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Review: Drug Dissolution and Solubility

Abstract

The review's goals are to: a) provide a clear overview of current solubility and dissolution science, b) describe common technologies for assessing solubility and dissolution, and c) recommend the best practice technique. The theories of solubility and dissolution that are required in drug development have been examined, with an emphasis on oral absorption. Dissolution had been elaborated with the equation. Low-water solubility drugs have slow rates of dissolving, which leads to issues with oral bioavailability. Insufficient bioavailability is frequently caused by poorly water-soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids. Noyes Whitney's equation has been discussed and elaborated in this review. Solubility concepts are revised. Significance points of both dissolution and solubility are related to the oral absorption of drugs.

Key Words: Dissolution, Solubility, Oral Drug Delivery

Introduction

To increase the efficiency of drug development, the most forward-thinking pharmaceutical corporations began utilizing combinatorial chemistry and high-throughput screening in the early 1990s. As a result, there are now more poorly soluble molecules in medication development and discovery, and poor solubility is a problem for the entire business (Lipinski, 2000). There is no doubt that oral delivery is the ideal method of dosing. The simultaneous processes of a drug's dissolution and intestinal membrane penetration in the gastrointestinal (GI) tract are known as oral absorption. Thus, incomplete and inconsistent oral absorption may be caused by low solubility, a low dissolution rate, and limited permeability. The simultaneous processes of a drug's dissolution and intestinal membrane penetration in the gastrointestinal (GI) tract are known as oral absorption(Henck & Byrn, 2007). The majority of a drug's intestinal membrane permeability is controlled by its chemical makeup. Only during drug discovery are medications of a chemical structure carried out under the present paradigm of drug discovery and development (Chen, Antman, Gesenberg & Gudmundsson, 2006). Consequently, whether or not solubility and dissolution may be improved upon later in the drug discovery process, a thorough evaluation of these properties is necessary. Many pharmaceutical companies routinely conduct various solubility experiments. Despite its seeming simplicity, the science of solubility and dissolution is actually highly complex and demands a deeper level of understanding than one may think (Kerns, 2001). For an oral formulation to be sufficiently absorbed by the body, the API must be well-soluble. The gastrointestinal membrane prevents the API from passing through and entering the systemic circulation if it is just partially or not completely dissolved in the GI fluids at the site of absorption. As a result, the desired physiological consequence won't happen. For solid formulations, bioavailability and therapeutic impact depend on both solubility and the rate of dissolution. The pace at which an API dissolves in a liquid is known as its dissolution rate, whereas its solubility refers to how much of it may dissolve in a solvent. The amount and rate at which the API dissolves in a restricted volume of gastrointestinal fluid are determined by these two parameters. Because of this, both have an instantaneous impact on the degree of absorption and, consequently, bioavailability. The basic factors

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that govern the rate, degree, and bioavailability of drug absorption have been elucidated: solubility, dissolution, and gastrointestinal permeability(Khadka et al., 2014).

Dissolution

The procedure in which a solid solute is solubilized in any solvent is termed as dissolution. Dissolution is a kinetic process and is determined by rate. The associated relationship between solid solute and solvent controls the dissolution process.

Drugs cannot be absorbed by the gastrointestinal lumen, if they do not dissolve completely. Thus, the dissolution rate from a disintegrated or whole solid frequently controls the absorption rate of drugs with poor aqueous solubility in the gastrointestinal tract (Blanchard, 1978).

Dissolution rate

Noyes-Whitney equation is often used for the assessment of the rate of dissolution. Noyes and Whitney suggested that the diffusion rate from **the stagnant layer** (narrow layer of a saturated solution formed immediately due to dissolution at the surface of the particle) determines the dissolution rate of solid solutes. (Figure 1). Thus they interconnected the solute's solubility gradient with the dissolution rate in their mathematical equation.

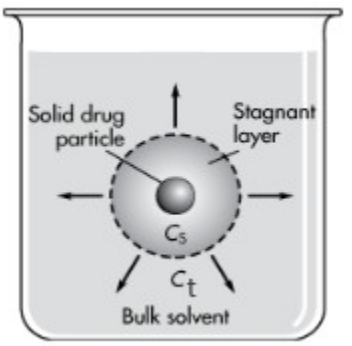

Figure 1: Solid drug particle dissolution in a solvent (Shargel, 1980).

It is a base for nearly all dissolution-based mathematical expressions. (Shargel, 1980).

The equation is as follows;

$$\frac{dm}{dt} = \left(\frac{D \times A}{h}\right) \times (C_s - C_t) \quad \text{Equation 1}$$

Where

D: Drug's diffusion constant

h: Thickness of stagnant layer

A: Surface area of drug particle

C_s: Saturation solubility

C_t: Drug concentration in bulk (Gibson, 2009)

Sink condition:

According to the Noyes-Whitney equation, "sink condition" is the state in which C_t does not affect the dissolution rate, due to insignificant concentration of C_t as compared to C_s.

Absorption of drug from the intestinal mucus lining results in the drug's consistent transport from the intestine, due to this sink condition is considered to be an *in-vivo* situation frequently.

