Review Article

An Updated Review of Dissolution Apparatus for Conventional and Novel Dosage Forms

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ABSTRACT

Dissolution testing of the drug formulation introduced in 1960 since then the importance of dissolution test has grown rapidly as have the number of tests and demands in quality control laboratories. Dissolution testing is an official test used by pharmacopeias for evaluating drug release of solid and semisolid dosage forms. The main applications of the dissolution testing include biopharmaceutical characterization of the drug product, as a tool to ensure consistent product quality and to predict in vivo drug bioavailability. Dissolution testing was developed initially for solid orals, later on its use is widened to a variety of novel dosage forms. Due to the complexities in the drug delivery of novel dosage forms there is a need in developing modified dissolution testing methods in order to characterize the invitro release of these dosage forms. Over the last three decades the dissolution test has come a long way and has evolved into a powerful tool for characterizing drug products and their in vivo performance. This review attempts to emphasize the most important developments in the field. The article represents the current updates in dissolution testing methods for conventional and novel pharmaceutical dosage forms and gives an insight to possible alternatives in drug dissolution testing design. The aim of this review is to represent all the potential standardized test methods which are needed to characterize the dissolution properties of a wide variety of dosage forms ranging from conventional to novel delivery.

Keywords: Dissolution, Invitro release testing, novel dosage forms, quality control.

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INTRODUCTION

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Drug dissolution testing plays an important role as a routine quality control test, for characterizing the quality of the product and also plays a major role in drug development. Dissolution testing is an official testing used by the pharmacopeias for evaluating drug release of solid and semi solid dosage forms. Drug related dissolution had gained interest only when it is considered as an important factor of drug bioavailability in 1950.The main purpose of this article is to review USP dissolution apparatus and to present an updated review of non pharmacopeial dissolution methods for testing conventional and novel dosage forms. Various dissolution Medias and their appropriate uses are also listed. The article also highlights the new dissolution testing apparatus and the scenario of dissolution research from past to present. Drug bioavailability includes Pharmaceutical availability /invitro availability. Among the various tests that are performed on the drug solids the dissolution test occupies the topmost position as a sensitive reliable test and also as a predictive tool for invivo drug bioavailability behavior [1-5].

Application of In Vitro Dissolution Studies

1. The invitro dissolution of a drug from dosage forms is employed as a primary aid in the characterization of formulations and also in biopharmaceutical characterisation of the drug product
2. Dissolution tests are a standard method listed to ensure the batch to batch conformity of oral dosage form
3. In R & D these tests assist in the formulation development of IR and MR dosage forms
4. Quality control procedure for monitoring the uniformity and reproducibility of production batch or both
5. Preformulation studies/drug candidate selection
6. Simulation of food-effects on bioavailability
7. Absorption prediction/ in vitro in vivo correlations
8. Supporting of waivers for bioequivalence requirements
9. Identification of critical manufacturing variables
10. Supporting of scale-up and post-approval changes

HISTORY OF DISSOLUTION TESTING

Foundation of dissolution research was laid down in 1897

1897-1960[6-9]:

- Noyes and whitney: Conducted first dissolution experiments and published an article "The rate of solution of solid substances in their own solution and suggested that dissolution rate was controlled by a layer of saturated solution that forms instantly around a solid particle.
- Brunner and Tolliczko: proved that dissolution rate depend on chemical and physical structure of the solid, surface areas exposed to the medium, agitation speed, medium temperature and overall design of the dissolution apparatus
- Nelson and Brunner : Relationship between dissolution rate and diffusion coefficient
- Hixson and Crowell: cube root law of diffusion.
- Experiments began with invitro–invivo correlations
- In 1934 Switzerland's Pharmacopeia Helvetica was the first regulatory body to introduce a disintegration test for tablets.

