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FACTORS AFFECTING ON THE SOLUBILITY AND BIOAVAILABILITY OF PHARMACEUTICAL DRUG AND DOSAGE FORM THROUGH SOLUBILITY MECHANISM.

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Abstract:

The study on solubility yields information about the structure and intermolecular forces of drugs. Use of the solubility characteristics in bioavailability, pharmacological action and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. General parameters affecting solubility are particle size, shape and surface area physicochemical properties of drugs, physical forms of drugs, solvents, pH of the medium, temperature and use of surfactants. This article also provides an overview of variables that can affect drug absorption following oral administration in recent years, including both physicochemical properties of the drug and physiological factors of the body. The oral absorption of a drug is a complex process depending upon these factors and their interactions with each other. Solubility and permeability are considered as the major physicochemical factor that affect the rate and extent of oral drug absorption, moreover other physicochemical properties always show their effects to drug absorption via affecting solubility and permeability.

INTRODUCTION:

Poorly soluble drugs present a problem in pharmaceutical formulations. Improving dissolution properties is a major obstacle that must be overcome because many new drugs discovered by combinatorial chemistry and high-throughput screening are poorly soluble, making them poor candidates as new drugs. The poor aqueous solubility and subsequent dissolution rate of any drug are one of the most considerable challenges during formulation design and development. For the last two decades, the drug discovery and selection of new chemical entity (NCE) have taken a comprehensive scrutiny process through the use of combinatorial screening tools such as combination high throughput screening (1). The drug molecules are classified as per the biopharmaceutics classification system (BCS), wherein a drug is considered as poorly aqueous soluble when the highest dose strength is not completely soluble in 250 mL aqueous media over the pH ranges of 1–8 at 37C (Vo et al., 2013). Nowadays, the pharmaceutical industry is facing major challenges to apply approaches that enhance the solubility and dissolution of poorly soluble drugs to get desired therapeutic effects (Kawabata et al., 2011). Various formulation approaches have been adopted to overcome the poor aqueous solubility problem It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability. Various methods to improve the dissolution of poorly soluble drugs have been reported. As solubility is an important determinant in drug liberation hence it plays a key role in its bioavailability. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[2-6] Solid dosage medicaments have to face several barriers and loss at sites in its sequential movement during gastrointestinal absorption takes place. Parenteral administration posses certain advantages if immediate physiological action is needed from a drug which usually can be provided by injecting an aqueous solution.

However, the major steps occurring during oral drug absorption can be regarded as part of a serial process. (1) The dissolution of the drug from the dosage form ; (2) The solubility of drug as a function of its physicochemical characteristics ; (3) The drug's effective permeability to the intestinal mucosa ; and (4) The drug's presystemic metabolism. There are many factors that may affect the above processes, and finally affect the rate and extent of oral drug absorption. These factors can be divided into three categories.[2,3] The first category represents physicochemical properties of a drug, including solubility, intestinal permeability, pKa, lipophilicity, stability,

surface area, particle size and so on. The second category comprises physiological factors, such as gastrointestinal pH, gastric emptying, small intestinal transit time, bile salt, absorption mechanism and so on.

The Biopharmaceutical Classification System :

The Biopharmaceutics classification system (BCS) has been one of the most significant prognostic tools created to promote product development in recent years (7) It is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability characteristics, which will substantially facilitate drug product selection and approval process for a large group of drug candidates. The goal of the BCS is to function as a tool for developing in vitro dissolution specifications for drug products that are predictive of their in vivo performance.[8]

According to the BCS, drug substances are classified as follows:

Class 1: High Solubility-High Permeability: generally very well-absorbed compounds.

Class 2: Low Solubility-High Permeability: exhibit dissolution rate-limited absorption

Class.3: High Solubility-Low Permeability: exhibit permeability rate-limited absorption.

Class 4: Low Solubility-Low Permeability: very poor oral bioavailability.

SOLUBLE: when the highest dose strength is soluble in≤250 ml water over a pH range of 1 to 7.5.

HIGHLY PERMEABLE: when the extent of absorption in humans is determined to be ≥ 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.

RAPIDLY DISSOLVING: when ≥ 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of ≤900 ml buffer solutions.

