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A BRIEF REVIEW ON PHARMACEUTICAL DISSOLUTION INTERLINKING THE ASPECTS OF SCIENCE AND REGULATION

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Dissolution is a multistep process describes the affinity of the solute and the solvent by which a solid substance interacts among the heterogeneous phases of solute -solute, solvent-solvent, and the solute-solvent interface to yield a solution. In the pharmaceutical industry dissolution testing of solid dosage form gives a signal of the operability of the dosage form in the biological system. The rate of absorption is partially or completely controlled by the dissolution of the drug from its dosage forms in the gastrointestinal tract. Dissolution, the vital quality control aspects, also ensure batch-to-batch uniformity in drug release, bioavailability, and the development of efficacious therapeutic dosage forms. It also ensures the evaluation of their critical biopharmaceutical parameters. Hence the study of dissolution is an interplay between the science and the development of the regulatory profile of a dosage form for quality control aspects. The present review focuses on the science, factors relevant to in-vitro dissolution, and therefore the role of its in pharmaceutical regulation.

KEYWORDS: *Dissolution, Quality control, In-vitro in-vivo correlation, Hydrodynamic, Regulations*

INTRODUCTION

Dissolution is defined as a mass transfer process by which a solid material enters the solvent to yield a solution. The process is a multistep heterogeneous mass transfer process. The heterogeneous process involves the removal of the solute from the solid phase, solid-solvent interface, and passage of the solute to the solvent by the convective or passive process. The phenomenon of a solid material going into the solvent is termed dissolution. Pharmaceutical dosage forms undergo dissolution in biological media upon oral administration, followed by absorption into systemic circulation[1]. Dissolution testing is done to ensure uniform drug release, bioavailability, quality of drug product, and helps to develop efficacious and therapeutic dosage forms[2].

A variety of drug-related factors that affects dissolution are the solubility of drug, polymorphism, amorphous form, complexation, salt formation, particle size, solid-state characterization, and co-precipitation in the solvent system.[3] All these factors are responsible for enhancing the specific surface area of the drug and hence the solubility. Hence solubility improvement is the prime criteria to improve the rate of dissolution[4].

Based on the Biopharmaceutical Classification System (BCS), drugs belonging to Class II and IV have poor water solubility[5]. The intrinsic dissolution rate can be improved by identifying the solid-state of the compound in terms of salts formation, anhydrous form or polymorph or cocrystals, and or by improving the solubility using novel formulation strategies like solid dispersion or inclusion complexation, and or by optimizing the particle size[6]. Super saturable solid micelles using surfactant and solid carriers can also be used to improve the dissolution and oral bioavailability[7].

The science of dissolution thus helps to predict in-vivo stimulation in an *in-vitro* way, development of ideal dissolution methods for different types of dosage form through *in-vitro* real-time test, analysis of hydrodynamics to

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predict the process errors, helps to develop an *in-vitro in-vivo* correlation and generation of several effective physiologically based pharmacokinetic (PBPK) models to assist drug development[8-10].

The interplay between the science and newer process development for analysis results in the development of the compendial methods for dissolution. Thus, Agency guidelines are generated for dissolution conditions, validation, quality control (QC) processes, which further supports Scale-up post-approval changes, allow application for biowaivers, guidance for BCS classification, and biopharmaceutics drug disposition and classification system[11].

Hence the current review discusses the science of dissolution, the prime factors relevant to dissolution, and its role in the regulation of the pharmaceutical dosage forms.

Science of dissolution

Intrinsic dissolution of the pure drug is defined as the rate of dissolution of the drug with a constant surface area at the liquid interface[12]. The rate of intrinsic dissolution is influenced by the solid-state properties of the drug-like crystallinity, polymorphism, amorphism, hydration, solvation, particle size, shape, and surface area[13].

Hence the mass transfer (M) is expressed by $\frac{dM}{dt} = -KA(Cs - C)$

Where K=Intrinsic dissolution rate constant, A= Exposed surface area, Cs and C are the saturation concentration and concentration at any time t respectively.