1950-1980[10-18]:

- In this period transformation occurred from studying the effects of physico chemical properties of drug on dissolution to correlation of dissolution to bio availability of dosage forms
- Disintegration became an official USP method
- The first official dissolution test for solid dosage forms using a rotating basket was incorporated by USP 18 in 1970.
- Rotating bottle method was developed to study the extended release formulations.
- Edward : Suggested that the rate of appearance of drug in the body/it's therapeutic effect is controlled by rate of dissolution if the absorption of the drug from GIT is rapid
- FDA published guidelines for dissolution testing
- USP began development of calibrators for dissolution testing

1980-2000[19-25]:

- Dissolution emerges as an essential tool for the development and evaluation of SR formulations
- In this period main emphasis is laid down on dissolution as a prognostic tool of oral drug absorption.
- USP : Classification of IVIVC
- Official dissolution equipments like rotating cylinder, reciprocating disk, reciprocating cylinder, flow through cell introduced.

OFFICIAL DISSOLUTION APPARATUS [26-28]

NON-OFFICIAL DISSOLUTION APPARATUS

Due to the significant difference in the formulation design among the novel dosage forms which in turn lead to a very different physicochemical characterization it is impossible to develop a single test system which could be probably used for the dissolution testing of all the novel dosage forms.

Table 1: List of the Official Dissolution Apparatus and their uses

Sr.No	Official name	Main features of the apparatus	Uses
1.	USP Apparatus 1	Basket	Tablets, capsules, Floating dosage forms
2.	USP Apparatus 2	Paddle	Tablets, capsules, enteric forms
3.	USP Apparatus 3	Reciprocating cylinder	Extended release drug product
4.	USP Apparatus 4	Flow through cell	Implants, powders, suspensions
5.	USP Apparatus 5	Paddle over disk	TDDS
6.	USP Apparatus 6	Cylinder	TDDS
7.	USP Apparatus 7	Reciprocating disk	Extended release drug products

Rather different apparatus, procedures and techniques are employed on case by case basis which could be dosage form, type of formulation or even product specific.

a) Buccal and sublingual tablets

These are the solid dosage forms when placed in mouth allow the active ingredient to dissolve in saliva and then absorb either via the oral route or by the buccal /sublingual mucosa in the mouth. Buccal/sublingual route is also suitable for medications that cannot or be taken by the oral route due to instability of drug at the low pH of the stomach, or their susceptibility to the hepatic first pass effect. These tablets are also advantageous for patients who are unable to swallow whole tablets. The need for the development of new dissolution apparatus for the buccal and sublingual tablets is, buccal dissolution differs with the G.I dissolution in following ways, Smaller volume of saliva, and there are challenges regarding the extend of drug delivery in the mouth as opposed to the oral route namely due to short residence time in the mouth is and finally the salivary composition differs from that of gastric fluids in a wider way. All the reasons discussed provide a need for the design of newer apparatus/modification in the standard USP apparatus for testing of buccal and sublingual tablets in order to mimic the invivo conditions for the accurate analysis of the dosage form. This novel system is given by Rohm & Haas Laboratories-springhouse comprises a single stirred continuous flow-through cell that includes a dip tube, a central shaft with propeller & a filter along with one inlet for saliva & one outlet for sample.

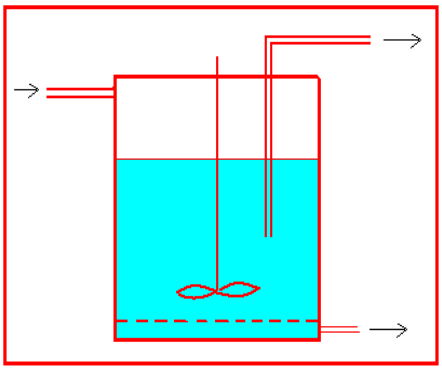

Figure 1: Schematic of Dissolution Apparatus for Buccal /Sublingual Tablets

Model-II

A new & simple dissolution apparatus developed by mumtaz & ching in 1999 .This apparatus is capable of evaluating the release of drug & bioadhesive properties of buccal tablets. Apparatus consists of a dissolution cell & an outer assembly, the cell has been designed in such a way that it hold's the chicken pouch membrane & bioadhesive tablet together &the cell also allows the dissolution medium to flow over them. The outer assembly is to provide adjustment of the angle of the flow of the medium over the cell. This device is based on the circulation of pre-warmed dissolution medium through a cell.