SOLUBILITY :-

A. Mechanism of Solubility:

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expression such as parts, percentage, molarity, molality, volume fraction, mole fraction [9-10].

Spontaneous passage of poorly water soluble solute molecules into an aqueous solution of surfactant is termed as solubilisation. As difference molecules interact, both repulsive and attractive forces are operative. The intramolecular forces and valence bond are given below:

B. Intramolecular forces:

· Dipole-dipole interaction (Keesome interactions)

· Dipole- induced dipole interaction(Debye interactions)

· Induced-dipole interaction-Induced-dipole interaction(London dispersion forces)

· Ion-dipole interaction

· Hydrogen bonds

Valence Bonds

· Electrovalent Bond

· Covalent Bond

· Homo-polar Bond

· Ionic Bond

· Heteropolar Bond

Factors influencing solubility of Drugs [11-14]

· **Solute related:**

Nature of solute- Size, Shape and surface area Physicochemical properties- melting point, heat of fusion, molar volume and pKa Physical forms- Salt, crystalline state, and polymorphism

· Solvent related: Nature of the solvent, i.e., Polarity, pH of the medium, volume of solvent employed.

· Environment related: Temperature and pressure.

· Formulation related: Other ingredients.

1. **Influence of particle size, shape and surface area**

Solubility increases with decreasing particle size. Since surface area of solids in contact with the medium increases, rapid dissolution is obtained. This increase in solubility ceases when the particle size reaches a particular point. Hence, particle size is critical and beyond a particular value, the solubility of solid decreases. Such a change arises because of the presence of an electrical charge on the particle, which is predominant in small particles. Symmetric molecules may be less soluble than unsymmetrical ones. If crystals are compact, they possess high lattice energy and therefore, will be lowered.

2. **Influence of physicochemical properties of drugs**

The melting points of solids are indicators of molecular cohesion and hence are useful for predicting the trend in a series of similar compounds. The other parameters are molar heat of fusion, entropy of fusion and molar volume. These are discussed in the theories of solutions.

Dissociation constant of drug is useful in predicting the extent of ionisation depending on the pH of the environment. In general, the ionised species have greater aqueous solubility than the un ionized species.

3. **Physical forms of drugs**

Some of the general principles are:

- Amorphous forms of drugs have greater aqueous solubility than the crystalline forms.

- Among crystals, metastable forms of drugs have greater aqueous solubility than the stable forms.

- Anhydrous forms of drugs have greater aqueous solubility than hydrates forms.

- Organic solvates of drugs have greater aqueous solubility than unsolvated forms.

- salt forms of drugs have greater aqueous solubility than non-salt forms, provided common ion

effect is not influenced.

4. **Influence of Solvents**

In the formulation, water or vegetable oils are normally used as solvents. The solubility of the drug is due to the polarity of the solvent that is dipole movement. In addition, hydrogen bonding between solute and solvent is essential. Therefore, structural features and presence of nonpolar and polar groups in the molecule are important. Syrups and liquid oral solutions are manufactured using water. The simple maxim of like-dissolve-like is the guiding principle. Poorly water soluble drugs are normally dissolved in non-aqueous vehicles such as liquid paraffin, arachis oil and ethyl oleate. In most cases, a mixture of solvents is used for maximum solubility of drugs.

5. **Influence of pH of the medium:**

Most of the drugs are weak electrolytes. Weak acids and weak bases undergo ionisation in solution. Drugs are more soluble in water when they are in ionised form. Unionised drugs are poorly water soluble. The extent of ionisation of drug in a solution depends on the dissociation constant and the pH of the medium. For example, alkaloidal salts are more soluble in acidic pH and begin to precipitate as the pH increases. On the other hand, phenobarbitone is more soluble in alkaline Ph and begins to precipitate as the pH decreases.

The relationship between pHp(of the preparation), solubility and pKa value of the drug is expressed as :

Acidic drugs: pHp = pKa + log s-s0/ s0

Basic drugs: pHp = pKa + log s0/S- s0

Where pKa = dissociation constant of drug, s0 = solubility of unionised form, moles/litre, S= overall solubility of drug,moles/litre.

If pH of the solution is known, solubility of drugs can be calculated using equations(1) and (2). Similarly minimum pH can be determined in order to maintain a solution of known concentration without precipitation.

