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Diffusion and Dissolution Parameters and Their Impact on Drug Release

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ABSTRACT

Dissolution and diffusion play a significant role in the release of the drug. The rate of diffusion and dissolution is likely by several factors like physicochemical properties of drugs, formulation factor, dissolution test parameters, etc. The drug release data was found from in-vitro dissolution studies, quantitatively correlated, and taken with various mathematical models viz. Zero-order model, first-order model, Higuchi model, Hixson-Crowell model, and Korsmeyer-Peppas mode, in addition, evaluated to understand the kinetics of drug release. The criteria for the most appropriate model were based on the high degree of coefficient of correlation of drug release. This review article aims to denote that diffusion and dissolution parameters show a significant impact on drug release.

1. INTRODUCTION

"Diffusion is defined as the movement of molecules from an area in which they are highly concentrated to an area in which they are less concentrated. The rate of diffusion can be studied by Fick's law of diffusion"[1]. Dissolution is the process by which a solid solute goes into solution form. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under uniform conditions of liquid/solid interface, temperature, and solvent composition. "Several theories have been suggested to explain drug dissolution by 1)Diffusion layer model/ Film theory. 2)Danckwert model/ Penetration or Surface renewal theory. 3) Interfacial barrier model/ Double barrier or limited salvation theory"[2]. Solid solubility in liquids involves the transfer of mass from a solid to a liquid phase. This process is composed of two consecutive stages. First is an interfacial reaction that results in the discharge of solute molecules from the solid phase. The second phase is the transport of solute away from the interfacial boundary under the impact of diffusion or convection. The overall rate of mass transfer in dissolution will be determined by the rate of the slowest stage. The Noyes-Whitney equation states that the rate of dissolution is proportional to the surface area (S) of the solid and the concentration gradient, Cs is the concentration of the boundary layer adjacent to the solid surface and C is the concentration of the medium. K is the dissolution rate constant. Hence, rate of dissolution dc/dt = KS(Cs – C) the rate of transfer depends on the rate at which the solute diffuses from the thin boundary layer into the bulk solution. K will depend on the diffusion coefficient of the solute and the thickness of the diffusion pathway and it will be influenced by dissolution parameters like temperature, agitation, changes in surface area, polymorphism of solids, change in viscosity of the medium[14]. The mathematical modeling of drug delivery has a substantial potential to facilitate product development and help to understand the release behavior of complex pharmaceutical dosage forms. This paper aimed was to make a brief review of the dissolution and diffusion parameters.

CONTENT

2. Theories of drug dissolution

Several theories have been proposed to explain drug dissolution. Some of the important ones are:

2.1 Diffusion layer model/ film theory[1,2]:

It is the simplest model where the dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces. Consist of two consecutive steps: Solution of the solid to form a thin film or layer at the solid/liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous). Diffusion of the soluble solute from the stagnant layer to the bulk of the solution this step is slower and is, therefore, the rate-determining step in the drug dissolution. Fick's law covers only diffusions under steady-state conditions, modifying it Noyes & Whitney established another equation.

$$dc/dt=k(cs-cb)$$

dc/dt= dissolution rate of the drug, K= dissolution rate constant, Cs= concentration of drug in the stagnant layer, Cb= concentration of drug in the bulk of the solution at time t

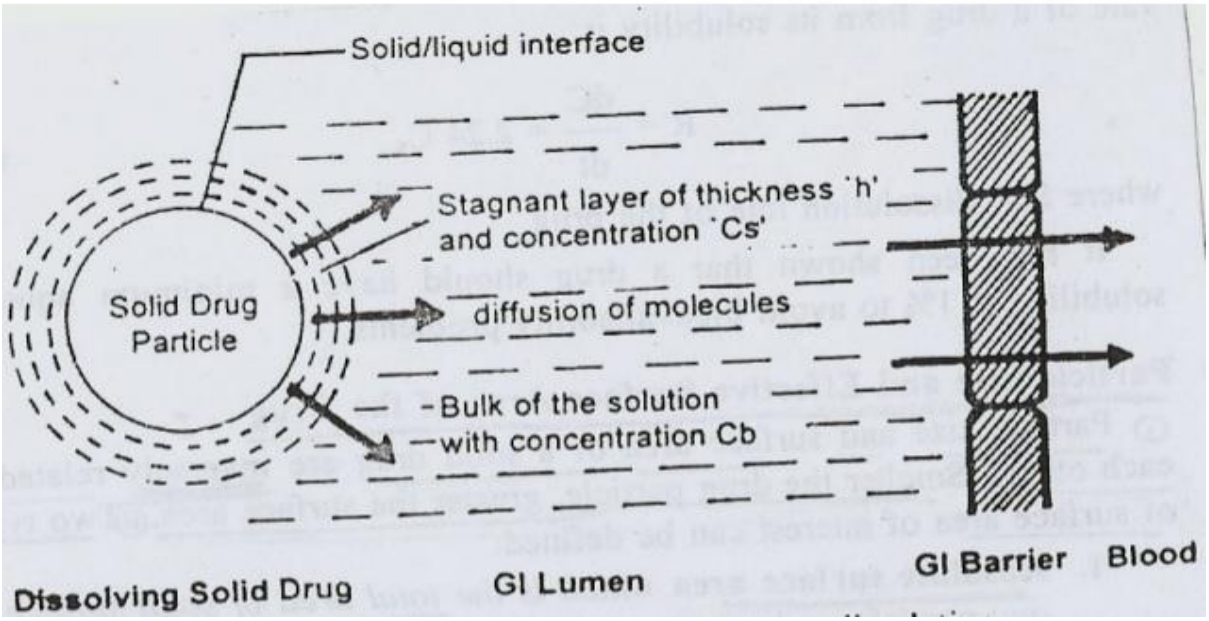


Figure: 1

Modified Noyes-Whitney's Equation:

$$dc/dt=DAKw/o(Cs – Cb)/vh$$

Where D= diffusion coefficient of the drug. A= surface area of dissolving solid. Kw/o= water/oil partition coefficient of the drug. V= volume of dissolution medium. h= thickness of the stagnant layer. (Cs – Cb)= Concentration gradient for the diffusion of the drug.

