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Dissolution: A Promising Tool in Drug Delivery

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Till date, the emphasis in dissolution has been only limited to calculating percent drug release as specified in different pharmacopoeias. But, now dissolution testing has become one of the most important tests in quality control of dosage forms. These *in vitro* dissolution studies can also be used to ensure acceptable *in vivo* performance. Therefore, it is desirable to develop dissolution testing that can assess the ability of a dosage form to release the drug completely and simultaneously indicate the drug's performance *in vivo*. The present review gives an insight about the various factors which must be taken into consideration to get perfect *in vitro in vivo* correlation.

The absorption of an orally administered drug depends upon the dissolution of drug into gastrointestinal tract (GIT) fluids and intestinal membrane permeation. Dissolution is a process by which a solid of only fair solubility characteristics enters into solution. Dissolution is defined as "taking up of substance by a liquid with the formation of homogenous solution". Dissolution testing has become one of the most popular tests in the quality control of dosage forms. These tests become especially more important if dissolution is the rate limiting step in drug absorption. In case of hydrophobic drugs (e.g. phenytoin, griseofulvin, spironolactone) dissolution is the rate limiting step. Thus, lack of adequate aqueous and lipid solubility of a drug often becomes a crucial obstacle in the development of oral dosage forms, as many drug candidates in the developmental stage exhibit high lipophilicity and extremely limited aqueous solubility. As a result of this poor dissolution behavior *in vitro*, *in situ* and *in vivo* absorption studies are mostly restricted.

OBJECTIVE OF DISSOLUTION STUDIES

In pharmaceutical industry, dissolution is used to ensure acceptable *in vivo* performance as well as to ensure that each batch confirms to product specification throughout the shelf life of dosage forms. The goal of dissolution testing is to assure the pharmaceutical quality of the product. By pharmaceutical quality we mean not only the ability to manufacture the product reproducibly and to ensure that it maintains its release properties throughout the shelf life, but also that the product's biopharmaceutical characteristics that is rate and extent of absorption can be relied on. It would therefore be desirable to develop dissolution tests that can assess the ability of the dosage form to release the drug completely and to simultaneously indicate how the product will perform *in vivo*. Dissolution has basically been used as quality control tests and for biopharmaceutical consideration.

Quality control tests:

Current pharmacopoeial dissolution tests were developed with the aim of studying the physical properties of the dosage form. The overriding concern for the quality control is to use conditions under which 100 % of the drug can be released. Important considerations are the reliability and reproducibility.

Biopharmaceutical considerations:

The cost of pharmacokinetic studies have increased dramatically in recent years. Anatomical and physiological differences in animal models and humans have lead to lack of correlation between results. Furthermore ethical considerations demand that the number of animals used in research be minimized. Thus there is an increasing interest in the development of dissolution tests that closely simulate the environment in the GI tract so as to establish perfect *in vitro in vivo* correlations[1].

APPLICATIONS OF DISSOLUTION TESTING

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In vitro dissolution test, is the single most important test procedure with adequate discriminating power for the purpose of quality control for batch to batch performance. In this study the percentage of drug dissolved at a set of predetermined sampling time points is measured under stated *in vivo* conditions. Early sampling time points are included to detect possible dose dumping, the middle time points help define the release profile and the later time points ensure that most of the dose goes into the solution. These quality control functions of the *in vitro* dissolution testing don't necessarily assume that the dissolution tests provide information concerning the *in vivo* behaviour of the batch but *in vitro* dissolution studies can be interpreted in terms of the *in vivo* performance of the batch. When a relationship has been established between *in vitro* dissolution characteristics and the *in vivo* performance of the batches in terms of bioequivalence it is described as *in vitro- in vivo* correlation[2].

***In vitro-in vivo* correlation:**

To justify the specification limits of the *in vitro* dissolution test, an attempt should be made to establish a meaningful correlation between *in vitro* release characteristics and *in vivo* bioavailability parameters. A predictive mathematical model describing the relationship between an *in vitro* property of an extended release dosage form (usually the rate or extent of drug dissolution or release) and a relevant *in vivo* response, e.g., plasma drug concentration or amount of drug absorbed, has been designed.

In vivo dissolution indicates the process of dissolution of drug in the gastro-intestinal tract. *In vitro* release indicates drug dissolution (release) from a dosage form as measured in an *in vitro* dissolution apparatus. *In vivo* release means *in vivo* dissolution of drug from a dosage form as determined by deconvolution of data obtained from pharmacokinetic studies in humans (patients or healthy volunteers).

