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Preformulation Testing Studies of Solid Dosage Forms.

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ABSTRACT

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredient in the fabrication of dosage form. Objective of Preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physico-chemical parameter of new drug substances. Among these properties drug solubility, partition coefficient, dissolution rate, polymorphic forms and solubility are plays important role in Preformulation study. Polymorphism having crystal and amorphous forms shows different chemical, physical and therapeutic description of the drug molecule. This article explains some properties and therapeutic for Preformulation parameters of drug.

Keywords: Preformulation, Solubility, Partition Coefficient.

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INTRODUCTION

Development of a new drug entity is a concerted effort and it takes us $800 million, and 10 to 15 years to develop a successful drug. Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipient. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Obviously, the type of information needed will depend on the dosage form to be developed. This information will describe a Preformulation program needed to support the development of tablets and granulations as dosage forms. During the early development of a new drug substance, the synthetic chemist, alone or in cooperation with specialist in other disciplines (including Preformulation), may some data that can be appropriately considered as Preformulation data. This early data collection may include such information as gross particle size, melting point, infrared analysis, chromatographic purity, and other such characterizations of the different laboratory scale batches. It is not only helps to guide dosage form selection; nut also provides insights into how drug products should be processed and stored to ensure their quality. Preformulation studies may have a significant impact on manufacturing, storage and performance of drug product. These data are useful in guiding and becoming part of the main body of Preformulation work. Once the formulation is ready to enter clinical trials, it is important to characterize mechanical properties of the formulation to ensure that it can be manufactured at a large scale in a reproducible and effective manner. On the other hand Particle size, surface area, dissolution and the means of enhancing rate of dissolution are important consideration in the Preformulation evaluation of sparingly soluble drugs.

Organoleptic Properties: [1]

A typical Preformulation program should begin with the description of the drug substance. The color, odor, and the taste of a new drug must be recorded using descriptive terminology. A list of some descriptive terms to describe the most commonly encountered colors, tastes and odors of pharmaceutical powders is provided in [Table 1.]

Table 1: Organoleptic properties of pharmaceutical powders.

Color	Odor	Taste
Off-white	Pungent	Acidic
Cream-yellow	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic	Intense
	Odorless	Sweet

	Tasteless

Purity: [2]

The Preformulation scientists must have some perception of the purity of a drug substance. Some early knowledge is necessary so that subsequent Preformulation and/or early safety and clinical studies are not compromised as to their validity. It is another parameter that allows for comparison with subsequent batches. The presence of aromatic amines, suspected of being carcinogenic, is an example. In these instances, discussions must be initiated with the chemist preparing the material so that re-medical action can be taken. Very often a problem batch can be made satisfactory by a simple re-crystallization. Thin layer chromatography (TLC) and high pressure liquid chromatography (HPLC) are of very wide- ranging applicability and are excellent tools for characterizing the chemical homogeneity of very many types of materials. Paper chromatography and gas chromatography are also useful in the determination of chemical homogeneity.

Surface Area:[3,4,5]

Various chemical and physical properties of drug substances are affected by their particle size distribution and shape. The effect is not only on the physical properties of solid drugs but also, in some instances, on their biopharmaceutical behavior. Size also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipient, mutual sieving (demixing) effects can occur making through mixing difficult or, of attained, difficult to maintain during the subsequent processing steps. This effect is greatest when the diluents and active raw materials are of significantly different sizes. Other things being equal, reasonably fine materials interdisperse more readily and randomly. However, if materials become too fine, then undesirable properties such as electrostatic effects and other surface active properties causing undue stickiness and lack of flow ability manifest. Not only size but shape too influences the flow and mixing efficiency of powders and granules. Reduction of the particle size to too small a dimension often leads to aggregation and an apparent increase in hydrophobicity, possibly lowering the dissolution rate and maki9ng handling more troublesome. When materials are ground, they should be monitored not only for changes in the particle size and surface area, but also for any inadvertent polymorphic or chemical transformations. Undue grinding can destroy solvates and thereby change some of the important characteristics of a substance. Some materials can also undergo a chemical reaction.