In the sink condition where Cs>>C, it becomes

$$\frac{dM}{dt} = -KA\mathrm{Cs}$$

The mass transfer is a diffusion process, hence combining the Fick's law of diffusion, the overall equation changes to Noyes Whitney Equation as follows,

$$\frac{\mathrm{dM}}{\mathrm{dt}} = \frac{\mathrm{DA(Cs\text{-}C)}}{\mathrm{h}}$$
$$\frac{\mathrm{dC}}{\mathrm{dt}} = \frac{\mathrm{DA(Cs\text{-}C)}}{\mathrm{Vh}}$$

Where D = Diffusion coefficient, A= Surface area, V= The volume of solution, and h= Thickness of the diffusion layer.

In a single component particulate system, the Hixson-Crowell cube root law explains the process of dissolution in terms of mass as described below[14]

$$W_o^{1/3} - W^{1/3} = Kt$$

Where Wo and W represent the initial and final weight of the powder after time t respectively, and K denotes the Hixson Crowell rate constant which is a product of dissolution rate constant, saturation concentration, and density.

Sometimes, many efforts to improve the solubility of the drug by the formation of salts and complexation or by co-crystallization methods, or by use of novel formulation strategies are not able to overcome the bioavailability issue due to low solubility[15]. The weak thermodynamic solubility may be the reason for poor dissolution behavior that results in insufficient drug exposure and hence low bioavailability after oral administration. Hence an early thermodynamic solubility assessment is desirable, which should be supported by apparent dissolution data. Therefore, apparent dissolution can be defined as dissolution rates from non-disintegrating compacts exposing a fixed surface area to a given solvent medium. The dissolution is based on the hydrodynamic boundary layer surrounding the solid and is greatly affected by the type of flow, described by Reynolds number[1,16].

Dissolution is explained with the classic theories of the diffusion layer model, Danckwert's model, and the interfacial barrier model.

The diffusion layer model states that the formation of a stagnant layer occurs around the solid from where the dissolution happens due to sink condition and the rate-limiting step is the dissolution. This entire process is described by Noyes Whitney and Hixson Crowell equations[17].

Danckwert's model states the eddies or packets from the agitating fluid of the dissolution medium when reaches the solid-liquid interface, absorb the solute by diffusion, and bring it to the bulk of the solution. In this continuous process, solute diffusion happens continuously by the new packets of the agitating fluids and thus the solid surface dissolves with time; hence, the theory is called surface renewal theory[18].

In the interfacial barrier model, mass transport is the rate-determining step of dissolution. An equilibrium establishes at the interface of the solid and liquid. Hence an intermediate concentration exists at the interface due to the solvation of the solid and

this model defines dissolution as a function of solubility rather than diffusion[19].

Hence the process of drug going into solution from the dosage form through *in-vitro* testing needs the simulation of exact process that a dosage form encounters in the biological environment.

Parameters relevant to dissolution testing
Biorelevant media for *in-vitro* dissolution

Biorelevant media simulates the gastrointestinal fluid during a fed and fasted state. Hence *in-vitro* dissolution in biorelevant media helps in the qualitative forecasting of the formulation and effects of food on dissolution. It can accurately simulate the pharmacokinetic profiles of the drug following oral administration. Hence it can have a great impact on optimizing the dosing conditions and product formulation[20&21]. Biorelevant media closely mimic the *in-vivo* condition *in-vitro* way. The composition of the simulated body fluids is capable to maintain the same pH, osmolarity, enzyme, or surfactant content as per the real body fluids. Few biorelevant media and their compositions are listed in table 1. Hence dissolution testing in biorelevant media can be used to assess bioequivalence and also during the assessment of post-approval formulation changes for certain kinds of drugs[24-25].