Hixon-Crowell's law of cubic root of dissolution takes into account the reduction of particle size and spatial change,

$$W01/3 – W1/3 = Kt$$

Where, W0=original mass of the drug, W=mass of drug remaining to dissolve at time t Kt=dissolution rate constant.

2.2 Danckwert model/ penetration or surface renewal theory[1,2]:

This theory assumes that solid-solution equilibrium is achieved at the interface and mass transport is a slow step in the dissolution process. The model could be visualized as a very thin film having a conc. Ci which is less than saturation, as it is constantly being exposed to fresh surfaces of liquid having a concentration much less than Ci, according to the model, the agitating fluid consists of a mass of eddies or packets that are continuously being exposed to new surfaces of solid and then carried back to the bulk of the liquid. Diffusion occurs into each of these packets during a short time in which the packet is in contact with the surface of the solid. Since turbulence extends to the surface, there is no laminar boundary layer and so no stagnant film exists. Instead, the surface is continually being replaced with fresh liquid.

Danckwert's model is expressed by the equation:

$$Vdc/dt=dm/dt=A\ (cs\text{-}cb)\ \sqrt{\gamma}D$$

Where, m = mass of solid dissolved Gamma (γ) = rate of surface renewal

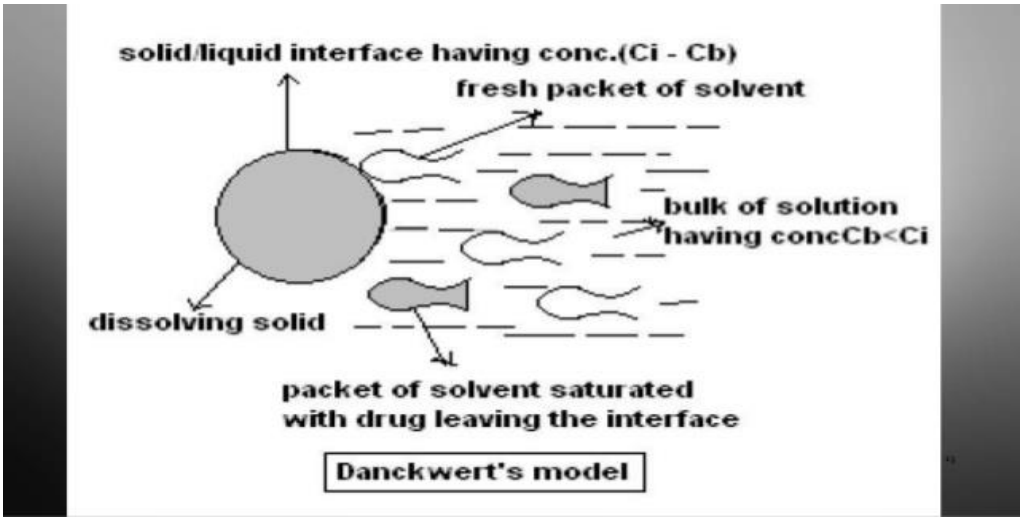


Figure: 2

2.3 Interfacial barrier model/ double barrier or limited salvation theory[2]:

The Diffusion layer model and Dankwert's model were based on two assumptions: 1) The rate-determining step that controls dissolution is the mass transport. 2) Solid solution equilibrium is achieved at the solid/liquid interface.

According to the interfacial barrier model, an intermediate concentration can exist at the interface as a result of the solvation mechanism and is a function of solubility rather than diffusion. When considering the dissolution of the crystal will have a different interfacial barrier given by the following equation,

$$G = ki\ (Cs - Cb)$$

Where G = dissolution per unit area, Ki = effective interfacial transport constant

In this theory, the diffusivity D may not be independent of saturation concentration Cs. The interfacial barrier model can be extended to both the Diffusion layer model and Dankwert's model.

3. Factor Affecting Dissolution Rate:

3.1 Physicochemical Properties of the Drug:

The several physicochemical properties of a drug that affect drug dissolution and its rate are solubility, particle size, polymorphism, salt form, pseudo polymorphism, complexation, wettability, etc.

3.1.1 Particle size

Surface area increases with decreasing particle size, a decrease in particle size, which can be accomplished by micronization, will basis on a higher dissolution rate. For example, micronization of poorly aqueous soluble drugs like griseofulvin, chloramphenicol, and numerous salts of tetracycline results in superior dissolution rates in comparison to the simple milled form of these drugs [3]. However, in cases of hydrophobic drugs like aspirin, phenobarbital, micronization results in a decrease in the effective surface area of such powders and thus a decrease in the dissolution rate. Three reasons have been proposed for such an outcome: 1) The hydrophobic surface of the drugs adsorb air onto their surface which prevents their wettability, such powders float on the dissolution medium. 2) The particles reaggregate to form larger particles due to their high surface free energy, which either float on the surface or settle at the bottom of the dissolution medium. 3) Extreme particle size reduction may impart surface charges that may prevent wetting, moreover electrically brought agglomeration may prevent intimate contact of the drug with the dissolution medium[1].

3.1.2 Salt form of the Drug:

Most drugs are either weak acids or weak bases. One of the easiest approaches to enhance the solubility and dissolution rate of such drugs is to transform them into their salt forms. It has always been anticipated that sodium salt dissolves faster than its corresponding insoluble acid[3]. Generally, with drugs with weak acidity, strong basic salts are prepared as sodium and potassium salts for barbiturates and sulfonamides. In the case of weakly basic drugs, a strong acid salt is prepared like the hydrochloride or sulfate salts of several alkaloidal drugs[1].