General Techniques for Determining Particle Size: [6]

Several tools are commonly employed to monitor the particle size. The most rapid technique allowing for quick appraisal is microscopy. Microscopy, since it requires counting of a large number

of particles when quantitative information is desired, is not suited for rapid, quantitative size determinations. However, it is very useful in estimating the range of sizes and the shapes. The preliminary data can then be used to determine if grinding is needed. A photomicrograph should be taken both before and after grinding. The range and sizes observable by microscopy is from 1µm upward. Most of these instruments measure the numbers of particles, but the distributions are readily converted to weight and size distributions. The latter way of expressing the data is more meaningful. There are many mathematical expressions that can be used to characterize an average size. These refer to average volumes or weights, geometric mean diameters, and relationships reflecting shapes, such as the ratio of an are3a to a volume or weight factor. There are some lists of the common technique useful for measurement of different size ranges given in [Table 2].

Table 2: Common technique for measuring fine particles of various sizes:

Technique	Particle Size (µm)
Microscopic	1-100
Sieve	>50
Sedimentation	>1
Elutriation	1-50
Centrifugal	<50
Permeability	>1
Light Scattering	0.5-50

Determination of Surface Area: [7]

The determination of the surface areas of powders has been getting increasing attention in recent years. The techniques employed are relatively simple and convenient to use, and the data obtained reflect the particle size. The relationship between the two parameters is an inverse one, in that a grinding operation that reduces the particle size leads to an increase in the surface area. The most common approach for determining the surface area is based on the *Brunauer-Emmett-Teller* (BET) theory of adsorption. An excellent discussion of the principles and techniques involved has been given by Gregg and Sing. Briefly, the theory states that most substances will absorb a monomolecular layer of a gas under certain conditions of partial pressure (of the gas) and temperature.

The BET equation is

$$\frac{1}{\lambda\left(\frac{P0}{P}-1\right)} = C - \frac{1}{\lambda mC} * \frac{P}{P0} + \frac{1}{\lambda mC}$$

Where, λ= grams of adsorbate per gram of adsorbent

Λm= value of that ratio for a monolayer

P= partial pressure of the absorbate gas

Po= vapor pressure of the pure adsorbate gas

C= constant

The constant C is the temperature- dependent, as are P and Po consequently, measurements are made under isothermal conditions. The equation is that of the straight line, and the inverse of the sum of bot6h the slope [(C-1)/λmC] and the y intercept (1/λmC) gives λm. Often the constant C is large and Equation (2) then simplifies to:

$$\lambda m = \lambda(1 - \frac{P}{Po})$$

A single point determination (using only one value of P) is then possible. Knowing the specific weight of adsorbate (λm) in a monolayer, it is possible to calculate the specific surface area (SSA) of the sample using the following equation:

$$SAA = \lambda m N A_{N2\,/M_{N2}}$$

Where, N= Avogadro number

A_{N2}=the area of the adsorbate molecule

$^{M}N_2$= the molecular weight of the adsorbate.

Solubility: [8]

Solid drugs administered orally for systemic activity must dissolve in the gastrointestinal fluid prior to their absorption. Thus, the rate of dissolution of drugs in gastrointestinal fluid could influence the rate and extent of their absorption. In as much as the rate of dissolution of a solid is a function of its solubility in the dissolution medium, the later could influence absorption of the relatively insoluble drugs. As a rule of thumb, compound with an aqueous solubility of greater than 1% $_{W/V}$ are not expected to present dissolution-related absorption problems. In the application of this rule, however, one must consider the anticipated dose of the4 drug and its solubility in the gastrointestinal fluid. A highly insoluble that is unstable in the highly acidic environment of the stomach. High solubility and consequent rapid dissolution could result in a decreased bioavailability. For these reasons, aqueous solubility is a useful biopharmaceutical parameter. The solubility of every new drug must be determined as a function of pH over the physiological pH range of 1 to 8. If the solubility is considered too low or too high, efforts to alter it may be undertaken.