6. Influence of Cosolvents

Frequently a solute is more soluble in a mixture of solvents rather than in a single solvent. The solvents, which are used to increase the solubility of a drug in water, are called as cosolvents. The phenomenon is known as cosolvency. Ethanol, propylene glycol, glycerine, PEG 300, and PEG 400(polyethylene glycols) are the commonly used cosolvents, since these are water miscible. The concept of cosolvency is applied in the manufacture of liquid dosage forms such as syrups, elixirs, injections, creams and lotions. In addition, solvents such as benzyl alcohol, dimethyl sulphoxide(DMSO), Dimethyl acetamide(DMA) and Dimethyl formamide(DMF) are used as supplementary solvents.

7. Influence of Temperature

Increase in temperature involves the absorption of heat and it influences the solubility of the drugs.

- If the dissolution involves positive hit of solution, a rise in temperature leads to an increase in solubility of solid. Example is potassium nitrate in water.

- Conversely if the dissolution of a solid involves the liberation of heat then an increase in temperature leads to decrease in solubility. Example is calcium acetate in water.

8. Influence of Surfactants

Surface active agents enhance the solubility of poorly water-soluble drugs due to the formation of micelles. This phenomenon is known as micellar solubilisation. For Example, Solubility of procaine is enhancing by 25% in aqueous buffer, owing to the formation of surfactant micells.

8. Influence of other ingredients

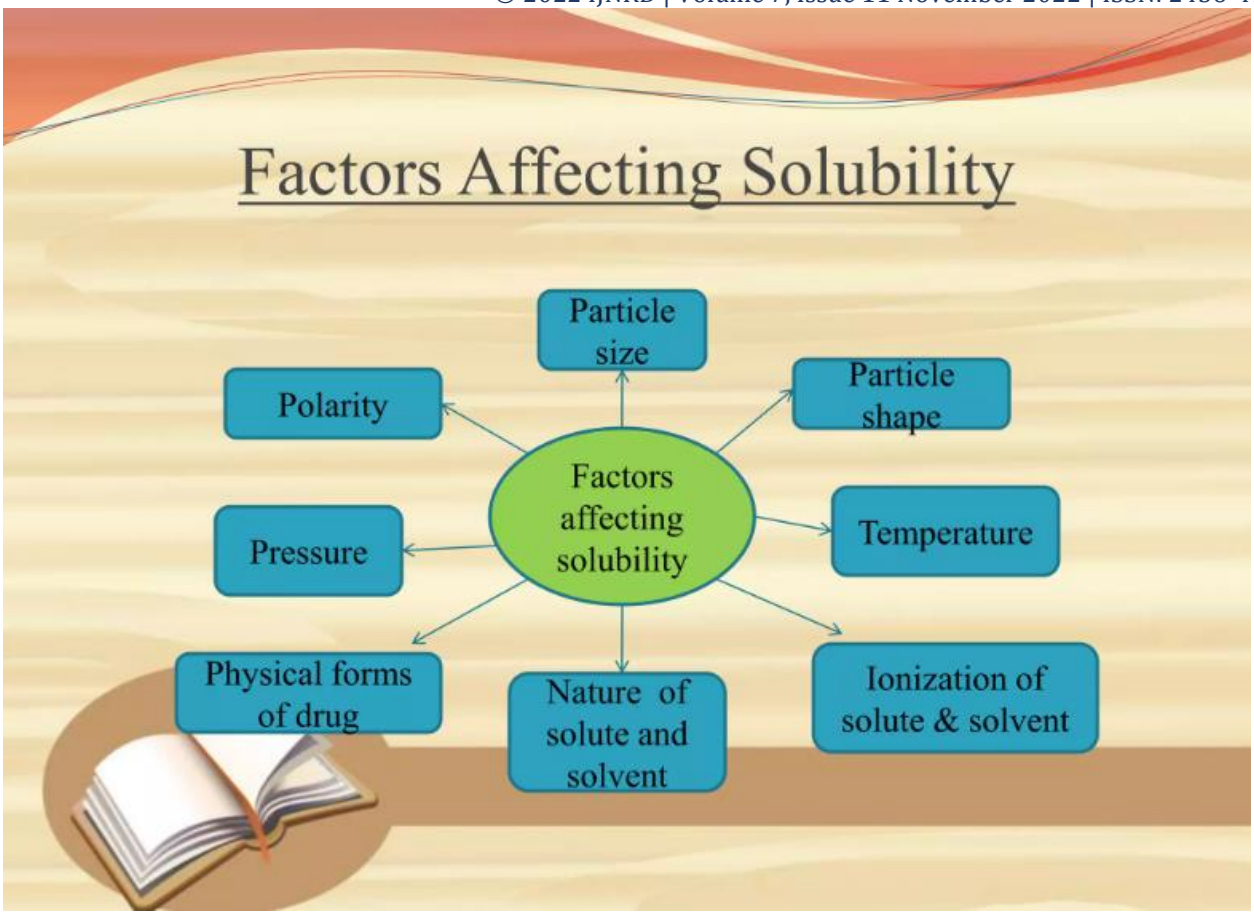
Several ingredients of diverse nature are added in the formulation of dosage forms. The solubility of a sparingly soluble electrolyte is decreased by the addition of a second electrolyte that posses a similar ion to the first. The phenomenon is known as common ion effect. The behaviour is predicted from the concept of solubility product.