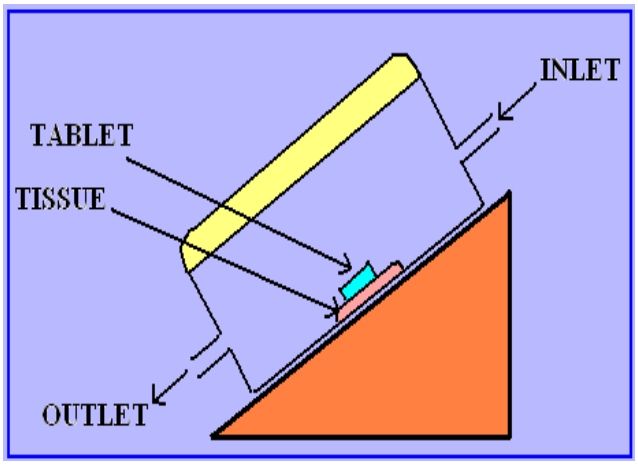

Figure 2: Schematic Drawing of the Dissolution Used By Mumtaz and Cnng (1995) Studying the Dissolution of Buccal Tablets.

b) Chewing gums and tablets

The medicated chewing gums are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed but not swallowed. They contain one or more active ingredients whish are released by chewing and are intended to be used for local treatment of mouth diseases or systemic delivery after absorption through buccal mucosa. Chewable tablets are usually uncoated. They are intended to be chewed before being swallowed. The chewing machine consists of a temperature-controlled chewing chamber in which the gum piece is chewed by two electronically-controlled horizontal pistons driven by compressed air (Figure). The two pistons transmit twisting and pressing forces to the gum, while a third vertical piston, ("tongue") operates alternately to the two horizontal pistons to ensure that the gum stays in the appropriate position. The temperature of the chamber can be maintained at 37±0.5°C and the chew rate can be varied. Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends using 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes per minute [29-30].

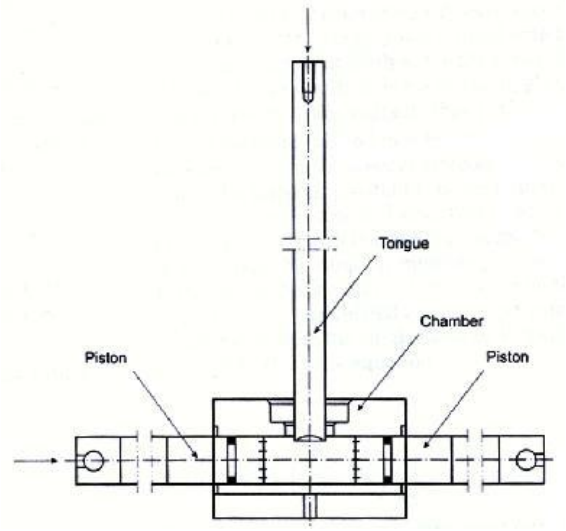

Figure 3: Chewing Gum Apparatus/3 Piston Apparatus for Testing Chewing Gums Tablets

c) Immediate release tablets

Immediate release dosage forms are intended for the rapid delivery of drug into the blood stream in which ≥85% of labelled amount dissolves within 30 min. Dissolution rate is the limiting step for the

drug absorption into the systemic circulation for immediate release dosage forms. Dissolution studies for this type of dosage forms are performed using the USP apparatus namely basket, paddle, rotating cylinder and flow through cell. Newer design for the testing of these dosage forms include mini paddle apparatus. Dissolution of typical high-potency, low-dose compounds require a reduction in vessel volume further accompanied by modification in apparatus design due to some draw backs in official apparatus which include unable to maintain quantitative levels of analyte during the dissolution test. The use of small-volume dissolution apparatus satisfies the need to provide accurate, reliable data for decision-making purpose during early developmental stages of the drug and also provides assurance of quality at the time when the formulation reaches scale- up production, and also provides assurance of product stability. The mini paddle is based on the USP paddle setup but the size is scaled down to exactly 1/3 of the USP paddle apparatus, volume used is 250 ml and the stirring rate of 100rpm is maintained. This gentle agitation speed is favorable in carrying out dissolution studies for immediate release as well as for rapid disintegrating dosage forms. The advantages of the mini paddle apparatus include, it require half a dose of drug than used for paddle apparatus ,smaller volumes of media is used offers various advantages in terms of substance, analytical, and material cost savings and this set-up is also a promising alternative in the case of highly potent drugs[31-37].

