Biorelevant and Discriminatory Dissolution Tests for Design and Development of Dosage Form: A Scientific Review

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Abstract : Recently, the use of biorelevant testing conditions has become standard in the characterization of new compounds and development of formulations. They can also be used as the basis for developing appropriate quality control test, under consideration of appropriate pH, buffer capacity and osmolality. Therefore, the approach described in the present paper might be very helpful for developing predictive and discriminatory methods in early formulation development for poorly soluble drugs and which could also be adopted for QC. In vitro biorelevant dissolution tests enabling the prediction of in vivo performance of an oral dosage form. The present paper involves information about dissolution media simulating fasted and fed states especially for poorly soluble drugs, effect of food on drug release and case example of biorelevant dissolution tests for prediction of in vivo performance of diclofenac sodium from an oral modified release pellet dosage form.

Keywords **- Dissolution; biorelevant dissolution media; fasted and fed state; poorly soluble drugs; discriminatory test.**

I. INTRODUCTION

When in vitro dissolution testing is utilized to anticipate the in vivo performance of a medication, it is important that the in vitro test should mimic the in vivo conditions as intently as would be prudent. A group of researcher led by Dr. Jennifer Dressman of the J.W. Goethe University, Germany has created biorelevant gastrointestinal media that mimic the fasted and fed states. These media have been utilized to examine the solubility and dissolution attributes of a most of drugs to empower prediction of in vivo absorption behaviour[3,9,19].

For setting up IVIVC the selection of a suitable equipment and appropriate instrument parameters, the utilization of bioiologically relevant dissolution media is essential. Several number of the dissolution media given in international pharmacopeia are not sufficient for this reason. During the most recent decade, biorelevant media have been created to simulate conditions in the stomach and small intestine when suppers, that is fasted and fed state[4,18]. In the present paper, the composition of these media and case of their application to anticipating food effects from in vitro investigations will be described. In vitro biorelevant dissolution testing is helpful for qualitative anticipation of formulation and studying food effects on the dissolution and availability of orally administered drugs. It has been seen that biorelevant media can give a more precise simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid. The utilization of biorelevant media can greatly affect the pharmacokinetic studies performed to optimize dosing conditions and product formulation[9].

II. DRUG DISSOLUTION

Dissolution is the process where a substance forms the solution. A dissolution test use to measure the degree and rate of formation of solution from a dosage form, for example, tablet, capsule, gel, suspension and so on. The disssolution of a medication is significant for its bioavailability and helpful adequacy. Dissolution and drug release are terms utilized conversely. Factors which influence the dissolution of a dosage form involves the natural properties of the API (e.g., solubility, wettability, particle size, surface area, morphology, polymorphs), the composition of formulation and attributes (e.g., excipients, hardness, manufacturing process), and the dissolution strategy utilized for its assessment (e.g., apparatus, medium, test conditions, sampling, and sample analysis)[11].

Dissolution of a medication in the physiological condition of the GI tract is the essential and significant step in the absorption of orally administered pharmaceutical dosage form, as only dissolved drug can permeate the mucosa at the absorptive sites in the GI tract[4]. The process of dissolution were clarified by certain models (theories) namely

1) Diffusion Layer Model (Film Theory)
2) Danckwert's Model (Penetration or Surface Renewal Theory)
3) Interfacial Barrier Model (Double Barrier Mechanism OR Limited Solvation Theory).

1) Diffusion Layer Model (Film Theory):

It is a simplest model wherein reactive or electrical forces are not involved in a dissolution of crystal. This hypothesis/ theory includes two continuous advances: First is 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 progression is typically fast (prompt). Second is diffusion of the soluble solute from the stagnant layer to the greater part of the solution, this step is slower, thusly the rate determining step in the drug dissolution. Fick's law covers just diffusions under steady state conditions, modifying it Noyes and Whitney set up another equation

dc/dt = k(cs-cb)

Where,

dc/dt= dissolution rate of the drug

K= dissolution rate constant

Cs= concentration of drug in stagnant layer Cb= concentration of drug in the bulk of the solution at time t

Modified Noyes-Whitney's Equation:

dc/dt=DAKw/o(cs-cb)/vh
Where,
D= diffusion coefficient of drug.
A= surface area of dissolving solid.
Kw/o= water/oil partition coefficient of drug.
V= volume of dissolution medium.
h= thickness of stagnant layer.
(Cs – Cb)= conc. gradient for diffusion of drug.