The different levels of correlation are; Level A correlation which means a predictive mathematical model for the relationship between the entire *in vitro* dissolution/release time course and the entire *in vivo* response time course, e.g., the time course of plasma drug concentration or amount of drug absorbed. Level B correlation is a predictive mathematical model for the relationship between summary parameters that characterize the *in vitro* and *in vivo* time courses, e.g., models that relate the mean *in vitro* dissolution time to the mean *in vivo* dissolution time, the mean *in vitro* dissolution time to the mean residence time *in vivo*, or the *in vitro* dissolution rate constant to the absorption rate constant. Level C correlation indicates a predictive mathematical model of the relationship between the amount dissolved *in vitro* at a particular time (or the time required for *in vitro* dissolution of a fixed percent of the dose, e.g., T %) and a summary parameter that characterizes the *in vivo* time 50 course (e.g., C or AUC_{max}).

In order to accomplish this, a number of techniques may be employed. These include, in order of decreasing predictive power: Comparison of the *in vitro* dissolution curve of the product with the *in vivo* dissolution curves generated by deconvolution of plasma level data or by other appropriate methods. Comparison of the mean *in vitro* dissolution time of the product to either the mean *in vivo* residence time or the mean *in vivo* dissolution time of the product derived by using the principles of statistical moment analysis. Comparison of the mean *in vitro* dissolution time to one mean pharmacokinetic parameter, e.g. T_{max}.

Other approaches are acceptable especially if the above methods fail to demonstrate a correlation. Examples of other approaches include demonstrating bioequivalence of the proposed formulation to formulations with dissolution profiles at the upper and lower limits of the specification, or alternatively, the specification limits may be derived from the spread of *in vitro* dissolution results of batches used in bioavailability testing. The choice of approach should be justified by the applicant.

VARIOUS APPROACHES USED TO ENHANCE DISSOLUTION RATE

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industries. A worldwide effort is being made to improve their solubility. The various approaches which are being used can be broadly categorized as chemical approach which consists of the prodrug approach and conversion of the drug to salt form or its polymorph exhibiting higher solubility[3,4]. The other approach is the formulation approach which consists of methods like colloidal carrier system (liposomes and microparticles)[5], use of surfactants/ cosolvents[6,7] and use of complexing agents such as cyclodextrins[8-11].

Recently, a newer technique i.e. Plasma irradiation has been investigated as a possible technique for increasing the dissolution rate of poorly soluble drugs. Plasma is a partially ionized gas, which contains an equal number of positive and negative ions and unionized neutral species such as molecules, atoms and radicals. It is created by subjecting a

gas (e.g. O_2) to a radio frequency potential in a vacuum chamber and it leads to production of electrons, which are accelerated by electric field and collide with neutral molecules leading to the production of free radicals, atoms and ions. In case of oxygen plasma, O_2 can be excited from ground state to higher electronic levels leading to formation of O_2^* and $O_2^{\cdot}$. Further dissociation reaction leads to the production of oxygen atoms and ions such as O^- and O^+. These oxygen radicals then react with the chemical groups on the surface of an exposed sample during plasma treatment which leads to the formation of O_2 containing functional group such as hydroxyl, carbonyl, and carboxyl group. The production of these oxygen atoms containing functional group leads to an increase in wettability and thus, increase in effective surface area available for dissolution thus, leading to increase in dissolution rate[12].

DISSOLUTION CONTROLLING PARAMETERS

When we carry out dissolution our major emphasis is always on pH of the medium but there are several other factors which are needed to be taken into consideration like pH at fed and fasted state, rate of agitation of paddle, volume of media, type of media, eccentricity of stirring device, sample probe size, geometry of vessel, type of vessel, vibrations from dissolution apparatus, dissolved gases and temperature of test medium. Besides these, there are other factors which lead to variation or which can affect the dissolution rate leading to deviated bioavailability of the drug. The various physicochemical and physiological parameters which influence the dissolution of drug in GIT are summarized in Table 1. We are not able to get a perfect *in vitro –in vivo* correlation since we are not able to mimic the *in vivo* conditions. Thus there is a need to develop dissolution tests that predict *in vivo* performance of drug products in a better way. This can be achieved if the conditions of GIT can successfully be reconstructed in the *in vitro* test systems. For this maintenance of sink conditions is the primary requirement.