Determination of solubility:

A semi quantitative determination of the solubility can be made by adding the solute in small incremental amounts to a fixed volume of the solvent. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. When some solute remains

undissolved, the total amount added up to the point serves as a good and rapid estimate of solubility. Solubility of an acidic or basic drug is pH-dependent and, as mentioned earlier, it must be determined over the pH range 1 to 8. Since such compounds favor their own pH environment dictated by their pKa values, it becomes necessary to adjust the pH values of their saturated solution. There is no general method for this pH adjustment. In some reported studies, authors used buffers of appropriate pH values [11-13], whereas others used hydrochloric acid or sodium hydroxide solutions [14-17]. Solubility determinations of poorly soluble compounds present their own unique problems. *Higuchi* and *Coworkers* demonstrated that the solubility's of such compounds could be overestimated due to the presence of soluble impurities. The saturation solubility of a poorly soluble compound is not reached in a reasonable length of time unless the amount of solid used is greatly in excess of that needed to saturate a given volume of solvent. This is because the final rate of approach to saturation is almost exclusively dictated by the surface area of the dissolving solid.

pH- Solubility Profile: [9]

The degree of ionization and therefore the solubility of acidic and basic compounds depend on the pH of the medium. The saturation solubility for such compounds at a particular pH is the sum total of solubility of ionized and unionized forms. *Kramer* and *Flynn* investigated relative contributions of the protonated and free basic forms of several drugs to their total solubility's under different conditions. For ionizable compounds a solution may be saturated with respect to one species or the other depending on pH. The pH at which solution is saturated with respect to both the ionized and unionized forms is defined as pH_{max} the pH of maximum solubility. For a base, the equation relating total solubility (S_T) to solubility's of protonated (BH^+) and free (BP form is

$S_T.pH<pH_{max} = [BH^+]_s (1+Ka/[H_3O^+])$

Where, the subscript $pH<pH_{max}$ indicates that the equation is valid only at pH values below the pH_{max} subscript $_s$ denotes saturation a species, Ka is the apparent dissociation constant, and $[H_3O^+]$ is the hydronium ion concentration. The equation applicable at pH values higher than the pH_{max}

$S_T.pH>pH_{max} = [B_s] (1+ [H_3O^+]/Ka)$

The corresponding equations for an acidic compound are

$S_T.pH<pH_{max} = [AH]_s(1+Ka/[H_3O^+])$

And

$S_T.pH>pH_{max} = [A^-]_s (1+ [H_3O^+]/Ka)$

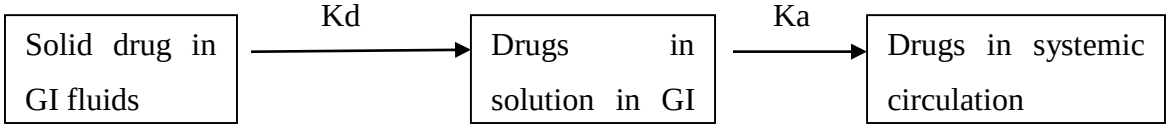
Where, $[A^-]$ and [AH] denote concentrations of ionized and unionized forms. Since ionizable compounds may be available in free or salt forms, one could use either in solubility experiments.

Solubilization:[10,11,12,13]

When the drug substance under consideration is not an acidic or basic compound, or when the acidic or basic character of the compound to the formation of a stable salt, other means of enhancing the solubility may be explored. The use of a more soluble metastable polymorph to enhance bioavailability of orally administered solids is one way to approach the problem. Other approaches to improve solubility or rate of dissolution include use of complexation and high-energy co precipitates that are mixture of solids solutions and dispersions. The approach, however, has practical limitations. The primary requirement is that the complexing or solublizing agent be physiologically inert. Thus, unless the solublizer is an approved excipient, this approach is not recommended. In this regard, the use of water-soluble polymers to form high-energy co precipitation is more acceptable. Griseofulvin is a water-insoluble, neutral polyethylene glycol antifungal antibiotic. Dispersion and solid solutions of Griseofulvin in PEG 4000, 6000 and 20,000 dissolve significantly more rapidly than the wette3d micronized drug. In the case of PEG 4000 and 20,000, this treatment provided supersaturated solutions. Subsequent studies with the PEG 6000 dispersion showed that, in humans, the dispersed drug was more than twice as available as from commercially available tablets containing the micronized drug. In the majority of cases, efforts to alter solubility's of drugs are undertaken to improve the solubility. Occasionally, the less soluble form is desired. Thus, in the case of clindamycin, the less soluble pamoate salt is preferred over the soluble hydrochloride hydrate to circumvent the problem of the unpleasant taste of the drug. Likewise, when a drug is inactivated by the acidity of gastric fluid, a less soluble form is preferred.