Table 1: Biorelevant dissolution media

Biorelevant media and composition		**References**
Fasted State Simulated Intestinal Fluid (FaSSIF) pH 6.5		(22)
Sodium taurocholate	3mM	
Lecithin	0.75mM	
Sodium Hydroxide	0.174g	
Sodium dihydrogen phosphate	1.977g	
Sodium chloride	3.093g	
Purified water qs	500mL	
Fed State Simulated Intestinal Fluid (FeSSIF) pH 5		(22)
Sodium taurocholate	15 mM	
Lecithin	3.75 mM	
Sodium Hydroxide(pellets)	4.04 g	
Glacial Acetic Acid	8.65 g	
Sodium chloride	11.874 g	
Purified water qs.	1000 mL	
Fasted State Gastric Fluid (FaSSGF) pH 1.8		(23)
Sodium chloride	2 g	
Hydrochloric acid concentrated	3g	
Triton X 100	1 g	
Deionized water qs ad	1 L	
Fed State Simulated Intestinal Fluid (FeSSIF) pH 5		(23)
Sodium taurocholate	15 mM	
Lecithin	3.75 mM	
Sodium Hydroxide(pellets)	4.04 g	
Glacial Acetic Acid	8.65 g	
Sodium chloride	11.874 g	
Purified water qs.	1000 mL	

Hydrodynamics

Dissolution is a mass transfer process that is influenced by thermodynamics and hydrodynamics. As the mass transfer is a convective or a diffusion process, hydrodynamics plays an important role to describe these processes. As per Noyes Whitney Nernst, and Brunner's equation, the boundary layer around the solid surface is the hydrodynamic boundary layer, which is greatly affected by the type of laminar or turbulent flow around it. When there is a change in the flow pattern, the momentum of the particle changes, and flow approaches turbulent, and that condition is described by Reynolds number. It is observed that separation from the curved surface from the dosage form occurs more rapidly from a laminar boundary layer than a turbulent one. Hence, a disturbance in the laminar and turbulent boundary layers affects the dissolution. If the flow exceeds at the close surface of the particle surface, the laminar flow turns turbulent and exceeds Reynolds critical value and that will dissipate as eddies[14,26]. If eddies are formed it enhances the mass transfer in the dissolution. This happens in the GI tract as a result of short bursts of motor activity and renders a sudden surge of flow. A cascade of energy thus happened when turbulences are created and transmitted from the larger eddies to the smallest eddies. The dissolution rate is also affected by the generation of the local fluid velocity to the dissolving surface. Local fluid velocities are present inside compendial dissolution devices from fixed flow rates which is difficult to predict. Computational fluid dynamics is used nowadays to analyze and solve problems of fluid flow associated with fluid mechanisms. The influence of various factors like the velocity of the fluid, rate of flow, the position of the tablet, rate of shear, the shape of the paddle, and formation of eddies can be studied to identify the critical factors affecting dissolution and its measurements[26-28].

***In-vitro in-vivo* correlation (IVIVC)**

IVIVC establishes a relation for dissolution and *in-vivo* execution of the drug product and thus serves as a quality control tool in drug product development. This correlation generates a mathematical relation that connects the *in-vitro* property, primarily dissolution of a dosage form with a relevant in-vivo response like plasma concentration of drug or the amount of drug absorbed. IVIVC helps to predict a small change in the formulation that causes a change in the *in-vitro* dissolution and evaluates the change in *in-vivo* absorption. Prediction of bioavailability/bioequivalence can be done with an established IVIVC model. It also supports post-approval manufacturing changes, changes in the manufacturing site, and issues associated with individual lots of manufactured products [29-32]. There are five different levels of IVIVC – Level A, B, C, D, and multilevel C. Level A correlations are considered for biowaivers, where the product shows a point-to-point relationship of their in-vivo and *in-vitro* data for a minimum of three formulation batches. The correlation can be applied by using deconvolution and convolution techniques[33].

In a recent study, Shleghm *et al* (2021) has established a correlation between the pharmacokinetics of the active metabolite of amiodarone to its *in-vitro* release data. Wagner-Nelson method was used to explain the monoexponential disposition process of the drug and its metabolite fraction in plasma[34].

Physiologically Based Pharmacokinetic (PBPK) Modeling

In the recent decades in silico simulation models specially PBPK models have established themselves as a significant analytical tool in understanding drug absorption from a dosage form and establishing IVIVC and the approval of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs)[35]. These models provide a mechanistic framework through which drug exposure in human can be predicted. They are beneficial in the development of generic drug products as it takes less time and effort. These models can extrapolate plasma concentration-time profiles from the *in-vitro* dissolution data thus supports biowaiver application and identifies the critical parameters affecting drug absorption from the dosage form. One such versatile application software approved by US FDA is GastroPlus™[36,37]. Computer simulation also helps to address the issues of dissolution of active metabolites and their pharmacokinetic effects, hence the bioavailability of the drug. The optimized dosage form obtained from *in silico* mathematical model can be explored to predict bioequivalence through this PBPK

modeling. Therefore, assessment of the impact of variations in dissolution conditions and the consequence of the in-vivo performance of the drug can be predicted from this model. Thus it can help the research and development group in the translation *of in-vitro* and *in-vivo* data at the early stage of drug development[38].