Sink conditions:

Drug concentration on both sides of epithelial layers of intestinal wall approaches equilibrium in a short time and that in the GI tract act as a natural sink (i.e. drug is absorbed instantaneously the moment it dissolves). Therefore under *in vivo* conditions there is no concentration build up. Hence retarding effect of concentration gradient on the dissolution rate doesn't occur as given in equation $dX_d/dt = (AxD/\delta)x(C_s - X_d/V)$; where, A is the effective surface area of solid drug, D is the diffusion coefficient of drug, δ is the effective diffusion boundary layer thickness adjacent to the dissolving surface, C_s is the saturation solubility of drug, X_d is the amount of drug already in solution and V the volume of dissolution medium. Maximum dissolution rates are predicted when $X_d=0$. As X_d increases, dissolution rate decreases. When dissolved drug is absorbed from the intestine, X_d is naturally kept low thus keeping dissolution rate to a maximum. Such conditions are described as sink conditions. *In vitro* systems should ideally maintain a sink condition and the dissolving solid should be bathed in fresh solvent. Thus sink conditions can be maintained by using large volume of dissolution media, adding selective adsorbents to remove dissolved drug, adding a water miscible solvent to dissolution media to increase drug solubility[13], developing a mechanism by which the

TABLE 1: FACTORS AFFECTING THE DISSOLUTION OF DRUGS FROM A FORMULATION.

Factor	Physicochemical parameters	Physiological parameters
Surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile
Diffusivity of drug	Molecular size	Viscosity of luminal contents
Boundary layer thickness		Motility patterns and flow rate
Solubility	Hydrophilicity, Crystal structure solubilization	pH, buffer capacity, bile, food components
Amount of drug already dissolved		Permeability
Volume of solvent available		Secretions, coadministered fluids

Physicochemical and physiological parameters important to drug dissolution in git[19]

dissolution medium is replenished constantly with the fresh solvent at a specified rate so concentration of solute never reaches more than 10-15% of its maximum solubility (slightly and very slightly soluble drugs give rise to difficulties in this respect)[14], using membrane to separate compartments so as to provide sink conditions/to prevent assay interfering components/ oil and paraffins from clouding the dissolution media[15] and lastly by removing the dissolved drug by partitioning it from aqueous phase of dissolution fluid into an organic phase placed either above or below dissolution fluid (e.g. hexane/chloroform)[16,17]. A similar study was conducted to evaluate the drug release from artemisinin tablets by two phase partition dissolution method, using an organic phase into which the investigational drug was completely partitioned and as result, drug was continuously removed from dissolution medium thus, maintaining the sink conditions. This method was chosen as a basis for further application on solid dosage forms containing a high dose of water insoluble drug[18].

FACTORS AFFECTING DISSOLUTION

Media:

An important factor in the design of dissolution test is the composition of dissolution media. It is generally held that medium should simulate the biological fluid found *in vivo* and should provide sink conditions for drugs so as to improve the possibility of better *in vitro-in vivo* correlation line. For example dissolution media based on 0.01 N HCl is used most of the times to mimic gastric pH. Caution should be exercised when selecting dissolution media[19] e.g. media containing phosphates may result in disintegration of sustained release matrices based on HPMC[20]. Decrease in the solubility of a sodium salt of a drug due to common ion effect also decreases the dissolution rate[21].

The choice of an appropriate medium for the *in vitro* tests is crucial so as to correctly forecast the effect of food in pharmacokinetic studies. Various biorelevant gastrointestinal media that simulates fasted and fed state have been developed. These media have been used to examine the dissolution characteristics of several classes of drugs (including poorly soluble weak bases and lipophilic drugs) to assist in predicting *in vivo* absorption behavior. Biorelevant *in vitro* dissolution testing is useful for qualitative forecasting of formulation and effects of food on the dissolution and availability of orally administered drugs. Biorelevant media can provide more accurate simulation of pharmacokinetic profiles than simulated gastric fluid/ simulated intestinal fluid. The composition of biorelevant media is summarized in Table 2.