9. Effect of other electrolytes:

The solubility of a sparingly soluble electrolytes may be increased by the addition of a second electrolyte that does not possess same ions. The ions produced by dissociation of electrolytes are strongly associated with oppositely charged ions.

C. Factors affecting Solubility[16-29]

The solubility of a compound depends upon the physical and chemical properties of the solute and the solvent as well as various other factors like:



Dig 1: Factor affecting on solubility of drug

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1. **Temperature**

Increasing the temperature of material solubility enhancement is often possible.

2. **Dielectric Constant**

The solubility is a function of dielectric constant of polar and nonpolar medium. Most often, with hydrophobic drugs, the solubility decreases with increasing dielectric constant.

3. **pH**

pH of a substance is related to its pKa and concentration of ionised and un-ionised forms of the

substance by the equation:

pH = pKa + log [A-/HA]

where pKa = Dissociation constant.

If the substance is brought outside its pKa (pH value where half of the substance is ionised and half un-ionised), then solubility will be changed because of introduction of new intermolecular forces, mainly ionic attraction forces.

4. **Solvent**

Solubility is greatest between materials with similar polarities and this is defined by hydrogen bonding.

Weak hydrogen bond liquid

Hydrocarbons, chlorinated hydrocarbons, and nitro-hydrocarbons.

Moderate Hydrogen bond liquid

Ketones, esters, ethers, and glycol mono-ethers.

Strong Hydrogen bond liquid

Alcohols, amines, acids, amides and aldehydes.

Particle size

The size of the solid particle influences the solubility because as particle becomes smaller, the surface area to volume ratio increases the surface area, which allows a greater interaction with the solvent.

Polymorphism

The capacity for substance to crystallize in more than one crystalline form is polymorphism. Polymorphs can vary in melting point. Since the melting point of the solid is related to its solubility, then polymorphs will most likely have different solubilities.

Salts

Salt selection is often a sought after approach to improve dissolution rate and oral absorption of poor soluble drugs. Water solubility increases in order of selected counter ions as follows:

Iodide<tosylate<glycolate<mesylate<acetate<chloride.

Pressure

The solubility of liquids and solids in water are not appreciably affected by increased pressure. The solubility of gases significantly increases with pressure. According to Henery's law, the increase in solubility is directly proportional to the increase in pressure.

Stearic factors

Solubility is also affected by dimension of structure and its configurations. Methods for Enhancing the solubility of Drugs. The ability to increase the aqueous solubility can be valuable aid to increasing efficacy or reducing adverse effects for certain drugs. Following approaches can be employed to enhance the aqueous solubility of a solid drug solute.

Use of co-solvent

The use of mixed solvent system is often necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, polyethylene glycol, glycerine, sorbitol and polyoxyethylene glycols can be used.

Hydrotrophy method

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute.

Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism".

Hydrotropics solutions donot show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.

Change in dielectric constant of solvent

The addition of a co-solvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect of a substance has on the energy needed to separate two oppositely charged bodies. A vacuum is arbitrarily given a dielectric constant of one. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium.