2) Danckwert's Model (Penetration or Surface Renewal Theory):
This theory/hypothesis assumes that solid-solution equilibrium is accomplished at interface and mass tranport is slow step in dissolution process. The model could be visualized as a very thin film having a conc Ci which is lower than the saturation, as it is continually being presented to new surfaces of fluid having a conc considerably less than Ci. As indicated by model, the fomented liquid comprise of mass of eddies or packets that are continually being presented to fresh surfaces of solid and afterward conveyed back to bulk of fluid. Diffusion occurs into each of these packets during brief time wherein the packet is in contact with surface of solid. Since turbulence really reaches out to surface, there is no laminar boundary layer thus no stagnant film exists. Rather, surface constantly being replaced with new fluid.
The Danckwert's model is represented by equation:
Vdc/dt=dm/dt=A (cs-cb) $\sqrt{\gamma D}$
Where,
m = mass of solid dissolved
Gamma (γ) = rate of surface renewal

3) Interfacial Barrier Model (Double Barrier or Limited Solvation Theory):
The Diffusion layer model and the Dankwert's model were based on two suspicions: 1) The rate determining step that controls dissolution is the mass transport. 2) Solid solution equilibrium is accomplished at the solid/liquid interface. As indicated by interfacial barrier model, an intermediate concentration can exist at the interface because of solvation mechanism and is a function of solubility instead of diffusion. While considering the dissolution of the crystal will have an alternate interfacial barrrier given by following equation,
G = ki (Cs – Cb)
Where,
G = dissolution per unit area
Ki = effective interfacial transport constant[11].

III. COMPENDIAL DISSOLUTION MEDIA

Simulated Gastric Fluid
The conventional medium to simulate gastric conditions in the fasted state has been simulated gastric fluid (SGF) of the USP. This medium contains hydrochloric acid and sodium chloride, as well as pepsin and water, and has a pH of 1.2. In spite of the fact that the medium tends to a significant number of the characteristics of gastric juice, there are a few perspectives that could be advanced, For example, most investigations of gastric pH show that the in all cases normal gastric pH usually lies in the range 1.5–1.9. For weak acids and neutral compounds, this little distinction has no effect in the dissolution characteristics, but for very poorly weak bases, the dissolution results in compendial SGF are probably going to overestimate the in vivo dissolution rate. Further deviations from gastric physiology are the pepsin concentration, which is exceptionally high contrasted with that present in gastric juice present under fasted state conditions and the surface tension of around 70 mN/m that doesn't consider the much lower normal surface tension of human gastric liquid, which has been more than once estimated as lying in the 35-to 50-mN/m range.

Water
Water is an attractive medium that as a result of its simplicity has been broadly utilized for quality control purposes. It could even be contended that it is physiologically relevant since numerous formulations are expected to be ingested with a glass of water. Besides, in those patients with hypochlorhydria (raised gastric pH), because of aging as well as co-treatment with H2 receptor antagonists and proton pump inhibitors, water might be a to some degree appropriate medium as it generally reflects the elevated gastric pH and the low buffer capacity. However, the pH of water may fluctuate with its source, and water has no buffer capacity. Along these, for the last reason, a superior other option, which would be more biorelevant in this unique situation, is a diluted HCl/NaCl solution or a diluted acetate buffer with a last pH of around 5.

Simulated Intestinal Fluid
An most commonly utilized medium for the simulation of small intestinal (SI) conditions in the fasted state is simulated intestinal fluid (SIF), a medium that was first explained as a standard test solution in the USP over 50 years prior. The only parameter that has been changed is the pH of the medium. As it was expected that the pH in the small intenstinal tract is very close to blood plasma, the pH of SIF was at first set at 7.5. In any case, subsequent assessments of the pH in the intestinal tract revealed that a pH gradient exists within the small intestinal system, that the pH turns out to be less acidic at progressively distal areas, and that pH esteems near 7.5 must be estimated in the terminal ileum. As drug absorption during SI entry is most efficient when drug release from the dosage form occurs at proximal SI sites, the more significant pH values are those in the duodenum and the proximal jejunum. The utilization of an in vitro medium with an unsuitably high pH conversely would most likely prompt false positive outcomes,

particularly for poorly soluble, weakly acidic drugs and enteric coated dosage forms. Hence, with USP 24/NF19, the pH of the compendial SIF was updated to pH 6.8, which can regularly be estimated in the mid-jejunum.