3.1.3 Polymorphism and Amorphism :

Depending on the internal structure, solid can be either be crystalline or amorphous. When a substance exists in other than one crystalline form, the diverse forms are designated as polymorphs and the phenomenon as polymorphism. These polymorphs may have different physical properties, such as dissolution rate and solubility [3]. For example, the amorphous form of novobiocin is 10 times more soluble than the crystalline form. Which increases the dissolution rate[1].

3.1.4 Hydrates/Solvates:

During their preparation, drug crystals may include one or more solvent molecules to form solvates. The most common solvate is water. If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms [3]. Thus, the anhydrous form of a drug has better aqueous solubility than the hydrates. The anhydrous form of Theophylline and Ampicillin has higher aqueous solubilities dissolve at a faster rate and show better bioavailability in comparison to their monohydrate and trihydrate forms respectively[1]. Solvates have a higher solubility than their nonsolvates. e.g. Chloroform solvates of Griseofulvin, n-pentanol solvate of fludrocortisone[3].

3.2 Dosage Form Factors:

Dosage form factors include numerous formulation factors and excipients incorporated in the dosage form-

3.2.1 Binders and Granulating Agents:

These materials are used to hold powders together to form granules or promote cohesive compacts for directly compressible materials and to ensure that the tablet remains intact after compression. Hydrophilic (aqueous) binders show a better dissolution profile with poorly wettable drugs like Phenacetin by imparting hydrophilic properties to the granule surface. Large amounts of such binders increase hardness and decrease the disintegration/dissolution rates of tablets. Non-aqueous binders like Ethyl Cellulose also retard drug dissolution[1].

Drug release reduced with increasing binder concentration, The release profile of drugs from the formulated tablets containing varying ratios of binders could be classified in decreasing order of performance by the binder: SCMC >gelatin> acacia [4].

3.2.2 Disintegrants:

These agents overwhelmed the cohesive strength of tablets and break them upon contact with water which is an important prerequisite to tablet dissolution. Nearly all the disintegrants are hydrophilic. A decrease in the amount of disintegrant can significantly lower bioavailability. Adsorbing disintegrants such as Bentonite and Veegum should be avoided with low-dose drugs such as Digoxin, Alkaloids, and Steroids as large amounts of dosage are permanently

advertised and only a fraction is available to absorb it. Microcrystalline cellulose is a very good disintegrant(and a binder too) but at high compression forces, it may retard drug dissolution[1].

3.2.3 Lubricants:

These agents can be used in the manufacture of tablets to aid the flow of granules, to reduce particle friction, and to adhere or adhere to particles to die and punches. Lubricants are hydrophobic (several metallic stearates and waxes) which inhibits wettability, penetration of water into a tablet which leads to a decrease in dissolution rate. The best alternative is the use of soluble lubricants like SLS and carbowaxes which promote drug dissolution [1][5].

3.2.4 Surfactants:

Surfactants are commonly used in formulations as wetting agents, solubilizers, emulsifiers, etc. They may improve or retard drug dissolution. Mechanisms involved in the increased absorption of the drug by use of surfactants Promotion of wetting (through an increase in effective surface area) and dissolution of drugs. E.g. Tween 80 with Phenacetin [1].

3.2.5 Diluents (Fillers):

Diluents are commonly added to tablet formulations if the necessary dose is inadequate to produce the necessary bulk. The solubility of the diluents selected is very crucial as it influences the disintegration, dissolution, and bioavailability of such drugs [6]. A diluent may be organic or inorganic. Amongst organic diluents, Carbohydrates are very widely used for example Starch, Lactose, Microcrystalline cellulose, etc. These hydrophilic powders are very useful in promoting the dissolution of poorly water-soluble, hydrophobic drugs like Spironolactone and Triamterene by forming a coat onto the hydrophobic surface of drug particles. Among the inorganic diluents, Dicalcium Phosphate (DCP) is most commonly used. One classic example of drug-diluent interaction resulting in poor bioavailability is that of Tetracycline and DCP. The reason is the formation of the divalent calcium-tetracycline complex which is poorly soluble and results in a decrease in dissolution rate[1]. This enhanced dissolution effects of the four hydrophilic diluents are in the order of Dextrose>Sucrose>Lactose>Mannitol. Dextrose and Sucrose act as effective hydrophilic diluents that can be employed to improve the dissolution rate of griseofulvin from compressed tablets[6].

3.2.6 Coatings:

The deleterious effect of various coatings on drug dissolution from a tablet dosage form is in the following order: enteric coat > sugar coat >non-enteric film coat. The dissolution profile of certain coating materials modifications on aging e.g. shellac coated tablets, in long-term storage, slowly dissolve in the intestine. This can, still, be prevented by incorporating little PVP in the coating formulation[1].

3.2.7 Complexing Agents:

The complex formation has been used to modify the physicochemical and biopharmaceutical properties of a drug. A complexed drug may have altered stability, solubility, molecular size, partition coefficient, and diffusion coefficient. When drug bioavailability is poor due to low solubility, drug solubility can be improved through the formation of a complex with cyclodextrin which results in an increase in rate.[7].Several examples where complexation has been used to enhance dissolution rate through the formation of a soluble complex e.g. ergotamine tartrate-caffeine complex and hydroquinone-digoxin complex[1].