Dissolution:

The absorption of solid drugs administered orally can be depicted by the following flowchart:



Where, Kd and Ka are rate constants for the dissolution and absorption processes, respectively. When dissolution is the significantly slower of the two processes (i.e. Kd<<Ka) the absorption is described as dissolution rate-limited. Since dissolution precedes absorption in the overall scheme, any change in the process of dissolution would influence the absorption. It is essential, therefore, to investigate the dissolution behavior of drug substances, especially those with moderate and poor solubility. Efforts are then undertaken to alter this process if deemed necessary. Also knowledge of comparative dissolution rates of different chemical (salt, ester, prodrug, etc.) and physical (polymorph, solvates, etc.) forms of a drug is necessary in selecting the optimum form for further development.

Intrinsic Dissolution: [14,15]

The dissolution rate of a solid in its own solution is adequately described by the *Noyes-Nernst* equation:

$$dc/dt = AD (C_s - C)/hV \quad (1)$$

Where,

dc/dt= dissolution rate

A = surface area of the dissolving solid

D = diffusion coefficient

h = diffusion layer thickness

C = solute concentration in the bulk medium

V = volume of the dissolution medium

C_s = solute concentration in the diffusion layer

During the early phase of dissolution, $C_s >> C$ and is essentially equal to saturation solubility S. surface area A and volume V can be held constant. Under these conditions and at constant temperature and agitation, equation (1) is reduces to

$$dc/dt = KS \quad (2)$$

Where, K = AD/hV = constant.

Dissolution rate as expressed in equation (2) is termed as the intrinsic dissolution rate and is characteristics of each solid compound in a given solvent under fixed hydrodynamic conditions. The intrinsic dissolution rate in a fixed volume of solvent is generally expressed as mg dissolved * ($min^{-1}cm^{-2}$). Knowledge of this value helps the Preformulation scientist in predicting of absorption would be dissolution rate-limited. *Kaplan* studied the dissolution of a number of compounds in 500 ml of medium ranging in pH from 1 to 8, at 37^0C, while stirring at 50 rpm. His experience suggests that compounds with intrinsic dissolution rates greater than 1mg $min^{-1}cm^{-2}$are not likely to present dissolution rate-limited absorption problems. For compounds with rates between 0.1and 1.0 mg $min^{-1}cm^{-2}$, usually more information is needed before making any prediction.

Particulate Dissolution: [16,17,18]

Particulate dissolution is another method of studying the dissolution of solids. Here no efforts are made to maintain the surface area constant. A weighed amount of powder sample from a particular sieve fraction is introduced in the dissolution medium. Agitation is usually provided by a constant-speed propeller. Particulate dissolution is used to study the influence on dissolution of particle size, surface area, and mixing with excipient. The rate of dissolution increased with a decrease in the particle size. Occasionally, however, one encounters an inverse3 relationship of particle size to

dissolution, where particle size reduction decrease or fails to improve the dissolution. This may be explained on the basis of effective or available, rather than absolute, surface area and it is caused by incomplete wetting of the powder. In such areas incorporation of a surfactant in the dissolution medium may provide the expected relationship. When dissolution is considered to be slow, a means of enhancing it may be sought. In the absence of a more soluble physical or chemical form of the drug, particle size reduction is the most commonly employed practice. Enhanced surface area, with a concomitant increase in the dissolution, can also be accomplished by adsorbing the drug on an inert excipient with a high surface area, such as fumed silicon dioxide.

Prediction Of Dissolution Rates: [19,20]

Since dissolution of solids is adequately described by the *Noyes-Nernst* equation, knowledge of different parameters in the equation should permit the calculation of theoretical rates. *Hussein* used this approach to predict the dissolution rates of many slightly soluble drugs. He used a value of $9.0*10^{-6}$ cm^2sec^{-1} for diffusion coefficient, a good approximation for most drugs, and a value of $50*10^{-3}$ cm for diffusion layer thickness when stirring at 50rpm. The value of Cs [equation 2] was approximated by saturation solubility. Surface area was calculated using the mean particle diameter and assuming a spherical shape. The following example illustrates *Husain's* method.