Compendial Media Simulating the Fed State

Right now, none of the guidance or international pharmacopeias describes media to simulate food impacts. Subsequently, water SGF and SIF are still the most regularly utilized dissolution media. In any case, as referenced previously, they don't consider extra key parameters of the changing gastrointestinal condition after food intake and are in this way not helpful to estimate any food effects[4].

IV. BIORELEVANT DISSOLUTION MEDIA

Fasted State Simulated Gastric Fluid (FaSSGF)

A few endeavors have been made to improve simulation of fasting conditions in the stomach. In the vast majority of these media, specific consideration was given to the simulation of the surface tension estimated in human gastric aspirates. In any case, in these media, non-physiologically significant surface active agents, lower than physiological pH values or by a wide margin too high concentrations of pepsin or bile salts, were used. During very nearly 10 years of utilization, they were appeared to often overestimate gastric disssolution since they induce solubilization impacts greater than would be physiologically relevant. Recently, a fasted state simulated gastric fluid (FaSSGF) containing pepsin and low measures of bile salt and lecithin was created by Vertzoni et al[4]. (see Table I for composition)[4].

Table I Sample Composition for Simulating Fasted State Gastric Conditions (FaSSGF)

FaSSGF pH 1.6		
Sodium taurocholate		80 µM
Lecithin		20 µM
Pepsin		0.1 mg/ml
NaCl		34.2 mM
HCl conc.	Qs ad	pH 1.6
Deionized water	ad	1.1
pH		1.6
Osmolality (mOsmol/kg)		120.7 ± 2.5
Buffer capac		-
Surface tension (mN/m)		42.6

Fed State Simulated Gastric Fluid (FeSSGF)

In the fed state, the luminal composition in the stomach will be greatly based on the composition of the meal ingested. The perfect medium representing initial gastric conditions in the fed state should have similar nutritional and physicochemical properties to that of meal, e.g., the standard breakfast prescribed by the US FDA to studying the impacts of food in BA and bioequivalence studies, have low inter-batch variability, and be easy to prepare. It should likewise be conceivable to control the medium to simulate changes in the composition with time because of gastric secretion and digestion, if desired. Clearly, it is important to compromise a portion of these ideals to accomplish a representative yet practical medium. Two choices that approach these details are milk and Ensure® Plus. While milk was first investigated as a dissolution medium around 20 years ago, the utilization of Ensure® Plus has been built up just a couple of years back. Both standardized homogenized cows' milk with a fat content of 3.5% (entire milk) and Ensure® Plus have a similar composition to a morning meal with regarding the proportion of sugar/fat/protein. As the stability of fresh milk at 37°C is an issue, heat-treated milk must be utilized. Besides, there might be variability in the composition of milk with source and season. Thusly, when comparing drug release from different dosage forms, it is important not to switch between various brands and qualities of milk.

Fasted State Simulating Intestinal Fluid (FaSSIF)

By a progression of tests in dogs fistulated at midgut, Greenwood showed that neither SIF nor another simple aqueous buffer have composition like those found under fasted state conditions in the small intenstinal tract. As they don't enough reflect all parts of physiological conditions, dissolution rates of drugs in such media may not give great expectations of the dissolution of drugs in vivo. In addition to pH, further significant physiological components not satisfactorily addressed with these standard media are buffer capacity, bile and pancreatic secretion, surface tension, osmolality, and the volume of intestinal contents. Because of these necessities, endeavors were made to make a biorelevant medium dependent on experimental information from the literature/articles. Specifically fasted state simulating intestinal fluid (FaSSIF) was developed to simulate fasting conditions in the proximal small intenstine. In addition to a stable phosphate buffer system that outcomes in a pH representative to values estimated from the mid-duodenum to the proximal ileum. The detailed composition of FaSSIF is given in Table II[4].