Even milk[22-27], artificial liquid meal and emulsions[28,29] have been used. However, composition of these media may not optimally be the same as the composition of meals usually administered in relevant bioequivalent/

TABLE 2: COMPOSITION OF BIORELEVANT MEDIA

Ingredients	Quantity taken		
	Fasted State Simulated Intestinal Fluid (FaSSIF)*	Fed State Simulated Intestinal Fluid (FeSSIF)**	Fasted State Simulated Gastric Fluid
Glacial acetic acid (g)	-	8.65	-
HCl	-	-	0.01-0.05 N
Lecithin (mM)	0.75	3.75	-
NaOH (pellets) (g)	0.174	4.04	-
$NaH_2PO_4.H_2O$ (g)	1.977	-	-
NaCl (g)	3.093	11.874	2
SLS	-		2.5
Sodium taurocholate (mM)	3	15	-
Purified water (ml)	500	1000	1000

*pH-6.5: Osmolality- 270mOsmol/kg ; Buffer capacity-10 ± 2 mEq/L/pH ** pH-5.0: Osmolality- 670mOsmol/kg; Buffer capacity- 76 ± 2 mEq/L/pH

bioavailability studies. With the use of milk as dissolution medium there are problems such as stability of medium during the test as well as variability in its composition with source and season. Simple fat emulsions can't adequately simulate the carbohydrate and protein content of the meal[30]. Macheras *et al.* 1987 carried out the dissolution of four controlled release theophylline formulations in milk with the objective of using milk as a food – simulating medium and establishing its importance as a dissolution fluid under conditions which are more akin to the *in vivo* situation. Lower dissolution profiles in milk than in buffer were observed for three of the formulations. However one of the formulations exhibited relatively similar dissolution profile in both media and thus use of milk as a food simulating medium in dissolution studies is suggested for the *in vitro* evaluation of the release rate of drugs from controlled release formulations[22]. However now a days intralipid emulsions have been suggested as an alternative to milk because they are not subjected to biological variation[28]. Even bovine serum albumin has also been used to simulate *in vivo* conditions[30]. Drug release from a controlled release formulation was studied at a 2h contact using peanut oil as a dissolution medium. An increase in pH was observed as peanut oil resembles a heavy fatty food[31].

Choice of medium is expected to play a very important role especially in the dissolution of different classes of drugs. Since with class II drugs (that is those having low solubility and high permeability) dissolution is the rate limiting step to absorption which depends upon wide variety of factors. One of them is media which needs to closely represent the permeability in the upper GI tract in order to achieve meaningful *in vitro-in vivo* correlation. A study was conducted by using different types of dissolution media like water (deionized), pH 5.9-7, SIF (simulated intestinal fluid) without pancreatin, SGF (simulated gastric fluid), SGFsp (simulated gastric fluid without pepsin), milk (Bovine milk with 3.5% fat), FaSSIF (fasted stated simulated intestinal fluid), and FeSSIF (fed state simulated intestinal fluid). Drugs from class II category, which were selected included danazol, ketoconazole and mefenamic acid. Results obtained from dissolution of danazol showed that its release was dependent on the concentration of solubilizing agent. A 30 fold increase in the percentage dissolution was observed within 90 minutes upon changing the dissolution medium from aqueous media without surfactants to FaSSIF. Use of FeSSIF/milk as dissolution medium resulted in an even greater increase in percentage drug dissolved (100 and 800 fold, respectively). Dissolution of mefenamic acid (weak acid) was found to be dependent upon pH and bile salt concentration which lead to an offset between increased bile salt concentration and lower pH in the fed state as compared to fasted state medium. Dissolution of ketoconazole showed complete dissolution from a tablet formulation in simulated gastric fluid without pepsin within 30 min, 70% dissolution in 2 hr under fed state simulated upper jejunal conditions but only 6% dissolution in 2h under fasted state conditions[32].

Kramer *et al.* homogenized the breakfast given in the pharmacokinetic study as the dissolution medium. The medium was standardized by addition of pH–6.8 buffer solution and resulting homogenous suspension was used for dissolution tests. Although the use of homogenized meal as a dissolution medium is directly relevant to meals administered in pharmacokinetic studies, this approach is not ideal due to variability in its composition and cumbersome and time consuming preparation[33].

Inclusion of alcoholic solvents (e.g. isopropanol) have been used for insoluble drugs (e.g. norethindrone). The dissolution rate increased in hydroalcoholic medium[34]. However, problems are induced by inclusion of cosolvents. Alcoholic solvents may retard dissolution rate by retarding disintegration as observed during dissolution of chlorthalidone into 40% aqueous methanol[35].