Sample calculation

Consider the dissolution of 22 mg of 60 to 80 mesh hydrocortisone in 500 ml water. The aqueous solubility of hydrocortisone is 0.28mg cm^{-3}. The 60 to 80 fraction (from sieve tables) corresponds to 212 µm or $2.12*10^{-2}$ cm in diameter. The density of hydrocortisone is 1.25 g cm^{-3}. The volume of a sphere is $4/3\Pi r^3$. Assuming that all particles are spheres of the same diameter, 22mg would correspond to

$$22*10^{-3}/1.25 \quad 3/4\Pi*(1.06)^3*10^{-6} = 3500 \text{ spherical particles}$$

The area of a sphere is given by $4\Pi r^2$. Therefore, the area of 3500 particles of average radius $1.06*10^{-2}$cm is

$$4\Pi*(1.06)^2*10^{-4}*3500 = 4.94cm^2$$

The dissolution rate according to equation (2) is

$$dc/dt = AD\ (C_s\text{-}C)/hV$$

Where, Cs can be approximated bye the solubility, and C, the concentration during the early phase of dissolution, is essential zero. Thus, for the sample of hydrocortisone,

Initial dissolution rate = $4.94*9.0*10^{-6}*0.28/5.0*10^{-3}*500$

$$4.97*10^{-6}mg\ cm^{-2}sec^{-1}ml^{-1}$$

Hussein showed a good correlation between the calculated and the experimentally determined dissolution rate of hydrocortisone, benzoic acid, L-dopa, and Griseofulvin. *Husain's* method does not provide for the concept effective surface area. It is nevertheless a useful approach, especially when the experimental determination of the dissolution cannot be accomplished.

Miscellaneous Properties: [21,22,23,24,25,26]

In addition to the physicochemical parameters described therefore, information pertaining to certain other properties, such as density, Hygroscopicity, flowability, compatibility, compressibility and wettability is useful to the formulator. These properties influence the process of manufacture and are important consideration when the active drug constitute the major portion of the final dosage form.

Density:

Knowledge of the absolute and bulk densities of the drug substances is very useful in forming some idea as to the size of the final dosage form. Obviously, this parameter is very critical for drugs of low potency, which may constitute the bulk of the final granulation of the tablet. The density of solids also affects their flow properties. In the case of physical mixture of powders, significant difference in the absolute densities of the components could lend to segretion.

Hygroscopicity:

Many drug substances exhibit a tendency to adsorb moisture. The amount of moisture adsorbed by a fixed weight of anhydrous sample in equilibrium with the moisture in the air at given temperature is referred to as equilibrium moisture content. The significance of adsorbed moisture to the stability of the solids has already been discussed. Additionally, the equilibrium moisture content may influence the flow and compression characteristics of powders and the hardness of final tablet and granulations. The knowledge of the rate and extent of moisture pickup of new drug substances permits the formulator to take the appropriate corrective step when problems are anticipated. In general, hygroscopic compounds should be stored in a well-closed container preferably with a desiccant. The sorption isotherm showing the equilibrium moisture contents of a drug substance and excipient as a function of a relative vapor pressure may be determined by placing samples in desiccators having different humidity conditions. *Zografi* and *coworkers* designed specialized equipment for more precise determination of the rate and extent of moisture sorption. Proper processing and storage conditions of drugs may be selected on the basis of sorption isotherms. A solid deliquesces or dissolve in the adsorbed layer of water when the relative humidity of atmosphere exceeds that of its saturated solution. The latter condition is called critical relative humidity or RH_0. The dissolution of a crystalline solid into adsorbed water (surface dissolution) would not be expected to occur below RH_0. However, *Kontny et al.* recently showed that mechanical processing of solids

such as grinding, milling; Micronization, compaction etc. can induce changes in their reactivity toward water vapor. As a result, the surface dissolution of drug may occur at a lower humidity, which may lead to chemical and physical instability problems during subsequent storage. Thus, whenever possible Preformulation study should be conducted with the form of material to be used in the final formulation. The moisture contents of excipient can also influence the physicochemical properties of solid dosage forms. The analysis of sorption isotherms of excipient such as cellulose and starch derivatives indicates that water may exist in at least two forms, "bound" (solid like) and "free". These two types of water may ne differentiated by measuring heat of sorption and by DSC and nuclear magnetic resonance studies. It has been suggested that serious stability problems may be avoided by minimizing free water in the excipient. On the other hand, it has been observed that the removal of unbound water reduces the ability of microcrystalline cellulose and compressible sugar to act as direct-compaction materials. This is because free water is needed to provide plasticity to these systems. Free water on the external surfaces of powders can also affect powder flow.