Table II Sample Composition For Simulating Fasted State Intestinal Conditions (FaSSIF)

FaSSGF pH 6.5	
Sodium taurocholate	3 mM
Lecithin	0.75 mM
NaH2PO4	3.438 g
NaCl	6.186 g

NaOH	qs ad	pH 6.5
Deionized water	qs ad	11
pH		6.5
Osmolality (mOsmol/kg)		270
Buffer c		12
Surface tension (mN/m)		54

Fed State Simulating Intestinal Fluid (FeSSIF)

As in the stomach, conditions for drud dissolution in the proximal part of the small intestinal tract are greatly based on whether the drug is dosed in the fed or the fasted state. After ingesting a meal, there are changes in both the hydrodynamics and the intralumenal volume. The pH of the chime after a solid meal is lower than the intestinal fluid pH in the fasted state, while buffer capacity and osmolality show a sharp increment. As well as these variables, the sharp increment in bile output could likewise be a significant impact on the BA of a drug. Likewise, specific interactions between the drug and ingested food components may happen. A dissolution medium for simulating the fed state small intestine should reflects these elements as close as could be possible. To more reflect the key parameters of the upper small intenstine after food ingestions, a fed state simulating intestinal fluid (FeSSIF), which at least partially meets these necessities, was developed around 10 years back[20,24,25]. The detailed composition of FeSSIF is given in Table III [4].

Table III Sample Composition for Simulating Fed State Intestinal Conditions (FeSSIF)

FaSSGF pH 6.5		
Sodium taurocholate		15 mM
Lecithin		3.75 mM
CH_3COOH		8.65 g
NaCl		11.874 g
NaOH pellets		pH 6.5
Deionized water	qs ad	11
pH		5.0
Osmolality (mOsmol/kg)		670
Buffer capacity (mEq/ pH/L)		72
Surface tension (mN/m)		48

V. METHODOLOGY OF BIORELEVANT DISSOLUTION TESTING

Dissolution can be influenced by drug substance factors (solubility, permeability, dissolution rate), dosage form factors (dissolution attributes, manufacturing procedures), and the strategies utilized for its assessment (apparatus, technique, dissolution medium). To develop a biorelevant dissolution test for oral dosage forms, the physiological conditions in the gastrointestinal (GI) tract that can influence drug dissolution (Table IV) should be taken into account as per the properties of the drug and dosage form. These conditions include the properties of GI fluids (composition, volume, pH), gastric emptying (particularly for non disintegrating systems), intestinal transit, GI motility and hydrodynamic patterns, GI enzymes, and the presence or absence of food. Selection of appropriate in vitro conditions (media and hydrodynamics) that simulate the in vivo conditions can tends to the generation of fruitful in vitro–in vivo correlations (IVIVC) or in vitro–in vivo relationship (IVIVR)[5].

Table IV In Vitro and In Vivo Dissolution Parameters

Parameter	In Vitro Dissolution	In Vivo Dissolution
Media	Compendial media USP media Biorelevant media	Gastrointestinal fluids
Volume	Variable according to apparatus used and simulated condition (fasted or fed state)	Variable according to condition (fasted or fed state)
Duration	Variable according to apparatus used, dosage form and simulated condition (fasted or fed state)	Variable according to dosage form and condition (fasted or fed state)
Hydrodynamic	USP Apparatus 1, 2, 3, 4	Gastrointestinal motility
Location	Constant*	Variation with time
Amount of drug	Constant in closed systems Decreases in open system	Decreases as drug is Absorbed

* Unless media change occurs (i.e., USP Apparatus 3 and 4)

Medium Selection

Unlike to compendial media (conventional buffers, USP media), biorelevant media should represent the gastric and intestinal condition in fasted and fed states. In these media, several properties, for example, pH, the presence of bile, the surface tension and the buffer capacity of the GI fluids are must have to consider. Bile salts and phospholipids may significantly affect the in vivo dissolution and transport in the small intestinal tract of poorly soluble drug substances. For cases in which lipid-based formulations were characterized, lipolysis could be accounted for by the addition of lipolytic degradation products to the dissolution media to simulate the fed state, since they play a significant role in the solubilization limit of the medium[4,5].