4. Dissolution Test Parameters:

4.1 Effect of agitation:

The association between the intensity of agitation and the rate of dissolution differs considerably according to the type of agitation used, the shape and design of the stirrer, and the physicochemical properties of the solid. Speed of agitation generates a flow that continuously changes the liquid/solid interface between solvent and drug. To sustain a reproducible laminar flow, which is essential for gaining reliable results, agitation should be maintained at a relatively low rate. Dissolution tests using high-speed agitation may lack discriminative value and can yield misleading results. The lowest value (25 rpm) is characteristic for suspensions (e.g., Ampicillin for Oral Suspension and Meloxicam for Suspension). The most rapid rotation speed for Apparatus 2 is listed in the dissolution method for Triptorelin Pamoate Injectable Suspension (200 rpm) and Fentanyl Citrate Lozenges (175 rpm)[15,16,17]. For example, A systematic survey was conducted on marketed tablets of chloroquine phosphate, griseofulvin, hydroxychloroquine sulfate, isocar-boxazide, primaquine phosphate, and sulfadiazine. To study the influence of agitation rate on the dissolution rate of these products, dissolution studies were conducted at paddle speeds of 50, 75, and 100 rpm with the USP apparatus 2 (paddle method). The dissolution rate increased

with increasing turbulence from 50 to 75 rpm. However, no significant increase in the dissolution rate was noted with an increase in the agitation rate from 75 to 100 rpm[8].

(Table 1): USP Apparatus and Agitation Criteria [9].

USP Apparatus	Description of the Apparatus	Rotation speed	Dosage form to be tested
I	Basket	50-120 rpm	Immediate release tablet, Delayed-release tablet, Extended-release tablet
II	Paddle	25-50 rpm	Immediate-release tablet, Delayed-release tablet, Extended-release tablet
III	Reciprocating cylinder	635 dpm (dips per minute)	Chewable tablet
IV	Flow-through cells	N/A	Extended-release tablet, Poorly soluble drug
V	Paddle over disk	25-50 rpm	Transdermal
VI	Cylinder	N/A	Transdermal
VII	Reciprocating disk	30 rpm	Extended-release tablets, Transdermal drug product

4.2 Effect of dissolution fluid:

The selection of a proper medium for dissolution testing depends largely on the physicochemical properties of the drug. The media typically used in dissolution studies include acidic solutions, buffers, surfactants, and surfactants with acid or buffers. Surface-active agents are used in dissolution test methods to improve the solubility or wettability of a drug. For example, the solubility of Mefenamic acid is affected by a change in ionic strength when SLS is used but not when CTAB(cetyl trimethyl ammonium bromide) is used[15,18,19].

(Table 2)

Dissolution fluid	example
water	Ampicillin capsule
Buffers	Azithromycin capsule
Simulated gastric fluid	Piroxicam capsule
HCL solution	Cimetidine tablet

(Table 3): Dosage forms with specifically recommended dissolution medium [9].

Sr.No.	Dosage form	Modulation in dissolution medium
1.	Semi-solid Topical Dosage forms (Creams, ointments, Gels)	• Depending upon the solubility of the drug substance, the receptor medium may be essential to contain alcohol and /or surfactant. • De-aeration is critical to avoid bubble formation at the interface with the membrane. • As with transdermal products the test temperature is usually set at 32^0C to reflect the usual skin temperature.
2.	Suppositories	• Lipophilic suppositories release the drug after melting in the rectal cavity and are significantly affected by rectal temperature (36.0-37.5□C). • The test temperature should take into account physical conditions but may also be more or less above the melting point e.g. at 37.0 – 38.5 °C (e. g. Suppositories, used for patients with fever).
3.	Oral Suspensions	• Rotating paddle method retaining an aqueous dissolution medium. • Sample introduction and agitation rate should be established on the basis of the viscosity and composition of the suspension matrix.
4.	Buffered or Effervescent	• Consider the physicochemical characteristics of the active ingredient (solubility, pKa or pKb, etc), buffered medium. Verify

	Tablets	buffering capacity and ionic strength of the media.
5.	Lipid filled Capsules	• An enzyme (lipases) in addition to surfactants to mimic digestion is a step that reduces the rate of dissolution. • Lipases more closely reflect physiological conditions, but it is costly.
6.	Chewing Gums	• Test media with a pH of 6.0 are commonly used since this pH corresponds to saliva pH values of 6.4 (adults) or 7.3 (children).
7.	Powders, Granules, Solid Solutions, and Solid Dispersions	• The dissolution behavior of these dosage forms may be largely influenced by their wettability, surface area, and particle size distribution. • For powders, when it shows poor wettability, it may be necessary to add a surfactant into the dissolution medium to obtain reproducible dissolution results. • Caution should be taken to use a level of surfactant that does not increase the solubility of the drug to the extent where the test is no longer discriminatory. Since solid solutions and dispersions usually lead to supersaturation of the medium, it is often of interest to run the in vitro release test somewhat longer so that the potential for precipitation can be evaluated.
8.	Parenterals: Implants and Microparticles	• The flow rate of the medium should be set very slowly. • As tests are often run over a very long period (e.g. Several weeks) measures have to be taken to recompense against evaporation and to prevent microbial growth in the medium. • The composition of the medium should be taken into account for the osmolarity, Ph, and buffer capacity of the fluids at the site of application, which is usually assumed to resemble that of plasma.
9.	Transdermal Patches	• The patch should be properly located so that the drug-loaded surface is exposed to the medium. • The pH of the medium ideally should be adjusted to 5.0-6.0, reproducing physiological skin conditions. For the same reason, test temperature is typically set at 32^0C
10.	Dosage form	• Depending on the differences in the solubilities of the active

	with more than one active ingredient	ingredients, it may be necessary to have separate sets of dissolution conditions, one for each API.

4.3 Influence of pH of dissolution fluid:

Variations in pH exert the greatest effect in terms of drug solubility. For weak acids, the rate of dissolution increases with increasing pH, whereas, for weak bases, the rate of dissolution increases with decreasing pH. For tablets containing active ingredients, whose solubility is independent of pH, the dissolution rate does not vary considerably with changes in pH of the dissolution medium unless they contain certain excipients that are influenced by pH. Example: The study discovered that carvedilol exhibited a typical weak base pH-dependent solubility profile with high solubility at low pH (545.1–2591.4 µg/mL within the pH range 1.2–5.0) and low solubility at high pH (5.8–51.9 µg/mL within the pH range 6.5–7.8[10].