Flowability: [27,28]

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder of granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The problem can be solved by selecting appropriate excipient. In some cases, drug powders may have to be pre compressed or granulated to improve their flow properties. During the Preformulation evaluation of the drug substance, therefore, its flowability characteristics should be studied, especially when the anticipated dose of the drug is large. *Amidon* and *Houghton* discussed various methods of testing powder flow. Some of these methods are angle of repose, flow through an orifice, compressibility index, shear cell, etc. no single method, however, can assess all parameters affecting the flow. When a heap of powder is allowed to stand with only the gravitational force acting on it, the angle between the free surface of the static heap and the horizontal plane can achieve a certain maximum value for a given powder. This angle is defined as static angle of repose and is a common way of expressing flow characteristics of powders, the angle of repose values range from 25 to 45^0, with lower values indicating better flow characteristics. There are number of ways to determine the angle of repose. The exact value of the measured angle depends on the method used. The value of the angle of repose determined from methods where the powders are poured to form a heap is often distorted by the impact of the falling particles. The method described by *pilpel* is particularly free of this distortion.

Compactibility/Compressibility: [27,28,29,30,31,32,33]

Tablet formulation is the multicomponent systems. The ability of such a mixture to form a good compact is dictated by compressibility and compatibility characteristics of each component. *Lueuenberger* and *Rohera* defined "compressibility" of a powder as the ability to decrease in volume under pressure, and compatibility as the ability of the powdered material to be compressed into a tablet of specified tensile strength. Some indication of the compressibility and compactibility characteristics of new substances alone and in combination with some of the common excipient should therefore be obtained as part of the Preformulation evaluation. Use of a hydraulic press offers one of the simplest ways to generate such data. Powders that form hard compact under applied pressure without exhibiting any tendency to cap or chip can be considered as readily compactible. The compactibility of pharmaceutical powders can be characterized by studying tensile strength, indication hardness, etc. of compact prepared under pressure. *Hiestand* and *Smith* used tensile strength and indentation hardness to determine three dimensionless parameters strain index, bonding index, and brittle fracture index to characterize tableting performance of individual components and mixtures. For the determination of the tensile strength, compact are placed readily or axially between two platens, and forces required to fracture the compacts are measured. Values of tensile strength calculated from the forces required radically and axially are called, respectively, radial and axial tensile strengths. *Jarosz* and *Parrott* suggested that a comparison of radial and axial tensile strengths of compact may indicate bonding strength of compacts in two directions and may be related to their tendency toward capping. They also used tensile strength to evaluate the type and concentration if binders necessary to improve the compactibility of powders. Hardiness is defined as the resistance of a solid to deformation and is primarily related to its plasticity. It is commonly measured by the static impression method (Brinell test). The Brinell hardness number (BHN) is then calculated by using the following equation:

$$\text{BHN} = 2F / \Pi D(D - \sqrt[2]{D - d}$$

Compressibility of powders is characterized form the density- compression pressure relationship according to the Heckel plot. The relevant equation is given below:

$$\text{Log } 1/1\text{-}\rho_{rel} = KP/2.303 + A$$

Where, ρ_{rel} is the relative density, P is the compressional pressure, and K and A are constants. Information about the extent of compression, the yield value or the minimum pressure required to cause deformation of solid and the nature of determination(plastic deformation, brittle fracture) etc., may be obtained from the Heckel plot.

Wettability:[34,35,36,37]

Wettability of a solid is an important property with regard to formulation of a solid dosage form. It may influence granulation of solids, penetration of dissolution fluids into tablets and granules, and adhesion of contacting materials to tablets. Wettability is often described in terms of a contact angle that can be measured by placing drops of liquids on compacts of materials. The more hydrophobic a material is, the higher is the contact angle, and a value above 90^0 (using water) implies little or no spontaneous wetting. Crystal structures can also influence the contact angle. A second method of determining wettability uses the Washburn equation. In this method, the distance a liquid penetrates into a bed of powder or a compact is measured. Problems associated with wettability of powders, namely, poor dissolution rate, low adhesion of film coating, and the like, may be solved by intimate mixing with hydrophilic excipient or by incorporating a surfactant in the formulation.

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