Supramicellar surfactant concentration may be used for drugs of low solubility. Addition of SLS to media increases the solublizing activity similar to that of naturally occuring bile salts, sodium cholate and sodium taurocholate[36]. Use of 0.4% SLS was proposed as an alternative to 0.1/0.01M HCl for the dissolution of rifampin because the drug was more stable in surfactant solution[37].

pH and buffer capacity:

Dissolution medium pH and buffer capacity may not only affect the dissolution of a drug but may also substantially influence dissolution of ionisable excipients present. Usually media containing HCl, citrate, acetate, phosphate or Tris in the pH range 1-7.6 are often used. However, buffer capacity of such media which have equivalent pH often varies (despite we have evidence that buffer capacity at a given pH can substantially influence the dissolution rate of ionizable drugs[38,39]). In this regard Prasad *et al.* studied the dissolution rate of two different commercial formulations of controlled release quinidine gluconate in different media. Dissolution profile using the paddle method at 100 rpm in different dissolution media revealed wide differences between the two products. Dissolution rates of two products were widely different in water, acetate buffer of pH 5.4 and phosphate buffer of pH

5.4 but dissolution profile were found to be similar for the products in simulated gastric fluid (no enzymes) and pH 7.4 phosphate buffer. The quinidine gluconate products dissolved more rapidly in acetate buffer than in phosphate buffer[40]. The results of this study demonstrate the importance of medium buffer composition as well as pH in determining drug profiles.

It has been reported that the buffer capacity *in vivo*, in the post ingestion 'water meal' and fed (solid meal) state is 10.2 (pH 6.7) and 76 mEq/l/pHunit (pH 5.2), respectively. More biologically relevant dissolution media having significantly different buffer capacities have also been proposed[19].

Values of gastric pH in fasted state fluctuate very rapidly over the pH range of 1-3. Therefore, suitable dissolution medium which simulates the fasted state gastric conditions and which have pH values between1.5-2.0 can be used. With ingestion of a meal, the gastric juice is initially buffered to a less acidic pH, which is mostly dependent on meal composition and usually the pH range (after ingestion) lies between 3-7. Depending upon meal size, the gastric pH returns to fasted state values within 2-3 hr. Thus only those dosage forms which are ingested after meal intake will encounter the elevated gastric pH under normal physiological conditions. Intestinal pH values (Table 3) are considerably higher than gastric pH values due to neutralization of acid with $H_2CO_3^-$ (bicarbonate) ion secreted by pancreas. pH gradient values rise between duodenum and ileum and pH values in colon are influenced by products of bacterial exoenzyme reactions[19].

TABLE 3: pH IN THE SMALL INTESTINE IN HEALTHY HUMANS IN THE FASTED AND FED STATE[19]

Location	Fasted State pH	Fed State pH
Distal Duodenum	4.9	6.2
	6.1	5.4
	6.3	5.1
	6.4	
Jejunum	4.4-6.5	5.2-6.0
	6.6	6.2
Ileum	6.5	6.8-7.8
	6.8-8.0	6.8-8.0
	7.4	7.5

Range of pH existing in different parts of Stomach.

The influence of buffering capacity of the medium on the dissolution of drug excipient mixtures have also been investigated. It was found that the presence of acid excipient in drug excipient mixtures decreased the dissolution rate of the drug and it was also reported that in presence of acid excipients, the enhancing effect of increasing the buffer strength on the drug dissolution rate was lowered. Thus it was concluded that the buffer capacity of the medium plays an important role in *in vitro-in vivo* correlation[41].

Further some of the buffers are isotonic and others are not e.g. USP phosphate buffer of pH 6.8 and 7.2 are not isotonic and have buffer capacity of 30-35 mEq/l while modified isotonic Sorsen's buffer of pH 6.5-7.4 can have greater buffer strength than USP phosphate buffer of similar pH. The influence of dissolution medium composition on *in vitro* release of ketoprofen from a series of ER products was investigated with an aim to study the impact of different buffer media on *in vitro-in vivo* relationship. Common dissolution media USP phosphate buffer of pH 7.2 (Buffer Capacity-26 mEq/l) and 6.8 (29 mEq/l), phosphate (modified isotonic) pH-6.8 (38 mEq/l) and fasted state simulated intestinal fluid without lipid components of pH-6.5(10 mEq/l) were used in USP-2 apparatus. Release profiles were compared with *in vivo* release profile. Despite of relative similarity in composition of media used, significant difference in the release profile were observed which reflects the impact of difference in media in relation to its buffer capacity, ionic strength and pH. As a consequence the quality and shape of *in vitro–in vivo* relationship can be changed significantly due to different buffer capacities[42].