Chemical modification of the drug:

By addition of polar groups like carboxylic acids, ketones and amines can increase solubility by increasing hydrogen bonding and the interaction with water.

Complexation Methods (inclusion complex or clathrates)

Considerable increase in solubility and dissolution of the drugs has been achieved by the use of Betacyclodextrins. Betacyclodextrin can solubilise water insoluble drugs. In the same way, the solubility of beta cyclodextrin can be significantly enhanced by the addition of some water soluble drugs, Such as sodium salicylate, or water-soluble polymers such as hydroxyl propyl methyl cellulose(HPMC)

to the aqueous solution. Other complexes like inorganic coordination, chelates, metal olefin, and molecular complexes can also be increased as complexation relies on relatively weak force such as London forces, hydrogen bonding and hydrophobic interactions.

Alteration of pH of solvent

pH of solvent when reduced causes solubility enhancement combined effect of pH and complexation on solubilisation is also synergistic in nature.

Use of surfactactants

surfactants are amphipathic in nature, meaning it has polar end (the circular head) and a non –polar end (the tail). When a surfactant is placed in water, it will form micelles. A non –polar drug will partition into the hydrophobic core of the micelle and the polar tails will solubilise the complex.

Use of hydrates or solvates

A crystalline compound may contain either a stoichimetric or nonstochiometric amount of solvent. Non stochometric adducts, such as inclusions, involves entrapped solvent molecules.with in the crystal lattice. A stoichiometric adduct, commonly referred to a solvate, is a molecular complex that has incorporated the crystallising solvent molecules nto specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as hydrate. A compound not containing any water within its crystal structure is termed anhydrous.Aqueous solubilities of anhydrous forms and higher than the hydrate forms.

Use of Soluble prodrug

Where in the physic chemical properties of the drug are improved by bioreverssible chemical alteration. The most common prodrug strategy involves the incorporation o polar or ionosable moiety into the parent compound to improve aqueous solubility. The post hoc pro drug approach has been successfully used to imrove water solubility of corticosteroids, vitamins and benzodiazepines.

Amorphous forms have atoms or molecules randomly placed as in a liquid and have higher thermodynamic energy than corresponding crystalline forms. Solubilities as well as dissolution rates are generally greater.

Application of ultrasonic waves

Solubility increases by use o ultrasonic vibrators. A n oscillator of high frequency(100-500KHz) is use and device is known as Pohlman whistle.

Solid dispersion method:

It reduces the drug particle size and changes the micro-environment of the drug particle, increase the rate of dissolution and absorption and thus changes the Biopharmaceutical properties of poorly alter soluble drugs. Solid dispersions are prepared by fusion, solvent evaporation an fusion solvent method.

Spherical crystallization [30]

Spherical crystallization is a particle design technique, by which crystallization and agglomeration can be carried out simultaneously in one step and which has been successfully utilized for improvement solubility of poorly water soluble drugs. General methods of spherical crystallization are spherical agglomeration, emulsion solvent diffusion and ammonia diffusion method. Factors controlling the process of agglomeration are solubility profile, mode and intensity of agitation, temperature of the system and residence time.

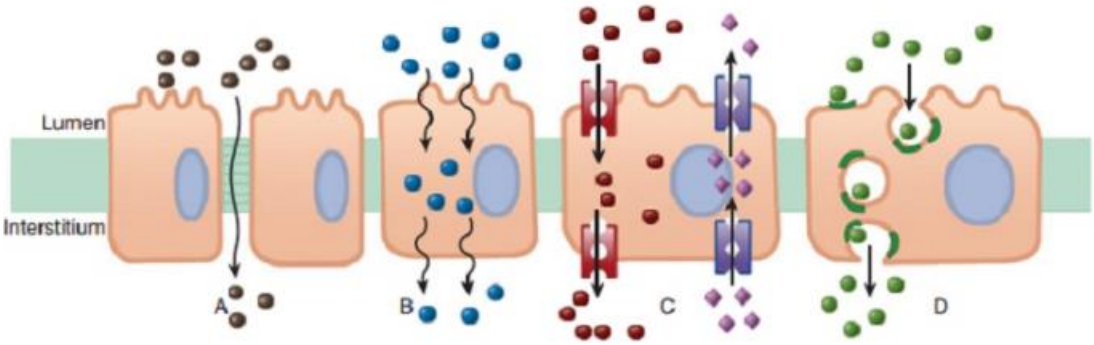
Methods for solubility Determination :

No universally acceptable method for determining solubility is known. Solubility of solids in liquids may be determined by phase solubility analysis, conductance, solute method and turbidity method. For determination of solubility of sparingly soluble salts several methods available are: Electrical method such as determination of solubility product by electromotive force method, and determination of conductivity of the solution; colorimetric method and radioactive method[31-35].

