximately, insufficient drug molecules are soluble in aqueous media (Lachman*et al.,* 1986).

There is also research found said that it is easier for a drug to reach maximum plasma level if with the increasing in solubility. "One of the major problems associated with poorly soluble drugs is that they have a very low bioavailability (Clugston and Fleming, 2000)." A drug's efficacy might also reduce along with low solubility and absorption. Hence, an efficacious product solution cannot be produced using drugs with low absorption because they are not a good fit substance. According to Ketan et al. in a 2012 article, "Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations." Requirement of lower dose of drug to reach therapeutic plasma concentration is much better besides can reduce its side effects to patient consuming the drug compared to the intake of higher doses. Therefore, increased solubility also helps reducing drug doses with great efficacy.

Furthermore, choosing solvents systems also consider solubility of a drug. According to Partel, based on an overview of parenteral suspension, solvent system choice usually relies on solubility, desired release characteristics also stability of drugs. From this statement, it can be said that highly soluble drugs give more reactions in solvent systems compared to less-soluble drugs. In addition, according to Minoru and Yuichi, (Myrdal &Yalkowsky, 2011) they said that "high concentrations of poorly soluble drugs in organisms may leads to crystallization and acute toxicity." This shows that increasing solubility could prevent these illnesses to develop in patients consuming poorly soluble drugs. One of disadvantages of solubility is it depends heavily on other species presenting in the solvent. For example, the 'common ion effect'. Solubility constants, which expressing the low solubility of ionic compounds in a saturated solution explains both undissolved and dissolved salts present in a compound equally (Martin, 2011).

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Techniques to improve the solubility are classified into physical and chemical modifications of the drug substance and also other techniques. Modifications of physical is when reduction of particle size occur. For example, micronization and nanosuspension. For crystal habit modification such as amorphous and polymorphs form, the dispersion of drugs in carriers involve eutectic mixtures techniques, dispersions of solid, solid solutions and also techniques of cryogenic. Modifications of chemical is due to the changes of pH, buffer usage, derivatization, complexation and also formation of salt. Miscellaneous Methods involve supercritical fluid process which adjuvant like surfactant is use, solubilizers, cosolvency, hydrotrophy and novel excipients.

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PARTICLE SIZE REDUCTION

The particle size of a drug is naturally the factor influencing a drug's solubility. The smaller the particle size, the bigger surface area to volume ratio which leads to greater interaction within solvent molecules resulting increase in the drug solubility.
Standard methods in reducing the particle size of drug like spray dying and comminution subdivide the drug's active substance by depending upon mechanical stress. An economic, reproducible and efficient means of enhanced solubility is permitted because of the particle size reduction. Nevertheless, the mechanical forces intrinsic to comminution such as grinding also milling, where these may convince degradation due to the drug product usually imparted by the mechanical forces. During processing an unstable active compound or thermosensitive compound, their thermal stress also needs to be considered during comminution and spray drying. In order to enhance a drug solubility, traditional methods are not very suggested especially for nearly insoluble drugs.

Furthermore, micronization method also can be used to reduce the particle size. This method action is by increasing a drug dissolution through widened surface area, still, equilibrium solubility will not be increased. Rate of dissolution can be improved by reducing the drug's particle size which its surface become wider, enhancing the reaction. Technique used in this method is milling where it is operated using rotor stator colloid mills yet micronization still inappropriate method to be used for highly dose drugs since drug's saturation solubility does not changed by this method (Blagden, 2007). Progesterone, Spironolactone diosmin and Griseofulvin can be implemented by these processes where micronization enhanced each drug's digestive absorption along with clinical efficacy and bioavailability (Vogt *et al.,* 2008; Chaumeil, 1998).

DISSOLUTION TESTING

In pharmaceutical development and also in the process of quality control, dissolution testing is the main test to perform. The dissolution testing haves a relationship between the invivo performance and also with the manufacturing Critical Quality Attributes, which relates in the field of Quality by Design (Aulton, 2002). The main reason to the dissolution testing is to have a better control of the product's activity through out its life cycle. With then, the development of a brand new method of USP dissolution which is by using 1 litre vessel with a basket and also a paddle are said to be well established [7,8].