FDA regulation on dissolution

In-vitro dissolution test sets the support for fixing requirements of the test, methodology, and acceptance criteria for any dosage forms to allow the release of the batch into the market. It also helps to identify several key physical characteristics of the drug product like shape, particle size distribution, crystal form, etc. The adopted manufacturing procedures have a great impact on these properties of the drug product and hence the solubility and dissolution. Hence it has become a routine quality control test for product specification, batch release, and estimation of shelf life of the product. The current regulatory perspectives on dissolution are presented in section 21 CFR 320.24(b)(5), and section 21 CFR 314.50(d)(1)(ii)(a) [39-41].

The guidance documents give information on the establishment of the dissolution test method, and fixation of dissolution specifications. The guidance characterizes the dosage form based on a single point or multipoint dissolution testing. The documents clarify the requirements for IVIVC and biowaivers. The guidance for bioequivalent or bioavailability studies requirements are associated with post-approval changes and thus dissolution tests are used as quality control for the dosage form and also as a replacement for Bioequivalence (BE) test [42].

To establish a dissolution method, high importance is given to the solubility profile, pKa, and the dissolution characteristics of the drug product[43]. In selecting the dissolution technique and requirements, the permeability of the drug or octanol/water partition coefficient calculation can be useful[44]. Dissolution requirements are developed in the Office of Pharmaceutical Science (OPS) in consultation with biopharmaceuticals and Chemistry Manufacturing Control (CMC) review staff.

For a specialized dosage regimen like transdermal, semisolid, and novel delivery systems the dissolution should be carried out in specific dissolution apparatus as mentioned in table 2 at specified compendial conditions.

More emphasis on dissolution has been placed on generic products and post-approval changes. A comparison of dissolution profiles under suitable test conditions can precisely characterize the products. Calculation of the dissimilarity and similarity factors f1 and f2 can be evaluated either for i) pre and post-change of the product or ii) comparisons of different strengths of products of a manufacturer or iii) comparison among different manufacturers of BCS class I drug products, thus can signal the bioequivalence of the products[46].

$$f1=\left\{\frac{[\sum|Rt-Tt|]}{[\sum Rt]}\right\}*100$$

$$f2=50Xlog\{\left[1+\left(\frac{1}{n}\right)\sum(Rt-Tt)^2\right]^{-0.5}X100\}$$

Where Rt= Reference standard dissolution at different time points and Tt= Test product dissolution at different time points.

Table 3 represents a summary of the regulatory requirements at pre-approval state on immediate-release (IR) or Modified release (MR) products for both new drug and generic drugs.

For post-approval changes, the requirement follows a comparison of dissolution profile and Bioequivalence study if IVIVC is not established.

Table 2: USP Dissolution testing apparatus

USP apparatus no	Name of the apparatus	Drug product Evaluated	Reference
I	Rotating basket	Tablets.	(45)
II	Paddle	Tablets, capsules, suspensions, modified release dosage forms.	
III	Reciprocating cylinder	Extended-release products.	
IV	Flow cell	Low water-soluble drugs.	
V	Paddle over disk	Transdermal drug products.	
VI	Cylinder	Transdermal drug products.	
VII	Reciprocating disk	Extended-release products.	

Table 3: Regulatory requirements at pre-approval state on immediate-release (IR) or Modified release (MR) products

Type of Drug Product	Regulatory requirements	References
Immediate Release (IR)		(47,48)
New Drug	Bioavailability study	
Generic drug	For BCS I- Dissolution For BCS II, III, and IV – Dissolution (Lower dose) and Bioequivalence study (higher dose**)**	
Modified release (MR)		
New Drug	• Bioavailability study for each strength • Food effect study and Multidose study	
Generic drug	• For Higher dose- Bioequivalence study and food effect study • For lower strength comparative dissolution profile (f2) in three dissolution media	

Biopharmaceuticals Classification System (BCS) and Biowaivers to set dissolution specification:

BCS classification system provides a new perspective on pharmaceutical dissolution and justifies the application for biowaivers [49-51]. The criteria for BCS guidance for biowaivers are listed in table 4. Biowaivers criteria for IR and MR products as per guidance are listed in table 5.