Volume of media:

In a typical USP dissolution test 900 ml of dissolution medium is employed. Sink conditions are maintained during dissolution but, during *in vivo* dissolution, the sink conditions may not exist, especially for those drugs with low aqueous solubility. Since the volume of gastric fluid available in animal species/human for dissolution is significantly lower than 900 ml, the dissolution test that uses a smaller and physiologically relevant volume of medium is more likely to predict the *in vivo* performance of a formulation, particularly for weak bases with low intrinsic aqueous solubility. The volume of stomach in fasted state may be as little as 20-30 ml.

A study was performed that demonstrates the importance of volume of medium in dissolution test to predict the bioavailability of formulations. BMS – 480188 which is

a weak base was used and its mesylate salt was prepared. Capsules containing mesylate salt alone (A) or mesylate salt with excipients including lactose, croscarmellose sodium, SLS, syloid, magnesium stearate (B) formulations were prepared. Both formulations showed similar dissolution profile in 1litre 0.01N HCl at 37°. But the reported bioavailability of A and B was 5.7 and 24% respectively (in monkeys). Since, very small amount of fluid is available in the stomach of monkeys, in fasted state so, 30 ml of 0.01N HCl was used as the dissolution medium *in vitro* to simulate the dissolution medium *in vivo*. When the dissolution studies were carried out using 30 ml of 0.01 N HCl it was found that the amount of drug dissolved from B was 80% greater than A after 2h. It was concluded from the study that the presence of excipients delayed the conversion of mesylate salt to the free base and dissolution test when carried out using 30ml medium showed greater percentage of dissolved drugs. This inhibitory effect of excipients was masked when dissolution was carried out using 1 litre medium because the concentration of dissolved drug was below the solubility limit of BMS 480188[43]. This study demonstrated the importance of volume of medium for *in vivo* dissolution test to predict bioavailability.

According to perfusion studies of Dillard *et al.* 1965, the volume of fluid in the jejunum and ileum varies from 120-350 ml. There was a considerable change in the volume of small intestine after ingestion of meal which may either be hypertonic (milk/doughnuts) and hypotonic (streak and water) meal. Volume was considerably higher following administration of hypertonic meal than after administration of hypotonic meal. This is because in case of hypertonic meal, net water efflux across the mucous into the human occurs due to the osmotic pressure difference, while in case of hypotonic meal, there is no water absorption from the meal[44].

In recent years, pharmaceutical companies have developed compounds which are highly potent. These result in a very low concentration of drug in 500 – 900 ml of dissolution media. With the discovery of such kind of potent drugs, which result in low level concentrations, appropriateness of apparatus 1 and 2 needs to be revisited. In developing dissolution methods for a new proprietary tablet that contains 200 µg of active drug, the early dissolution time points cannot be quantitated using the current assay method. In order to increase the concentration several opinions were tried. The first was to use multiple unit tablets in a single vessel using either 500 or 900 ml. of media but, this approach did not provide dissolution data on individual units. Another option was to use a 200 ml conversion vessel offered by Van-Kel Technologies Inc. which can be used with the standard apparatus 2 dissolution apparatus. The conversion kit is ideal for tests where a smaller volume is required. The kit consists of 200 ml glass vessel which is 203 cm long with a 42 mm diameter and contains a Teflon coated mini paddle (381 cm long, 29.8 mm Paddle diameter with a 63.5 mm shaft)[45].

Sampling probe size:

When *in vitro* dissolution rates were determined using USP paddle method some tablet formulations consistently gave higher dissolution rates when sampled with an automated sampling system than when sampled manually. This difference was traced to turbulence caused by the filter tipped probes used in automated sampling. There is a direct relationship between the displacement volume of the sampling probe and the increase in the dissolution rate for the sample used. Thus displacement volume of sampling probes used with automated samplers should be as small as possible to reduce interference with the dissolution test[46].