Hydrodynamics

In in vitro trials, hydrodynamics reflects the design of the dissolution apparatus, the agitation force, volume of the dissolution medium, the flow, and viscosity of the medium; and practical issues, for example, the position of the dosage form during the investigation. The selection of the most suitable hydrodynamics is important for the advancement of a biorelevant dissolution technique. Generally, four fundamental kinds of dissolution apparatus are utilized in the development of biorelevant dissolution testing:

• Rotating basket (USP Apparatus 1)
• Rotating paddle (USP Apparatus 2)
• Reciprocating cylinder Bio-Dis (USP Apparatus 3)
• Flow-through cell (USP Apparatus 4) (closed or open system)

Modifications of these apparatus and new mechanical assembly are additionally proposed in explicit cases, for example, the dissolution stress-test device for dosage forms that demonstrate sensitivity to physical stress events during gastrointestinal transit. USP Apparatus 1 and 2 (referred to as closed systems) are the most utilized due to they are comparatively simple, powerful and robust and are sufficiently standardized. They are generally the principal choice for solid dosage forms and quick and extended/prolonged release dosage forms, however they are not suitable for all drugs and dosage forms. Issues with homogeneity in the vessel, dispersion in the vessel with areas of high concentration, or agglomeration can show up. Paddle and basket speeds of 50–100 rpm and 50–150 rpm, respectively, are generally utilized for the establishment of IVIVCs; examination of lower agitation speeds has been proposed for better representation of in vivo hydrodynamics. USP Apparatus 3 and 4 are suitable for drugs and dosage forms where dissolution at different pH levels or consecutive changes of media are expected to mimic in vivo dissolution(i.e., controlled release formulations). For Apparatus 3, dip rates of 10–15 dpm have been proposed for tests under fasted-state conditions. Apparatus 4 offers a multiple cell types and can be especially useful for particular drug and dosage forms (i.e., multiparticulate dosage forms, suspensions). It can work as either an open or closed system, which is significant for poorly soluble drugs. Time period of exposure to the different media and relative flow rates should be intended to accomplish a balance between the volumes of GI fluid and the physiological residence times in the GI lumen. Flow rates in the range of 4 and 8 mL/min have been proposed for tests that simulate fasted and fed state conditions[5,23].

Drug Substance and Dosage Form Considerations

For IR dosage forms containing BCS Class II or IV drugs, solubilisation of acive pharmaceutical ingredient and formulation properties have a considerably impact on in vitro and in vivo dissolution. In vitro dissolution profiles in biorelevant tests (biorelevant media in combination with biorelevant hydrodynamics according to drug formulation properties) should be assessed during development, and afterward an IVIVC or IVIVR can be set up between the in vitro dissolution and in vivo performance. The

biorelevant dissolution test should be designed by in accordance with the release pattern of the drug formulation and the simulated fasted or fed state conditions. Biorelevant dissolution testing was demonstrated for the forecast of both in vivo behavior of lipophilic, poorly water-soluble drugs[5,21,22].