A dosage form is said to be efficacious when the drug gets extracted from the dosage form in the surrounding media and undergoes dissolution. This multistep process influences absorption of the drug into the systemic circulation and hence the overall bioavailability of the drug. The fundamental process of drug release from a dosage form is to develop an in-*vitro* method for dissolution which can characterize the biopharmaceutical factors associated with the formulation. Therefore, the dissolution test becomes a pivotal analytical test used for the evaluation of dosage form. It helps to detect physical changes in the drug and drug product. It assists to optimize the level of factors associated with product manufacturing. Therefore, the development of a robust and reproducible test method will be able to identify any key changes that affect the product performance. It should also be capable to identify the differences between test and reference formulations or different batches of test formulations. The key parameters such as type of apparatus, selection of dissolution media, and rate of agitation must be evaluated for the test products. During the early phases of the drug development process, to establish the formulation efficacy, *in-vitro* dissolution testing strengthens the product performance. Thus, agency guidelines are generated for dissolution conditions, validation, quality control processes, which further support Scale-up post-approval changes, allow application for biowaivers, guidance for BCS classification, and biopharmaceutics drug disposition. Hence, dissolution testing remains one of the most elementary least expensive quality control tools for pharmaceutical industries to assure product performance and a signal to bioequivalence. Futuristic development is focused on the possibilities to extend and improve IVIVC and make real-time release testing authenticity.

Table 4: Briefing of BCS based Biowaivers specifications

Specifications	Conditions	Reference
Drug	Highly soluble and high permeable	(50)
Dissolution Condition	Vol-900mL Media- Buffer pH-1.2, 4.5, and 6.8 or simulated gastric fluid without enzymes Apparatus - Paddle Type at 50rpm, or Basket at 100 rpm	
Limits	Dissolution ≥ 85% in 15 min and Similarity factor f2 ≥ 50	

Table 5: Criteria for biowaivers for Immediate release (IR) and Modified release (MR) products

Type of Products	Example	Limits for Dose strength	Reference
IR	Drug products of BCS class I only	• Higher-strength meets the criteria of Reference listed product • Lower strength meets the higher strength comparison criteria(f2)	(52)
MR	Extended-release products	• Lower strength meets the criteria of higher strength • Same release mechanism in the buffer of pH1.2, 4.5, and 6.8 media	

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نشـرة العلـوم الصيدليـــــة
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مراجعة موجزة عن الذوبانية فى الصيدلة - الربط بين الجوانب العلمية و اللوائح

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الذوبان هو عملية متعددة الخطوات تصف التقارب بين المذاب والمذيب والذي تتفاعل من خلاله مادة صلبة بين المراحل غير المتجانسة من المذاب–المذاب والمذيب–المذيب والواجهة بين المذاب والمذيب لإنتاج محلول ، وفي صناعة المستحضرات الصيدلانية فإن اختبار الذوبان لأشكال الجرعات الصلبة يعطي إشارة إلى قابلية تشغيل الشكل الصيدلي في النظام البيولوجي. يتم التحكم في معدل الامتصاص جزئيًا أو كليًا عن طريق ذوبان الدواء من أشكال جرعته في الجهاز الهضمي ، كما يضمن الذوبان ، باعتباره جانبًا حيويًا من جوانب مراقبة الجودة ، توحيد إطلاق الدواء من دفعة إلى دفعة ، والتوافر البيولوجي ، وتطوير أشكال جرعات علاجية فعالة. كما أنه يضمن تقييم العوامل الصيدلانية الحيوية الحرجة. ومن ثم فإن دراسة الذوبان هي تفاعل بين العلم وتطوير الملف التنظيمي لشكل الجرعه كجانب من جوانب مراقبة الجودة. تركز هذه المراجعة على العلم والعوامل ذات الصلة بذوبان الأدوية في المختبر ودوره في التنظيم الصيدلاني.