PERMEABILITY :-

Permeability is another important factor in achieving desirable oral bioavailability. The above critical property of permeability should contribute to the correspondingly unique way about how substances (including drugs) “travel through” cellular membranes. So to discuss physicochemical properties affecting permeability, one need first get to know the structure of cellular membranes and how drugs pass through these membranes (Fig 2)[36]. In the Fluid Mosaic model, the structure of cellular membranes is described as an interrupted phospholipid bilayer capable of both hydrophilic and hydrophobic interaction [37]. The two most common ways for the absorption of drugs are passive transfer by diffusion across the lipid membranes and passive diffusion through the aqueous pores at the tight junctions between cells. These two processes are referred to as transcellular and paracellular absorption, respectively. The ability of a drug to diffuse across the lipid core of the membrane is clearly dependent on physicochemical properties. Thus transcellular absorption is the predominant pathway for more lipophilic molecules. In contrast, the paracellular route of absorption is particularly

important in determining the efficiency of absorption of hydrophilic compounds, the restricted diameter of the 170 aqueous pores (typically 3 to 6 Å in humans)means that molecular size also becomes important in the ability of polar molecules to utilize this pathway, which is thought to be possible only for small hydrophilic molecules (MW < 200) [38,39,40].



Dig: Mechanism of absorption of drug based on their nature.

ABSORPTION :

A) Physiological properties affecting drug absorption :

The successful functioning of oral medication depends primarily on how the gastrointestinal (GI) tract processes drugs and drug delivery systems. Many factors are involved in oral drug delivery, the measured oral bioavailability of a particular drug can be broken into components that reflect delivery to the intestine (gastric emptying, PH, food), absorption from the lumen (dissolution, lipophilicity, particle size, active uptake), intestinal metabolism (phase I and/or phase II enzymes), active extrusion (drug efflux pumps) and finally first-pass hepatic extraction. All these factors play an important role in the performance of orally administered dosage forms, and to understand how they affect oral drug absorption can greatly contribute to the drug discovery process (41).

1. Bile salts:

The presence of bile may improve the bioavailability of poorly water soluble drugs by enhancing the rate of dissolution and/or solubility. Bile salts can increase drug solubility via micellar solubilization. The increase in the rate of dissolution also may occur via a decrease in the interfacial energy barrier between solid drug and the dissolution media (via enhanced wetting), leading to an effective increase in surface area[42].

Gastric emptying and Intestinal transit time:

Furthermore, gastric emptying and GI transit time are important parameters for the onset and the degree of drug absorption. It is well known that the gastric emptying rate is an important factor affecting the plasma concentration profile of orally administered drugs, and the intestinal transit rate also has a significant influence on the drug absorption, since it determines the residence time of the drug in the absorption site. The reason why the residence time is also a critical factor for drug absorption is that there is the site difference in absorbability for some drugs. Lipka and co-workers [43] demonstrated the significant effect of gastric emptying on the rate and extent of celiprolol absorption and its role with respect to influence the occurrence of double peaks.Based on the assumption that gastric emptying and intestinal transit rates will vary directly with the strength of the contractile activity characteristic of the fasted state motility cycle. Oberle and co-workers[44] concluded that variable gastric emptying rates due to the motility cycle can account for plasma level double peaks. Furthermore, variable gastric emptying rates combined with the short plasma elimination half-life and poor gastric absorption of cimetidine can be the cause of the frequently observed plasma level double peaks.