VI. EVALUATION AND SELECTION OF BIO-RELEVANT DISSOLUTION MEDIA FOR A POORLY WATER-SOLUBLE NEW CHEMICAL ENTITY

It is always a challenge for formulators and investigators/analyst to build up an appropriate dissolution technique for a poorly water-soluble drug 1. Solubility improvement/enhancement of the poorly water-soluble drug utilizing an appropriate medium is normally required so as to obtain significant experimental information. Adding a surfactant to the medium is a typical method to achieve higher solubility in the development of dissolution technique. As a general rule, sink conditions are required for most dissolution studies 2. The purposes behind sink conditions can be: (a) the interpretation of the mechanism and pattern of drug release from dosage form is a much simpler under a sink condition than a non-sink condition; (b) that in most cases the dissolved segment of the drug will be absorbed into the blood circulation system rapidly, and it is believed that the drug release will in all probability happen under sink conditions in vivo. Generally, a sink condition necessitates that the drug solubility be ten times the total concentration of drug in the vessel, or possibly more prominent than three times. The Hixson–Crowell cube root law applies to dissolutions under sink conditions. In few of cases the solubility is equivalent to the theoretical concentration of drug in the vessel, which is called non-sink conditions. A negative square-cubic root equation was obtained by considering the non-sink condition as an uncommon instance of the Hixson–Crowell law. On the other hand the solubility is lower than the total amount of drug per volume of the medium, an over-saturated condition will be gotten and incomplete dissolution will be observed. Since it isn't desirable to have an incomplete dissolution of drug, the over-saturated condition is certainly not a typical choice in the dissolution assessment. In any case, for a bioenhanced formulation, the solubility of the formulation may not be equivalent to the bulk drug, so utilizing solubility obtained from bulk drug as the standard for choosing a dissolution medium should be reconsidered. For most nonionizable and poorly water-soluable drugs, pH of the dissolution medium has less impact on dissolution, but surfactants added to the dissolution medium will enhance drug solubility fundamentally. A colloid systen, which contains surfactant micelles, will help keep up an poorly water-soluble drug solubilized in an aqueuos medium. The dissolution of the drug can be adjusted by changing the surfactant concentration in the medium. Generally nonionizable and poorly water-soluble drugs, pH of the dissolution medium has less impact on dissolution, but surfactants added to the dissolution medium will enhance drug solubility significantly. A colloid system, which contains surfactant micelles, will help keep up an poorly water-soluble drug solubilized in an aqueous medium. The dissolution of the drug can be adjusted by changing the concentration of the surfactant in the medium. Concentration can be a key issue in the development of an effective formulation for a poorly water-soluble drug.

The surfactant media enhance the apparent intrinsic dissolution rate of new chemical substance linearly because of an increase in solubility. A low concentration of surfactant in the medium has a superior bi relevence than higher concentrations of the surfactant in media for the pooly water-soluble drugs. This recommends making sink conditions (based on bulk drug solubilities) by utilizing a high concentration of a surfactant in the dissolution medium may not be an appropriate way to developing a bio relevant dissolution technique for a poorly water soluble drugs[13,15,17].

VII. IN VIVO - IN VITRO CORRELATIONS FOR A POORLY SOLUBLE DRUG

Whenever demonstrated to be predictive of in vivo conduct, the dissolution test may diminish the requirement for costly human bioequivalence studies (Shah and Lesko, 1995). By understanding the connection between physico-chemical properties of the drug substance and physiological parameters significant for dissolution and absorption it may be conceivable to characterize the most appropriate dissolution test conditions. Compendial dissolution media frequently fail to yield IVIVCs for class II drugs on the grounds that significant physiological parameters are not considered. While optimising composition of the medium the physiological importance should consistently be of prime thought. So as to more readily predict in vivo behaviour, Galia et al. (1998), invented two biorelevant media, FaSSIF and FeSSIF, representing to fasted and fed states of the upper jejunum, individually. The two media contained physiologically relevant concentrations of pure bile salt and phosphatidylcholine. However, the fed state medium does not represent the presence of digested lipids in the intestinal tract and may tends to underestimates of dissolution for highly lipophilic drugs[13,14,17,27,28].

BCS Class II compounds have an in vivo absorption limited principally by drug dissolution in the gastrointestinal (GI) tract. During early drug development, it would be very valuable to have a predictive in vitro dissolution test that correlates with in vivo absorption. Such a test could be utilized when screening new formulations as well as changes in existing formulations with regards to their effect on bioavailability. BCS Class IV compounds are additionally characterized by low water solubility, but with limited permeability across the gut wall. Correlation of in vivo information with dissolution testing is therefore even more uncertain than for Class II compounds, however the presence of a correlation could demonstrate similarly as useful in formulation development[29,30,31]. Correlations between in vitro dissolution tests and in vivo absorption might be almost certain when physiologically relevant conditions are utilized. Generally, it is believed that BDM might have the option to all the more precisely speak to the physiological conditions present in vivo compared with more simple media[15].

VIII. REGULATORY PERSPECTIVES

Biorelevant in vitro performance testing keeps on developing with our increasing understanding and desires from in vitro predictive tests and can serve as a connection between the dosage form and it's in vitro and in vivo performance. Biorelevant approaches can be utilized as learning devices for characterizing the impact of formulation factors on dispersion, drug precipitation, dissolution and stability, and potential interactions between APIs, dosage forms, excipients and the in vivo condition. Understanding the components affecting bioavailability and optimizing the dosage form for improving bioavailability and other different aspects of dosage form quality continue to be significant objectives of our pharmaceutical community.