4.4 Effect of surface tension of the dissolution fluid:

The incorporation of surface-active agents in the dissolution medium is expected to enhance the dissolution rate of a poorly soluble drug in solid dosage forms by decreasing the interfacial tension and micelle formation. The addition of surfactant can increase significantly the dissolution rate because of better penetration of the solvent into the tablet resulting in greater availability of the drug. Surfactants can be classified as a) Anionic (e.g. Sodium lauryl sulfate [SLS] b) Cationic (e.g. Cetyl trimethyl ammonium bromide) c)Zwitterionic (e.g. Alkyl betaine) d) Non-ionic (e.g. Tween).

The micelle of surfactant molecules mimics the bile acid aggregates in the small intestine; the surfactant enables the diffusion and transport of the free solute into the bulk medium. Since dissolution is a combined effect of solubility and diffusivity, the micelle size will have an effect on the dissolution rate of molecules when different surfactants are used[18].

4.5 Effect of viscosity of the dissolution medium:

If the interaction at the interfaces, occurs much faster than the rate of transport, such as in the case of diffusion-controlled dissolution processes, it would be estimated that the dissolution rate decreases with an increase in viscosity. The degree of dissolution of benzoic acid in

aqueous sucrose and methylcellulose solutions is consistent with the viscosity of the dissolution medium. [11].

4.6 Effect of the presence of unreactive and reactive additives in the dissolution medium:

When neutral ionic compounds such as Sodium Chloride and Sodium Sulfate or nonionic organic compounds such as Dextrose were added to the dissolution medium the benzoic acid solubility was directly dependent on its solubility in a particular solvent. When certain buffers or bases were added to the aqueous solvent, an increase in the dissolution rate was observed.

4.7 Volume of dissolution medium and sink condition:

The suitable volume of the dissolution medium depends mainly on the solubility of the drug in the selected fluid. If the drug is poorly soluble in water, a reasonably large amount of fluid should be used if complete dissolution is to be expected. To minimize the effect of the concentration gradient and maintain sink conditions, the concentration of the drug should not exceed 10 – 15% of its maximum solubility in the dissolution medium selected.Volume generally 500ml,900 ml and 1000ml used[15].

4.8 Deaeration of the dissolution medium:

The presence of dissolved air or other gases in the dissolution medium may impact the dissolution rate of certain formulations and lead to variable and unreliable results. Soluble air in distilled water can significantly lower its pH and as a result, affect the rate of dissolution of pH-sensitive drugs. Another severe effect is the tendency of the dissolved air to be released from the medium in form of a tiny air bubble. These bubbles collect at the surface of the dosage form thereby acting as a hydrophobic barrier between solvent and solid surface. This inhibits wetting and lowers the dissolution rate[12]. Some drug products are known to be tremendously sensitive to dissolved gas, the presence of air bubbles should be expected to increase the measurement uncertainty in dissolution testing. In USP Apparatus 2, released air bubbles deposit on the paddle shaft, the release of air bubbles alters the hydrodynamics of the system by changing the fluid flow characteristics in the dissolution vessel[13].

4.9 Effect of temperature of the dissolution medium:

Drug solubility is temperature-dependent, therefore the temperature is carefully controlled during the dissolution process. Generally, a temperature of 37°±0.5^{0}C is maintained during

the dissolution determination of oral dosage forms and suppositories. For topical preparations as low as 30° C and 25°C have been used. The test temperature is 45 °C for Dexamethasone Implant (intravitreal), 40 °C for Mesalamine Suppository, and 38 °C for Prochlorperazine Rectal Suppository [15].

5. Diffusion Parameter:

Drug Solubilisation[20]:

"The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute".

Methods of Solubility Enhancement:

Surfactants:

The most common method of dissolving an insoluble substance is to reduce the interfacial tension between the solute surface and the solvent for better wetting and salvation interaction.

pH adjustments:

Modification of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase the water solubility of ionizable compounds. As per the pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of the drug.

Particle Size Reduction:

Micronization or nanonization is one of the approaches to improve the solubility of drugs by an increase in surface area and saturation solubility by means of reduction of the particle size to the sub-micron level. Particle size is a critical parameter that should be strictly controlled during the preformulation studies of any formulation. Although the decrease in the particle size is a successful way to enhance the solubility.

Formulation Factor:

Formulation factor: like type and amount of binder, filler, disintegrating agent, the lubricant used in formulation, which affects the rate of diffusion [1].

Temperature: Higher temperatures increase the energy and therefore the movement of the molecules increases, increasing the rate of diffusion. Low temperatures reduce molecular strength, thereby reducing diffusion rates.

Solvent Density: As solvent density increases, the diffusion rate decreases. Molecules slow down because they have a very difficult time getting into a crowded place. If the medium is less dense, then the diffusion rate increases.

The concentration of drug at diffusion site:

The rate of diffusion increases with an increase in the concentration of the drug at the diffusion site, the faster the rate of diffusion. The lower the concentration of the drug at the diffusion site, the lower the rate of diffusion [1].

Surface Area of Diffusion:

The greater the surface area, the faster the rate of diffusion [1]

Application Of Drug Release Data On Mathematical Models:

Different mathematical models are used to understand the kinetics of drug release described below.