d) Soft gelatin capsules/ Liquid-filled capsule [38]

Soft gelatin capsules/ Liquid-filled capsules can be composed of either hydrophilic or lipophilic components. Conventional dissolution testing using USP 2 rotating paddle apparatus can be used in case of hydrophilic capsule dissolution but the USP recommended official testing procedures suffers serious disadvantages and it becomes difficult to operate official operating dissolution procedures when it comes to the case of lipophilic formulations. The rotating paddle can have disadvantages for lipophilic formulations which include; it might be difficult to keep the formulation immersed. Also, emulsified formulations might separate at the liquid–vessel–air interface, and formulations could adhere to the paddle or beaker walls. The rotating basket has an advantage over paddle in keeping the formulation immersed, but this procedure also suffers from draw backs such as blockade of meshes, or most of the viscous oily vehicle will remain entrapped within the basket hence resulting in failure to release drug into the aqueous phase. The standard dissolution basket pores (40 meshes) and lack of appropriate hydrodynamic conditions within the basket will result in causing significant limiting effect on drug release from the oleaginous formulations. The reciprocating cylinder which offers good mechanical agitation but suffers from the drawback of having limited media volume. With the consideration of drawbacks that official USP apparatus suffer regarding testing of lipophilic formulations the need of developing newer apparatus or modification of the existing ones arises and the apparatus which are used for the successful testing of lipophilic formulations (lipid filled soft gelatin capsules) include , the modified dual chamber flow-through cell, as recommended for lipophilic suppositories. The figure below shows the schematic view of this device. The working includes rising of the lipid content due to its lower density after rupturing of the capsule. When the lipid phase reaches the triangular area top of the left side cell, it stays there. Thus the dissolution medium continuously extracts the drug from the lipid layer as it flows through the cell. The dissolved drug can now be determined using a conventional fraction collector and be analyzed in the medium.

Another procedure is recommended by Pillay & Fassihi for testing of lipid –filled soft gelatin capsules known as Pillay & Fassihi model. This model uses a modified two-phase dissolution media system by a novel approach. The organic phase media is used to extract the lipid content of the soft gelatin capsules. The model also encompasses ring or mesh which is used in conjunction with the paddle method to

study the influence of the position of various dosage forms on release behavior and it is also used to prevent the sticking of the soft gelatin capsule to the rotating paddle.

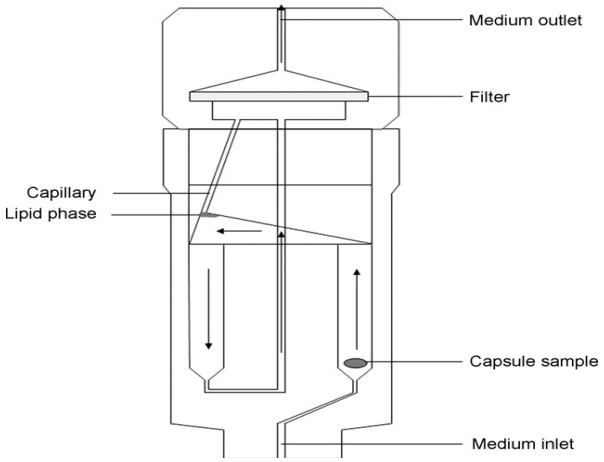

Figure 4: Schematic View of Flow-Through Cell Designed for Lipid-Filled Soft Gelatin Capsules

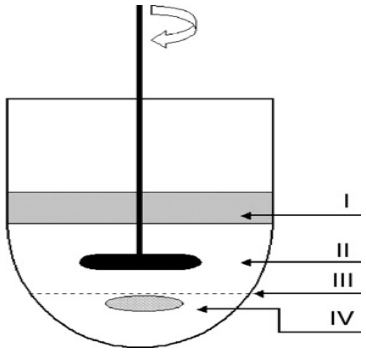

Figure 5: Schematic View of Apparatus for the Dissolution Testing of Lipid Filled Soft Gelatin Capsules