Biorelevant in vitro release testing may likewise give great synergy with QbD in process development where there is an emphasis on connecting critical quality attributes and in vivo product performance. Clinically relevant dosage form particulars are established when linking the critical quality attributes of a dosage form to its in vivo performance. The regulatory value of in vitro release/dissolution testing is its ability to characterize drug products and involve in decision making including guaranteeing quality

assurance through a linkage to batches utilized in clinical studies, data on batch to batch consistency, and deciding differences in dosage forms, in vitro dissolution testing, as mentioned in guidance documents, can serve as a surrogate for bioequivalence studies to assess effect of post-approval changes and comparison of products from various sources. There are at present no official regulatory definitions or necessities for utilization of biorelevant media in vitro release testing. Advantages of biorelevant in vitro testing as a learning and predictive tool for dosage form characterization, design and performance are recognized. Bioequivalence assessments, by definition are regulatory decision making tools with existing bioequivalence criteria.

IX. EVALUATION OF DISSOLUTION MEDIA

Biorelevant testing may prompt better understanding of in vivo performance particularly for low solubility drugs (BCS Class II and IV drugs) and might be progressively significant in the present drug development condition where the scene has been moving to development of a more prominent number of poorly soluble drugs and highly sophisticated dosage forms. Biorelevant approaches can start from utilizing physiologically relevant pH values and standard dissolution apparatus as mentioned in guidance for industry documents to more complicated media to mimic in vivo conditions, for example, food impacts and alcohol dose dumping to combine biorelevant media with novel innovations or novel uses of existing technologies that enable isolated as well as composite evaluations of drug release. For generic immediate release or delayed release oral dosage forms, often an current FDA or USP dissolution method is suitable for ensuring drug release, so method development practices with or without biorelevant media and no need of apparatus. The Office of Generic Drugs additionally tries to achieve consistency in choosing dissolution strategies for generic extended release dosage forms; however, it might be important to develop these methods for extended release products dependent upon the situation. The various types of conditions can be assessed during the development of a dissolution method (type of apparatus, addition of surfactant, speed of stirrer, pH, volume, medium), and selecting biorelevant options may facilitate understanding and in this way development of a strategy fit for achieving an IVIVR or IVIVC[16,32].

X. DISCRIMINATORY DISSOLUTION MEDIA

Discriminating Power of a Method

The discriminatory power of the dissolution method relies upon the method's capacity to recognize changes in the performance of drug products. Preferably, the dissolution test conditions should distinguish/discriminate product changes that may influence biopharmaceutical product performance. However, except if an IVIVR or IVIVC exists for the product, variations in dissolution behaviour may or may not reflect variations in the in vivo performance of product.

To decide whether a dissolution method can discriminate the effect of product changes, the method needs to be challenged. The most widely recognized approach to challenge the discriminatory power power of the method is to test drug products manufactured with differences as a result of changes in the characteristics of the API (e.g., particle size, bulk density, crystal form), composition of drug products (e.g., drug loading, excipients identity/type and levels), manufacturin procedure of dosage form (e.g., type of dosage form, equipment variables as under or over granulation), and impacts of aging (e.g., humidity,temperature). These experiments should be designed dependent upon the situation , dependent on a DoE, in consultation with the galenist, scientific expert, chemist and analytical specialist. At this stage the coordination between the expertises is clearly a key factor. In this way, the change in the drug product can be assessed versus the change in the dissolution information. If the information show a quantifiable difference for the key variables, at that point the method might be considered a discriminatory test for critical manufacturing variables. Any differences in the dissolution rates because of the selected variables may or may not have effect on the in vivo product performance[33].