Recent studies focuses to evaluate the possible of available small volume USP2 dissolution equipment for dissolution testing of drug products, especially solid drugs. The small sized vessel or paddle equipment will then have an advantage of where it can be easily fitted without adaptation on the USP2 system. Therefore, there are many mechanism of dissolution founded for drug products which are in solid. Some of the examples are, extended release and also immediate release, which are screened using both of the dissolution testing, the normal and also the small volume.

IMPORTANCE OF DISSOLUTION TESTING

Dissolution testing is a must for all drug products especially solid oral dosage forms. This test is important throughout the development for product release and stability testing. This determine the approval of drug products to the market. It is an essential analytical test used to detect any changes in physical in active ingredient and formulated product. The ability of the drug to dissolve in the fluids of the gastrointestinal tract which then being absorbed into the circulation

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will affect the effectiveness of an oral dosage. Hence, dissolution rate of tablets or capsule is vital to this process. This test also play important role in the generic pharmaceutical industry. It is applied in formulation enhancement, manufacturing process monitoring and as a test to control the quality of drug products. Other than that, dissolution testing functions to measure the rate of drug release from a dosage form. This is to optimise the dosage form in order to produce desired therapeutic effect. Dissolution is an *in-vitro* test. The *in vivo* performance of drug products can be predicted. Determination of successful *in vitro-in vivo* correlation (IVIVC) or worst case, a relationship between the two can be identify by selecting an appropriate *in-vitro* conditions. Finally, identify studies of the bioequivalence (BE) related to Scale-Up and Post-Approval Changes (SUPAC) requires dissolution testing. Therefore, the effort of FDA to decrease the burden of regulatory and needless human studies in development of drugs without noticing the quality of the drug products (BP, 2009).

ADVANTAGE AND DISADVANTAGE OF DISSOLUTION TESTING

There are seven types of USP apparatus which used for dissolution testing. Apparatus 1 or 2 are most use for drug products such as tablets and capsules. These Apparatus 1 and 2 also known as basket and paddle respectively. These two USP Apparatus 1 and 2 have some common advantages and disadvantages. The advantages are they are apparatus that are usually use for testing the dissolution. They are also first choice apparatus for solid oral dosage forms. Other than that, both of these apparatus are standardized which easy to use and operate. Most floating solids use USP Apparatus 1 but the disadvantage is that it requires sinker. Volume of the dissolution media is limited for Apparatus 1 and 2, the hydrodynamic conditions are not known. Shaft wobble, location, and coning will affect the results of dissolution (Amidon*et al.*, 1995).

For advantages of USP Apparatus 3 are dissolution can be programmed in different media for various time and the media can be easily changed. It attempts to reflect the changes of pH and allow times transit in the gastrointestinal tract. The disadvantages are the dosage forms that disintegrate have very low results, foaming occurs due to surfactants and also dissolution media's volume is very small.

USP Apparatus 4 advantages include there are no limitation about the media's volume used, low soluble drugs are preferring to use this apparatus and gastrointestinal transit can be simulating for dissolution testing. There are disadvantages using this apparatus which are the precision of pump might affect the results and lead to experimental error of fractioned primary data when computed to cumulative profiles. For USP Apparatus 5 which is the apparatus of Paddle-over-Disk, USP Apparatus 6 refers to Cylinder Apparatus and USP Apparatus 7 or also known as Reciprocating Holder Apparatus. This three apparatus are used to evaluate the transdermal patches (Yellela, 2010).

FACTORS AFFECTING RATE OF DISSOLUTION

The bioavailability of drugs is very important, and one of the factors affecting it is the rate of dissolution. The rate of dissolution of drugs are related with the formulation factors, the physiologic factors of the human bodies and also the physiochemical properties of the active ingredients of the drug. To make sure that the drugs achieve its reproducibility, it is very important to analyze the formulation variables, and also the physiochemical of the active ingredients (Aulton, 2002).