I = organic phase, i.e., 100 ml
II = aqueous phase
III = ring/mesh
IV = position of capsule

No one single test method is suitable for all liquid-filled capsules. However, the set of available methods described above should enable the selection of an appropriate test in most cases.

e) Transdermal drug delivery system (TDDS)[39-41]

TDDS are self-contained, discrete dosage forms that, when applied to intact skin, are designed in such a way to deliver the drug through the skin to the systemic circulation. The components of the TDDS include an outer covering (barrier), a drug reservoir along with a drug release–controlling membrane, a contact adhesive applied to some or all parts of the system and a protective liner that is removed before the patient applies the system. Currently used USP apparatus for inviro dissolution testing of the patches include the paddle over disk/disk assembly method (USP apparatus 5), the rotating cylinder (USP apparatus 6), the reciprocating holder (USP apparatus 7), and a paddle over extraction cell method and Franz diffusion apparatus. The paddle over disk method is the most widely used method because it is simple and easy to reproduce. Along with the paddle and vessel of the USP 2 this apparatus include stainless steel disk assembly which holds the transdermal system at the bottom of the vessel .The disk assembly is positioned in such a way that the release surface is parallel with the bottom of the paddle blade and exposed to the medium. The paddle over disk procedure with a watch glass–

patch–screen sandwich assembly could be a suitable method .The configuration of this assembly ensures that the patch is prevented from floating during the entire testing period. The pH of the medium ideally should be adjusted to pH 5–6, reflecting physiological skin conditions and the test temperature is typically set at 32°C and a distance of 25+2 mm is maintained between the paddle blade and the surface of disk assembly. The paddle rotated at One hundred revolutions per minute. In the rotating cylinder the basket and shaft of the USP 1 apparatus is replaced with stainless steel cylinder and maintain temperature as 32°C. Apparatus 7 (Reciprocating Holder Method, the assembly consists of a set of calibrated solution containers made of glass or other suitable inert material, a motor and drive assembly to reciprocate the system vertically and a set of suitable sample holders. The cell method includes an extraction cell along with the paddle and vessel assembly .The extraction cell is made of chemically inert materials and has a support to hold the patch and a cover to position the patch at the center and to limit its releasing surface.

f) Poorly soluble compounds

Based on BCS classification low solubility compounds are defined as compounds whose highest dose is not soluble in 250 ml/less of aqueous media from pH 1.2-7.5 at 37°C. Most poorly soluble compounds in immediate-release (IR) formulations have solubility of less than 1–2 mg/L in the pH range of 2–8. Many challenges has to be overcome in order to identify a single dissolution/appropriate physical test method to provide a measure of product consistency as well as bioavailability for dosage forms containing poorly soluble compounds . The challenges include developing and validating the test method, ensuring that the method is appropriately discriminatory and is satisfactory, and establishing an in vivo–in vitro relationship (IVIVR) or correlation (IVIVC). Satisfying all of these challenges and developing a meaningful dissolution method is a huge task, because the extent of release is too low (i.e., one cannot get 100% of the dosage form dissolved) and secondly, the rate of release is too slow (i.e., one cannot get dissolution fast enough for a convenient test).Dissolution test development for poorly soluble compounds early in the drug development stage should mainly emphasize on physical and chemical properties of API and the dosage form design and matrix (cohesive properties of the drug)because these factors will guide us in the selection of the dissolution medium and the apparatus. The oral formulation dissolution characteristics should first be evaluated using media with the physiological pH range of 1.2-6.8 because poorly soluble drugs include those with adequate aqueous solubility at either acidic/neutral pH levels. The existing compendial methods for poorly soluble drugs include USP 1 Basket type with agitation speed maintained at 50-100 rpm, USP 2 paddle apparatus with agitation speed of 50-75 rpm. Basket accomidate 500-1000ml standard vessels as well a 2000-4000 larger vessels. Higher vessel volumes are preferred for poorly soluble compounds for complete release of a drug from its formulations.USP 3 types are used to estimate the release profile in the GIT by the usage of different media in the vessels. By the design of the USP 4 it allows for a controlled pH and volume change of dissolution medium throughout the test and utilizes the principle of flow-through technique in order to evaluate the in-vitro release rate of poorly water-soluble compounds and applicable to identify effect changes in formulation on dissolution rate. Conventional apparatus fail to correlate pH changes with the dissolution profile of the poorly soluble drugs hence cannot be treated as ideal ones for dissolution testing of these compounds. In order to predict the "in-vivo" dissolution behavior of these pharmaceuticals, it is necessary to conduct a dissolution test that simulates the pH changes in the G.I.T and provide us with the predictive results. Novel multi-compartment dissolution apparatus for poorly soluble drugs include two reservoirs gastric and intestinal(1 & 2 respectively) with volume 5 liter each and the output rate is 2ml/min Gastric reservoir has 0.1N HCl to mimic secretion of acid from gastric lining and intestinal reservoir has 1.2M alkaline borate buffer to mimic intestinal