The dissolution method will in general tends to evolve depending upon its utility for drug development and should be re-evaluated and optimized (if necessary) when human bioavailability information are available from the clinical formulations. During further method development, optimization, and before selection of the final method, the formulations used in the late stage clinical studies are tested utilizing various medium compositions (e.g., pH, ionic strenght, surfactant composition). The impact of hydrodynamics on the formulations should also be assessed by altering the agitation speed of the dissolution apparatus. If the non-bioequivalent batch is found during a bioequivalency study, the dissolution methodology should be additionally changed to allow differentiation of non-bioequivalent batches from the bioequivalent batches by dissolution specification limits, if possible. This would assure batch-to-batch consistency within a range that ensures comparable biopharmaceutical performance in vivo. When a discriminating method is developed, a similar strategy should be utilized to release formulation batches for future investigations, if possible. The biorelevant method may not generally be feasible, and may or may not be equivalent to the QC method because of the scope and limitations of such a method[35,36,37].

XI. DEVELOPING DISCRIMINATORY DRUG DISSOLUTION TESTS AND PROFILES

Drug release (or dissolution) testing is an analytical procedure used to analyze release pattern of drugs in pharmaceutical products, generally solid oral dosage forms, for example, tablets and capsules. This test takes up its advantages from the way that if a drug from dosage form is to create its effect, it must be released from the product and generally should be dissolved in the gastrointestinal (GI) tract fluids. Thus, a drug dissolution test might be considered as a indication of potential drug release and absorption qualities of a dosage form not only in humans but also in animals. Therefore, a dissolution test is frequently considered as a surrogate for the evaluation of accessibility of drugs in the body, generally named bioavailability. This connection of dissolution (in vitro) to drug release in the body (in vivo) as generally determined by bioavailability assessment is officially termed as in vitro–in vivo relationship (IVIVC).This idea of IVIVC, in a quantitative and additionally subjective format, provides the reason for the evaluation of quality of the dosage forms. Thus, the dissolution test isn't just a process for design and development of dosage forms but at the same time is broadly utilized as a quality control strategy as a result of this in vitro–in vivo association.

To reflect absorption behaviour of drug in vivo or, more precisely drug release in vivo, drug dissolution tests are conducted in vitro, mimicking the physiological condition of the GI tract.The GI tract condition is represented by gentle stirring of dosage forms in aqueous based solutions, for example, 0.1 N HCl or buffers having pH values in the range of 4–7.5.The cumulative percent of a dissolved drug at various time points is estimated and may be accounted for as a plot of % drug dissolved versus sampling times.The coming about graph is ordinarily reffered to as a "dissolution profile"and gives a methods for examination with in vivo

drug release to build up absorption attributes of drugs from dosage forms in humans. Further, because of the previously mentioned in vitro–in vivo association, it is commonly considered that if a dissolution profile of a test product matches that of a reference product, at that point the test product should act comparably to the reference product in vivo (i.e.,both will have comparative bioavailabilities and will be considered as bioequivalent). On the other hand, if the profile of the test product is different in relation to that of the reference product, then the test product may behave diversely in humans. This practice of describing dissolution results or profiles is usually referred to as giving discriminating dissolution profiles, and the test as a discriminatory test. That is, a dissolution test is relied upon to separate whether dissimilar products are from different manufacturing batches of a similar products or from various products, for example, generics. It is generally imperative to take note of that the term of "discrimination"should be identified with and dependent on closeness or uniqueness of in vitro outcomes to in vivo outcomes as it were. It is further important to take note of that a test should possibly be considered as discriminatory if dissolution profiles obtained are different for different in vivo profiles (i.e.,products should be bioinequivalent). If dissolution profiles are obtained differently for product with the equivalent or dissimilar formulation properties but with similar in vivo characteristics, they may not be considered as discriminatory profiles, and the test that produces such profiles ought not be considered as an discriminatory test. The differences in profiles for dosage forms having equivalent release attributes in vivo (i.e., for bioequivalent products) should be considered as an expected and acceptable variation in dissolution results from acceptable dosage forms with no negative therapeutic outcomes. Such contrasts in dissolution profiles should provide the basis of setting tolerences for quality control purposes for adequate dosage forms and not be predicted as a discriminatory test.

However, there seems, by all accounts, to be some confusion in the literatures in regards to the expression "discriminating profiles", which is utilized for profiles from both bioinequivalent and bioequivalent formulations. That is, differences in profiles dependent on differences because of some formulation or manufacturing attributes with no reference to in vivo drug release attributes are often temed as discriminatory profiles. This may not be an exact understanding of the idea of discriminating profiles[34].

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XII. REFERENCES

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