At specified test parameters, variables other than **A**, **C_s** and **h** become constant. **A**, **h** and **C_s** depend on time. When there is no precipitation, surface area (A) decreases with the passage of time; particle diameter affects the thickness of the layer which is diffused (h); when the dissolution of total solute concentration is completed then the bulk solution is maximized towards its highest value. Moreover, the initial solute component is composed of drug particles dispersion with various sizes and surface areas, as no drug solute particle is mono-dispersed (Abdou, 1989).

To consider all or some of these factors, equation (1) modifications have been derived (Hintz & Johnson, 1989).

The Noyes-Whitney equation displays that the physical and chemical properties of the drug, solvent and formulation affect the dissolution rate in a flask.

Solubility

The amount of solute dissolved at a particular temperature in a given amount of solvent (mass or volume) is termed solubility. Usually, solubility refers to a short form of "saturation solubility."

Saturation Solubility

At specified environmental parameters, the largest solute mass that dissolves in a solvent is called saturation solubility.

Intrinsic Solubility

The solubility of uncharged forms of proteolytic drugs is called intrinsic solubility (Gibson, 2009).

Solubility and dissolution are two different phenomena. Solubility provides us with information regarding the ultimate outcome irrespective of the time taken to reach it whereas dissolution rate informs us about the time taken to reach the endpoint but not about the endpoint itself. Solutes vary not only in the extent to which they are dissolved but also in the time taken to reach their solubility limits. So, it is possible for a solute to have poor solubility in a solvent with a rapid dissolution rate (Smith, 2016).

Another difference is that a substance may be insoluble in a certain solvent (e.g. zinc in hydrochloric acid) but it can be dissolved in it by way of a chemical reaction (e.g. zinc may react with hydrochloric acid and result in the formation of hydrogen gas, and zinc chloride which is soluble in hydrochloric acid) (Savjani *et al.*, 2012).

Significance:

- Drug dissolution and solubility data gives important information about the following;
- Whether or not the drug absorption and its bioavailability be limited by its dissolution to the extent that it may become clinically ineffective.
- Substances/techniques or methodologies that should be adopted to increase the drug solubility, especially for insoluble drugs.
- Types of dissolution tests applied in the Pre-clinical Phase.
- Formulation principles to be adopted in case of modified release dosage forms.
- Formulations with poor solubility present challenges for the pharmaceutical development industry. Digoxin, phenytoin, and chloramphenicol are a few examples. Medications, especially those used orally, may not dissolve well in water. Low bioavailability could arise from this, resulting in inadequate exposure and physiological effects on the body.
- For medical professionals, dissolution is crucial since medications need to be in solution in order to be absorbed and have a physiological effect on the human body. The rate of disintegration of solid preparations, including pills and suppositories, influences the speed at which a medication enters the body and is absorbed. Formulating medications often take aqueous solubility into account.
- Thus, the ability of the drug to dissolve and solubilize in an aqueous medium is an integral part of not only early drug discovery but also in the formulation development phase (Gibson, 2009).

Aspects of Solubility in Candidate Drug Screening

Solubility as a Selective Tool

Drug solubility as an impediment to absorption has not been screened widely even though for drug absorption in the GI tract, it is considered a crucial factor. Drug solubility has been considered a parameter of high-throughput screening (HTS) because its determination must be necessary along with drug permeability predicting models.

Some drugs with low aqueous solubility have beneficial clinical effectiveness e.g. Candesartan cilexetil has about 0.1 mg/ml aqueous solubility and is an efficacious anti-hypertensive agent, so the effectiveness of solubility as a selective tool has not been completely assessed. On the contrary, in the development phase use of drugs with better solubility will reduce the chances of failure and may also evade inflated costs, setbacks or even cessation of the project.

Choice of vehicle;

For drugs with poor aqueous solubility, the *in vitro* or HTS assays are the pivotal point. Vehicles are used to augment the solubility of drugs with poor solubility because such drugs cannot be properly assessed experimentally as their insolubility in a buffer solution

of in vitro system results in a very low concentration which is difficult to detect. Nevertheless, the membrane may show noxious effects, if solvents based on a surfactant system are used (Oberle *et al.*, 1995; Ingels *et al.*, 2007), and can also result in the misinterpretation of permeability values.

Nephelometer

Now determination of solubility using little amounts of numerous compounds can be achieved by screening them using new methods e.g., the nephelometer. A nephelometer is not an exact tool as it is based on turbidimetric determinations. All the same, nephelometer can assist in the initial assessment of solubility of poorly soluble drugs and can help in the comprehension of screening results and also help in devising experiments including the use of vehicles.

Conclusion

Dissolution and solubility are important parameters for the absorption of drugs. Bioavailability has been largely hinder by these two factors. Therefore it is extremely important that factors affecting these parameters should be studied in detail. There should be interventions to manipulate these factors and increase dissolution along with solubility for the required substance. Poor solubility reduces the rate of absorption of many drugs leading to lower bioavailability. Sub-therapeutic effects can be seen through it. So, this review considers many parameters for the effective study of dissolution and solubility. The process through which a solid phase transitions into a solution phase is known as dissolution. An examination of a drug's solubility can also reveal details about its composition and molecular interactions. It is a difficult challenge for researchers and pharmaceutical scientists to use solubility features in bioavailability, pharmacological effects, and solubility augmentation of diverse weakly soluble substances. An inventive method for resolving solubility and rate-limiting step issues in poorly water-soluble medicines that offer a rapid start of action is dissolution enhancement.

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