Not even the sampling probe size, the sampling procedure in dissolution test apparatus generates great interest. According to USP 23 sampling should be done in a manner so as to withdraw a specimen from zone mid way between the surface of dissolution media and the top of the rotating basket or blade, not less than 1 cm from vessel wall. However in USP Apparatus 1 and 2 dissolution tests the samples are traditionally taken with a probe placed into the vessel. The probe adds turbulence if it remains in the liquid phase. Lift devices can be installed to move probes in and out of the vessel at the required sampling time. To overcome these problems Hollow Shaft $_{TM}$ sampling system has been introduced and it allows for sampling at short intervals of time down to 20 seconds per sample. Hence analysis of fast release drug is possible and by using this, no significant differences exist between the samples taken normally or by means of Hollow Shaft ™.

Agitation intensities:

There should be appropriate agitation intensities for *in vitro* dissolution rate measurements so as to reflect *in vivo* conditions. Solid dosage forms are exposed to relatively low agitation intensities after oral administration and it is often mandatory to use similar mild agitation conditions for predictive *in vitro* dissolution tests. Proportionality between dissolution rate and square root of stirring rate is demonstrated by rotating disks[47].

In the upper GI tract, there are basically four motility

patterns-no activity (quiescence), segmental movement, propagative movements (short/long large) and tonic contractions. In fasting stomach, long periods of little or no motor activity occur. The quiescent phase is modeled by a stagnant system. In small intestinal segment, propagative motility is a function of fed and fasted states. Segmentation is a free dominant mixing pattern in small intestines and is characteristic of fed state. Segmental contractions tend to occur over very short distances typically less than 2 cm and are severe to mix the luminal contents thoroughly. In stomach and small intestines, movements of luminal contents are virtually always in distal direction. In proximal colon, mixing can occur longitudinally as well as laterally[19]. Thus the purpose to maintain these hydrodynamic conditions in *in vitro* dissolution test is to mimic these movements. Uncontrolled variability typical of dissolution test is likely as a result of hydrodynamic effect (i.e. how well the luminal contents are mixed), since, the test is conducted in a small agitated vessel operated at Reynold's number in the transitional regime. Hydrodynamics have been shown qualitatively to influence dissolution test performance. Changes in agitation speed can affect the ability to correlate *in vitro* dissolution tests with *in vivo* performance. The hydrodynamic influences of geometrical changes, such as size and shape of vessel and placement of sample probes should also been examined, in order to have a perfect *in vitro – in vivo* correlation.

Recently a study was also conducted to examine the hydrodynamic environment within the USP Apparatus II at common operating conditions. Computational analysis was used to examine hydrodynamic environment. Computations are used to obtain the data which cannot be measured with experiments, specifically the distribution of shear forces within the media and along the wall. Results indicated that shear environment was highly non-uniform and increasing the paddle speed from 50-100 rpm did not improve the shear homogeneity. This uneven distribution of shear hydrodynamic forces was a direct cause of dissolution testing variability[48].

Visualization studies were performed using dye released from a non-disintegrating tablet in a rotating basket apparatus to show that shear patterns can be unstable across the surface of a tablet. The study also explored the impact of tablet position to further characterize the hydrodynamics within the device[49].

The USP has recently discussed potential changes in dissolution testing including operation in the laminar regime that may provide more uniform environments. Evaluation of dissolution environment in the manner demonstrated here will contribute important benefit to the development of rigorous dissolution tests, potentially preventing many problems[48].

Vibrations:

Sources of variation like temperature, pH, type of medium etc. can be controlled by using well calibrated instrument. Difficulty arises with eccentricity of stirring device, shape of vessel, vibration of dissolution medium where it is difficult to detect whether they are in normal conditions or not. The current USP dissolution calibrators were introduced to control unseen vibrations of the dissolution apparatus. Abnormalities in other factors besides vibration in dissolution apparatus can also be detected by USP calibrators.