1) Zero Order Model[14,21,22]:

According to the principles of pharmacokinetics, drug release from the dosage form can be represented by the equation-

$$C_0 - C_t = K_0 t$$

$$C_t = C_0 + K_0 t$$

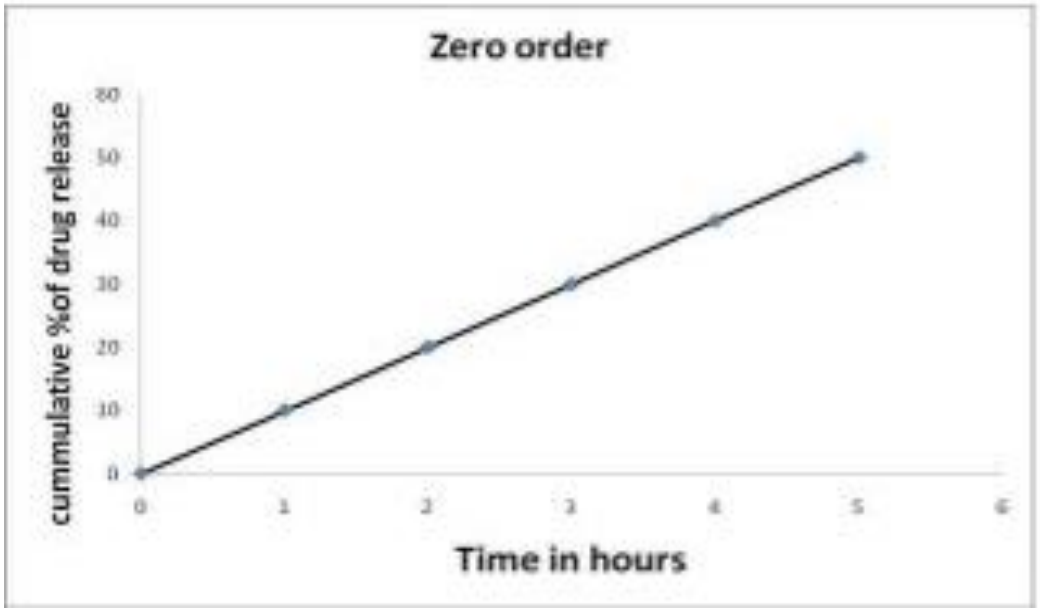
C_t is the amount of drug released at time t,

C_0 is the initial concentration of drug at time t=0,

K_0 is the zero-order rate constant.

Therefore, zero-order kinetics describes the process of drug release regularly in the drug delivery system and the level of drugs in the blood remains constant during delivery. Hence

to study the drug release kinetics data obtained from the in-vitro dissolution study is plotted against time i.e., cumulative drug release vs. time.



(Graph.1)

Hence the slope of the above plot gives the zero-order rate constant and the correlation coefficient of the above plot will give the evidence whether the drug release follows zero-order kinetics or not.

2) First Order Model [14,21,22]:

The release of the drug following the kinetics of the first order can be represented by the equation –

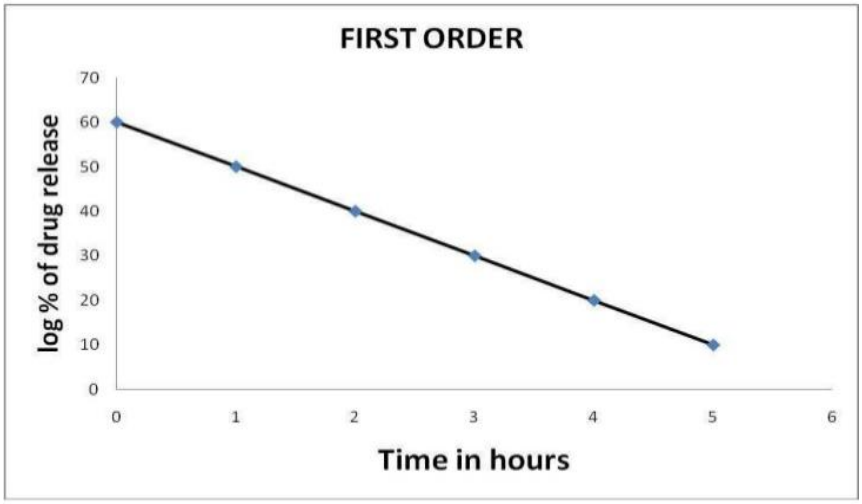
$$dC/dt = -K_1C$$

K1 is the first-order rate constant, expressed in time-1 or per hour. Hence it can be defined as that first-order process is the one whose rate is directly proportional to the amount of drug reacting i.e., greater the concentration faster the reaction. Hence, it follows linear kinetics. After rearranging and integrating the equation,

$$\log C = \log C_0 - K_1 t/2.303$$

C_0 is the initial concentration of the drug,

C is the concentration of drug remaining at time t.



(Graph.2)

Hence to study the drug release kinetics data obtained from thein-vitro dissolution study is plotted against time i.e., log % of the remaining drug to the time vs. time, and the slope of the plot gives the first-order rate constant. The correlation coefficient of the above plot will give the information whether the drug release follows first-order kinetics or not.

3) Higuchi Model[14,21,22]:

The release of a drug from a drug delivery system (DDS) comprises both dissolution and diffusion. Various mathematical equations models describe drug dissolution and/or release from DDS. In the modern era of controlled-release oral formulations, the 'Higuchi equation' has become a prominent kinetic equation in its own right, as evidenced by using drug dissolution studies that are recognized as an important element in drug delivery development. Today the Higuchi equation is considered to be one of the most widely used and well-known statistics of controlled releases. The Higuchi model expression is given by the following equation:

$$ft = Q = A\sqrt{D}\,(2C - \mathrm{Cs})t$$

Where Q is the amount of drug released in time t per unit area A,

C is the initial drug concentration

, Cs is the drug dissolve in the matrix media,

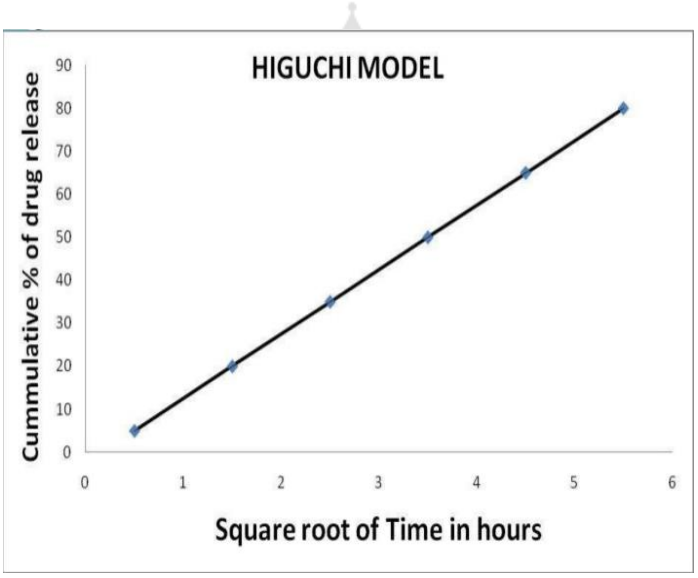
D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix substance.

The simplified Higuchi model can be labeled as follows;

$$ft = Q = KH \times \sqrt{t}$$

Where KH is the Higuchi dissolution constant.

It is important to note that a few assumptions are made in this Higuchi model. These assumptions are: (i) the initial drug concentration in the system is much higher than the matrix solubility (ii) Perfect sink conditions are maintained (iii) The diffusivity of the drug is constant and (iv) The swelling of the polymer is negligible. The sink conditions are achieved by ensuring the concentration of the released drug in the release medium never reaches more than 10 percent of its saturation solubility.



(Graph.3)

The data obtained from the in-vitro dissolution study is to be plotted as cumulative percentage drug release versus Square root of time. Drug dissolution from several types of modified release pharmaceutical dosage forms can be described by the above equation like some transdermal systems and matrix tablets with water-soluble drugs.

4) Korsmeyer-Peppas Model[14,21,22]:

When it has been established that the prime mechanism of drug release is diffusion-controlled from the Higuchi plot then comes the release of the drug follows which type of diffusion. Korsmeyer (1983) found a simple relationship that describes the release of drugs from the polymeric system. Korsmeyer and Peppas put forth a simple relationship which described the drug release from a polymeric system following which type of dissolution and he represented an equation as:

$$\mathbf{Mt/M\infty = K_{kp}t^{n}}$$

Mt/M∞ is a fraction of drug released at the time,

$$\log(Mt/M\infty) = \log Kkp + n \log t$$

Mt is the amount of drug released in time t,

M∞ is the amount of drug released after time ∞,

n is the diffusional exponent or drug release exponent,

Kkp is the Korsmeyer release rate constant.

The n value is used to characterize different release mechanisms as given in the tabular form.

(Table 3)

Release exponent (n)	**Drug transport mechanism**
0.5	Fickian diffusion
0.45<n=0.89	Non -Fickian transport
0.89	Case II transport
Higher than0.89	Super case II transport

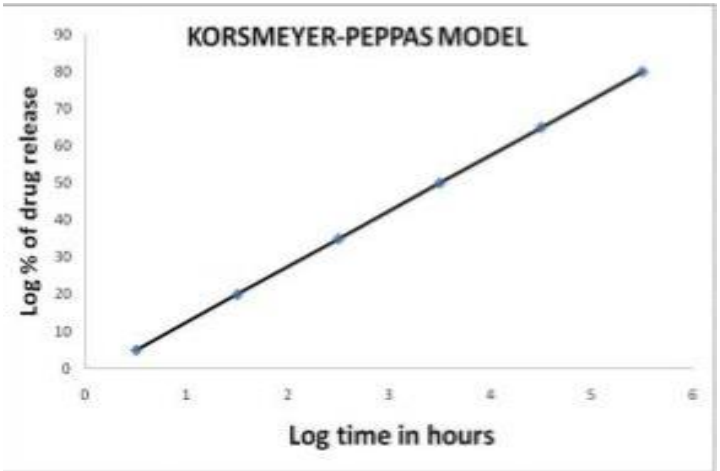


Fig:This plot explains diffusion mechanism by which drug diffuses from dosage form.

(Graph.4)

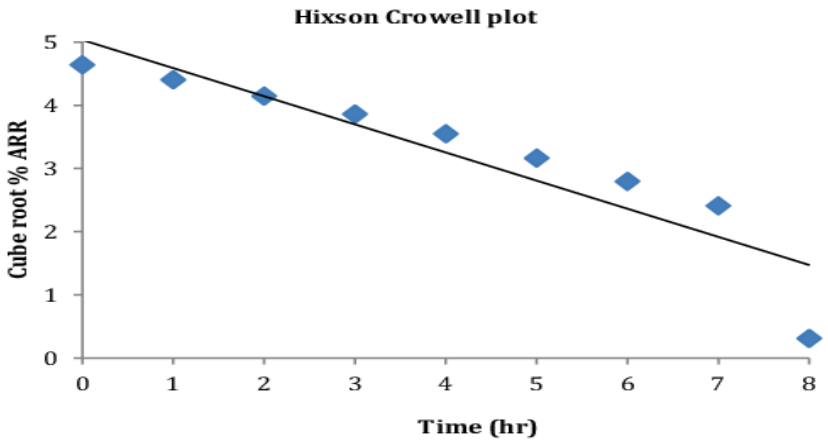
To study release kinetics a graph is plotted between log cumulative % drug release log(Mt/M∞) vs. log time (log t). The slope of the plot was constructed which described the release exponent or the diffusion exponent.

5) Hixson-Crowell model[14,21,22]:

Hixson-Crowell model was suggested by Hixson and Crowell in 1931. The Hixson-Crowell cube root law designates the release from systems where there is a change in surface area and diameter of particles or tablets. Hence, particles of regular area are proportional to the cube root of its volume. From the above concept, Hixson-Crowell recognized a relationship between drug release and time which can be represented by equation as-

$$\sqrt[3]{W0} - \sqrt[3]{Wt} = K_{HC}\, t$$

Where W0 is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at time t, K_{HC} is the Hixson-Crowell constant describing surface volume relation.