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1. Physicochemical Properties of active ingredients of the drug

1.1. Ionized VS Unionized Forms

Drug dissolution happens more rapid in salt forms which is in the ionized forms. This is because, salts which is in the ionized forms of weak electrolytes is more hydrophilic than the salts which is in unionized forms. The ionization of drugs relates with the environmental pH where the dissolution expected to occurs. When taking oral drugs, the pH will varies from about 5.0 to 7.0 in the intestine, and from 1.5 to 3.0 in the stomach. Other than that, because of the low pH in the stomach, which is between 1.5 to 3.0, weak bases will then dissolved readily. This is because of the high protonated fraction of the ionized form. Meanwhile it is not the same for weak acids. Since the pH at the intestine is between 5.0 to 7.0, the fraction ionized will become higher. The relationship that we can use which is even though the rate of dissolution increases together with ionization level, it is important to know that drugs which is in unionized forms are more highly absorbed.

1.2. Particle Size

According to Noyes Whitney, rate of dissolution of particles is directly proportional to the surface area. The reduced of a particle sizes will then therefore increase the surface area. As for drugs which are low in hydrophilicity, a reduced in particle size can improve the dissolution rate and also the bioavailability of the oral drugs. One of the methods reduce the parcticle size is by using micronization method. This will then improve the effective surface area which available for the dissolution of the drug (Aulton, 2002).

2. Formulation Factors

2.1. Solid dosage forms

In the cases of oral administration drugs such as tablets and also capsules, for a pharmacological action to occur, it needs to reach the blood circulation. Therefore, those formulations needs to be dissolve in the gastrointestinal fluid for absorption to occur. For tablets, the process of dissolution is mainly for drugs which is less soluble. The process mainly to form a fine particles which by disintergration and also deaggregation. The disintergration process is mainly affected because of the use of binders or also known as binding agent during wet granulations. Therefore, poly(N-vinylpyrrolidone) which is a polymeric binders is shown to have an effect in increasing the rate of dissolution of the drugs which is lipid soluble. This is probably because of the enhancement of the wetting effect on the surface. When adding starch and also lactose which acts as diluents also will increase the rate of dissolution of the drugs which is lipid soluble and in the form of tablets and also capsules. Meanwhile stearic acid, which is a lubricating agent can affect in a decrease of dissolution rate. It acts by making a hydrophobic layer on the particle which hinders the interaction together with the aqueous medium. Besides, the compression forces also play an important role which will effects the disintegration of the drugs, as well as the process of dissolution, especially in the formulation of a tablet (Aulton, 2002).

3. Physiologic Factors

3.1. Gastric Emptying and Intestinal Transit Rate

Non-digestible materials or particles took around 5 minutes to around more than 2 hours to pass through the stomach. It depends on what type of material or particles taken and also if there is any presence of food inside the stomach. Gastric emptying rate actually have an effect on the drug on how much of it will be dissolve before it goes down along the gastrointestinal tract. The

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transit time of drugs in a solid form in the upper intestine also have an effect on dissolution, bioavailibility and also the absorption of drug.

3.2. Variability of pH

pH is also one of the factors which associated with the dissolution of drugs, especially because of the different parts in the gastrointestinal tract. When a person is fasting, the pH inside the stomach may be as low as 1.2. Meanwhile during the normal fed state, the pH value increases and may be around 3.5 or above. It depends on what type of food and also the amount of food that we take. Inside the gastrointestinal tract, the pH is around 8.4 at the large intestine and also 5.4 at the small intestine. Drugs which has the properties of a weak acids usually tends to not fully dissolve in the acidic pH at the stomach. This is because, only a few of the drugs will be ionized, and the rest will be in the intestine. Next, for drugs which has the properties of a weak base usually tends to dissolve better in the stomach. This will then lead to an increase of drugs that is ionized. We can relate the relationship of the pH and also the dissolution as a function of the pKa of the drug (Aulton, 2002).

CONCLUSION

Absorption of drug from gastrointestinal is crucially requires solubility and drug dissolution which defined as determination of rate for oral absorption low hydrophilic drugs. Drugs' solubility can be enhanced using various techniques discussed above either one or combined methods. In order to achieve of an excellent desired formulation such as decrease in dose frequency, low production cost, good oral bioavailability and better patient compliance, methods of enhancing solubility must be chosen properly in the first place. Characteristics of drug such as chemical and physical nature, solubility, melting point, absorption site, pharmacokinetic characteristic and others, requirement of dosage form like strength, types of drug release either immediate or modified and formation of capsule or tablets and others, and requirements for regulatory such as approved excipients, drug's maximum daily dose and analytical accuracy are the factors where selection of solubility enhancement method depends on them.

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