It was reported that dissolution rate of an active ingredient from enteric coated granules determined by both the paddle and rotating basket methods was increased by extraordinary vibration of dissolution apparatus which was not detected by USP calibrators. This suggests that current USP calibrators are not sensitive enough to evaluate the vibration levels of dissolution apparatus, and that the enteric coated granules might be useful as a calibrator for evaluation of vibration levels of dissolution apparatus[50]. A collaborative study using enteric coated granules of cefalexin was performed to develop a dissolution standard for evaluating vibration levels for dissolution apparatus. Results indicated that dissolution rates of cefalexin from enteric coated granules were significantly increased by dissolution apparatus at high levels of vibration in the rotating basket method, while they were not affected by vibration level by paddle method[50]. A study was conducted in which hydrodynamic flow around a dosage form in the GI tract in humans was compared with *in vitro* drug release. Two different types of controlled release paracetamol tablets A and B were prepared. The former tablets showed an agitation speed dependent release at a high speed range 50-100 rpm while latter showed this characteristic at low speed range (10-50 rpm). The mean release amount time profile of tablets A and B in humans showed biphasic characteristics and the first phase of absorption profile of A and B was close to their *in vitro* profile at a paddle speed of 10 rpm. *In vivo* profiles were also superimposable on *in vitro* dissolution curve obtained by flow through cell method at a flow late of 1 ml/min (velocity 0.89 cm/min). Results indicated that hydrodynamic flow around the dosage forms in the human GI tract is extremely low corresponding to a paddle speed of 10 rpm in paddle method or a velocity of 1 cm/min in flow through cell method. Thus, it was concluded that presence

of destructive forces and low hydrodynamic flow are essential conditions for establishing a useful *in vitro* dissolution testing system[51].

DIFFERENT TYPES OF DISSOLUTION APPARATUS

According to USP, different types of apparatus are[52] apparatus 1: A rotating mesh (40 mesh standard) basket in a hemispherical vessel, apparatus 2: A rotating paddle in a hemispherical vessel, apparatus 3: A reciprocating cylinder in a cylindrical vessel, apparatus 4: A media flow through cell, apparatus 5: A rotating paddle over a disk in a hemispherical vessel, apparatus 6: A rotating cylinder in a hemispherical vessel and apparatus 7: A reciprocating holder in a cylindrical vessel (disk, cylinder, pointed rod, spring holder, angled disk). Above described compendial apparatus in USP can be regarded as closed system stirring methods which operate under finite conditions. Another approach would be to operate under infinite sink conditions by applying an open flow through system. Thus apparatus of both closed and open system will increase the fundamental understanding in terms of *in vitro* dissolution properties of a given solid dosage form. The flow through dissolution apparatus has been successfully used to study dissolution of conventional and controlled release tablets and hard and soft gelatin capsules[53-55]. The reproducibility, robustness and ruggedness of this dissolution technique had been established[56-58]. It is a useful tool to study the oral solid dosage form.

The various advantages offered by the flow through dissolution apparatus includes that sink conditions can always be attained even for poorly water soluble drugs because the fresh medium is continuously supplied during dissolution test and testing conditions i.e. composition of test fluid, pH and flow rate can be flexibly modified during the dissolution process depending on the physicochemical properties of sample formulation[59]. Recent studies suggested that flow through method could be a useful alternative to dissolution method in official compendia[60-63].

The application of flow through dissolution apparatus has been shown in several research papers[64-67]. Introduction of this method solves the problem of sink conditions specially when investigating poorly soluble compounds by continuously exposing the formulation with a flow of fresh solvent. A study was conducted using salicylic acid tablets as test formulation. The results obtained by flow through method were compared with paddle method and it was concluded that flow through apparatus does not produce larger variation expressed in terms of range of amount dissolved at various times compared to paddle method[68]. In another study, a poorly water soluble drug was formulated as controlled release dosage form and *in vitro* dissolution test was performed by using flow through type dissolution method to predict *in vivo* drug release behavior. Theophylline, acetaminophen and phenylpropanolamine HCl were formulated into controlled release dosage form. *In vivo* drug release behaviour was observed by measuring the residual of drugs in preparation recovered from GI tract after oral administration. *In vitro* release profile obtained by flow through method combining sink and non-sink conditions were similar to their *in vivo* profiles. This study demonstrated that flow through method combining both sink and non- sink conditions gave a good *in vitro–in vivo* correlation regarding drug release behavior for controlled release multiple unit dosage forms[69]. Similar dissolution studies conducted on poorly soluble compound (i.e. PD198306) in a flow through dissolution apparatus, showed that loading the drug powder into the dissolution cell in the form of suspension provide best dissolution profile in terms of rate and extent of dissolution[70].

CONCLUSION

It is very apparent that dissolution studies play a very important role to assure the pharmaceutical quality of product. Poor dissolution behaviour *in vitro* is attributed to a number of factors. In order to achieve a perfect *in vitro in vivo* correlation it is necessary to consider all the above factors.

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