Liver metabolism:

The liver is the major organ for drug metabolism, thus the prediction of human hepatic clearance is of great value in study factors affecting oral drug absorption. Lin and co-workers [45] provided an excellent discussion of factors that can affect the clearance, which can further affect the overall bioavailability of drugs. The hepatic clearance was described as follows:

$$CLH = (Qh \cdot fB \cdot CLint,h)/(Qh + fB \cdot CLint,h)$$

$$EH = (fB \cdot CLint,h)/(Qh + fB \cdot CLint,h)$$

where Qh is the liver blood flow, CLint,h is hepatic intrinsic clearance, fB is the unbound fraction of drug in the blood, and EH is the hepatic extraction ratio, which is defined as the fraction of the drug entering liver that is metabolized during its transit through the liver. Therefore, only a portion (1-EH) of the dose passed through the liver will escape metabolism.

Intestinal Metabolism

It is also quite important to consider small intestine as a potential site of drug metabolism. Substantial drug loss can occur via intestinal efflux mechanisms, gut wall metabolism (both PhaseI and Phase II), and the degradation within the gut lumen. The cytochrome P450s (CYPs) are the major enzymes involved in the metabolism of drugs. Some of the CYP isoforms present in the liver are also expressed in the gut wall epithelium, the major one is CYP3A4, which in the small intestine approaches 50% of the hepatic level, and act as the major phase I drug metabolizing enzyme in humans. Both CYP3A4 and the multidrug efflux pump, MDR or P-Glycoprotein (P-gp), are present at high levels in the villus tip enterocytes of the small intestine, the primary site of absorption for orally administered drugs. These proteins are induced or inhibited by many of the same compounds and demonstrated a broad overlap in substrate and inhibit specificities, suggesting that they act as a concerted barrier to dug absorption[46].

Food Effect:

The effect of food on drug oral bioavailability is extremely complex. Based on the physicochemical properties of the compounds, physiological changes induced by the intake of food mainly happen in slowing of gastric emptying rate and the increase in gastric pH. The pH differences in the contents of the upper GI tract between fed and fasted states can influence the dissolution and absorption of weakly acidic and basic drugs. Elevation of gastric pH following a meal may enhance the dissolution of a weak acid in the stomach but inhibit that of a weak base. Furthermore, food inhibits the rate of gastric emptying, prolonged retention in the stomach may increase the proportion of drug that dissolves prior to passage into the small intestine, which is the primary site of drug absorption.[47] Elevated gastric pH may afford enhanced bioavailability of acid-labile drugs such as penicillin, erythromycin, and digoxin. For example, under acidic conditions, digoxin is hydrolyzed to the digoxigenin aglycone derivative, which has reduced pharmacodynamic activity.

Formulation Effect:

The Noynes-Whitney equation describes the variables that can affect drug dissolution[48]: $dm/dt=(D \cdot S/V \cdot h)(Cs - Ct)$ where dm/dt is the dissolution rate; D is the diffusion coefficient; S is the surface area; h is the thickness of the dissolution film adjacent to the dissolving surface; Cs is the saturation solubility of the drug molecule; Ct is the concentration of the dissolved solute; and V is the volume of the dissolution medium. Among these factors, two variables that can be controlled by formulation are surface area and solubility. Increasing the surface area (S) of a drug particle can enhance the dissolution rate of the drug. Drug particle size can be reduced to increase the effective surface area available for dissolution, which can be achieved by using wetting agents that lower the surface tension of the dissolution medium. However, since the amount of the above surface-active agents needed to enhance in vivo drug dissolution rate may have effects on drug safety, these agents are not generally used in product formulations.[48] Drug particle is also important in determining the dissolution behavior of a drug. The shape factor for any non-isometric particle cannot be considered to be constant over the dissolution event, as is commonly assumed.

Conclusion: Drug absorption is a highly complex process, which is based on both physicochemical properties of the drug and physiological conditions of the body. Therefore, in years scientists have been striving for improving the above two aspects to achieve desirable drug absorption, thus to screen out, optimize a large number of drug candidates and consequently promote drug development. In particular, solubility and permeability are the most important physicochemical properties affecting drug absorption; furthermore most other physicochemical properties (such as lipophilicity, pKa, molecular size, logP value, hydrogen bonding dynamics, and so on) are all correlated to solubility and permeability, and through their positive or negative effects on solubility and permeability to finally affect drug bioavailability. Therefore, solubility and permeability can be considered to act as the “final bridge” toward drug absorption.

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