(Graph.5)

To study the release kinetics a graph is plotted between cube root of drug percentage remaining in matrix versus time. This equation is used for the analysis of dissolution data of conventional dosage form, dispersible dosage form, or immediate release dosage form. Hence, if the correlation coefficient of the above equation is higher, then we can infer that change in surface area during the process of dissolution has a significant effect on drug release.

1)The kinetic models that fit the dissolution data are evaluated by comparing the correlation coefficient(r) values obtained in various models.2) The model that gave a higher 'r-value is considered the best fit model.

CONCLUSION:

Diffusion and dissolution parameters show a significant impact on drug release. Dissolution and diffusion parameters can assist as a source of information on various aspects of dissolution testing like apparatus, dissolution medium, rotation/pulsation speed, test conditions, etc. Mechanism of drug release from a dosage form can be inferred by using Mathematical models. The model which has the highest correlation coefficient (r) value shall be considered as the best model.

REFERENCES:

1. D.M. Brahmankar Sunil B. Jaiswal, Biopharmaceutics and Pharmacokinetics, Vallabh Prakashan, Nagpur.1995.pgno.16-25.
2.Deepika B, Tasleem J, Raju KN, Sarojini S, Sri KS. Journal of Pharma Research.
3. Sanket B. Gavhane 1, ShubhrajitMantry, Sumit A. Joshi 1, Ganesh Y. Dama and Sourav Mohanto.Enhancement of poor oral absorption drug via lipid formulation: self-emulsifying drug delivery system. IJPSR, 2020; Vol. 11(3): 1042-1056

4.Chime SA, Brown SA, Ugwu CE, Agubata CO, Obidike TC, Onunkwo GC. Effect of binder type and concentration on the in vitro properties of Alstoniaboonei tablets. International Journal of Pharmaceutical Science Review and Research. 2012;16(2):5-9.
5. Potnuri NR, Rao DG, Rao SA, Reddy GM, Reddy SS. Effects of binders, lubricants, and fillers on drug release from diltiazem hydrochloride bi-layered matrix tablets obtained by direct compression and wet granulation technique. International Journal of Pharmacy. 2012;2:117-28.
6. Umeh ON, Azegba JC, Ofoefule SI. Effect of hydrophilic diluents on the release profile of griseofulvin from tablet formulations. Indian journal of pharmaceutical sciences. 2013 Nov;75(6):726.
7. Sahin J, Ozdemir N. Study on increasing the solubility and dissolution rate of sulfamethoxazole by cyclodextrins. African Journal of Pharmacy and Pharmacology. 2018 Aug 22;12(24):329-40.
8. Shah VP, Gurbarg M, Noory A, Dighe S, Skelly JP. Influence of higher rates of agitation on release patterns of immediate-release drug products. Journal of pharmaceutical sciences. 1992 Jun 1;81(6):500-3.
9. Vaghela B, Kayastha R, Bhatt N, Pathak N, Rathod D. Development and validation of dissolution procedures. Journal of applied pharmaceutical science. 2011;1(3):50-6.
10. Hamed R, Awadallah A, Sunoqrot S, Tarawneh O, Nazzal S, AlBaraghthi T, Al Sayyad J, Abbas A. pH-dependent solubility and dissolution behavior of carvedilol—a case example of a weakly basic BCS class II drug. AapsPharmscitech. 2016 Apr;17(2):418-26.
11. Braun RJ, Parrott EL. Influence of viscosity and solubilization on dissolution rate. Journal of pharmaceutical sciences. 1972 Feb 1;61(2):175-8.
12. Fliszar KA, Forsyth RJ, Li Z, Martin GP. Effects of dissolved gases in surfactant dissolution media. Dissolution Technologies. 2005;12(3):6.
13. Nithyanandan P, Deng G, Brown W, Manning R, Wahab S. Evaluation of the sensitivity of USP prednisone tablets to dissolved gas in the dissolution medium using USP Apparatus 2. Dissolution Technologies. 2006;13(3):15.
14.Paarakh MP, Jose PA, Setty C, Christoper GP. Release kinetics–concepts and applications.Int. J. Pharm. Res. Tech. 2018;8(1):12-20.
15.Shohin IE, Grebenkin DY, Malashenko EA, Stanishevskii YM, Ramenskaya GV. A brief review of the FDA dissolution methods database. Dissolution Technol. 2016 Aug 1;23(3):6-10.
16. Shah VP, Gurbarg M, Noory A, Dighe S, Skelly JP. Influence of higher rates of agitation on release patterns of immediate-release drug products. Journal of pharmaceutical sciences. 1992 Jun 1;81(6):500-3.
17. Seeger N, Lange S, Klein S. Impact of vibration and agitation speed on the dissolution of USP prednisone tablets RS and various IR tablet formulations. AapsPharmscitech. 2015 Aug;16(4):759-66.
18. Fotaki N, Brown W, Kochling J, Chokshi H, Miao H, Tang K, Gray V. Rationale for selection of dissolution media: three case studies. Dissolute. Technol. 2013 Aug 1;20:6-13.
19. Chang CM, Bodmeier R. Effect of dissolution media and additives on the drug release from cubic phase delivery systems. Journal of Controlled Release. 1997 Jun 2;46(3):215-22.
20.Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. International journal of pharmaceutical sciences and research. 2011 Oct 1;2(10):2501.
21. Raza SN, Khan NA. Role of mathematical modeling in controlled release drug delivery. Int J Med Res Pharm Sci. 2017;4(5):84-95.
22. Gouda R, Baishya H, Qing Z. Application of mathematical models in drug release kinetics of carbidopa and levodopa ER tablets. J. Dev. Drugs. 2017;6(02):1-8.

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