conditions. The compartments include gastric compartment (A) of volume70 ml and removal of content by side arm mimics the pylorus opening, intestinal compartment (B) of volume 400 ml to mimic in-vivo conditions and absorption compartment(C): it gets fluid at the rate 4ml/min Magnetic stirrer (D&E) agitation speed 75 rpm with heating capacity and a filter (F) to prevent entry of the un dissolved particles is present [42, 43].

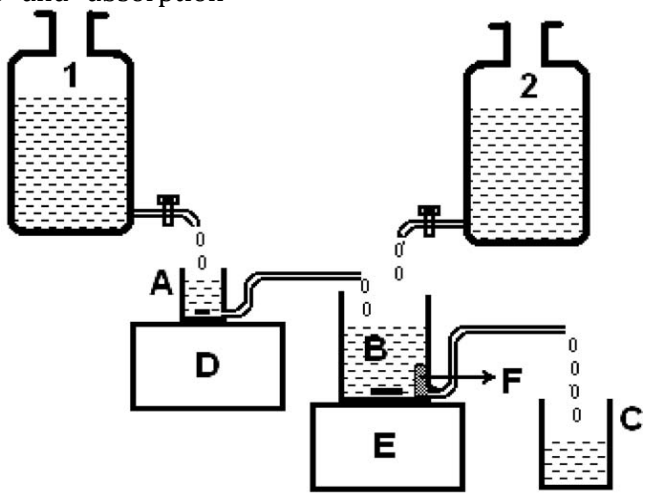

Figure6: Schematic View of Multi Compartment Dissolution Apparatus for Poorly Soluble Drugs

g) Floating tablet

Floating tablets are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The draw backs faced by the conventional USP (Apparatus 2) during the testing floating drug delivery systems are, the volume of dissolution medium (900 mL) is very high as compared to stomach content, adherence of dosage form on the shaft, Problems faced during sample collection and the major drawback is the test does not mimic the release of acid from stomach lining and gastric emptying through pylorus opening. The USP (Apparatus 4) also suffers from a set of drawbacks which include, the inability in examining the floating ability as the dosage form remains stationary during the test in the cell and the usage of high flow rate (50 mL/min) . Traditional invitro methods suffers from drawbacks such as sticking of the tablet to the agitating device, unable to mimic the invitro condition and these are poor predictors of invivo performance of floating dosage forms. To overcome these disadvantages a more reliable method has been proposed. The proposed method is essentially a modification of the Rossett-Rice test, which is a popular in vitro test for evaluating the acid neutralization efficiency of antacids. In the proposed method, a side arm is provided at the bottom of the beaker to mimic gastric emptying phenomenon. Flow-through cell conditions are simulated with respect to availability of fresh dissolution medium around the dosage form. High stirring rate (300 rpm) is used in the Rossett-Rice test. In short, the modified test mimics a wide variety of invivo conditions as mimics the gastric volume (70 ml), gastric acid secretion rate (2 ml/min) and emptying of liquid through pylorus opening and the method also overcomes the sticking problem and sample collection problem which are faced during the usage of conventional apparatus for testing floating tablet [44,45].

Another model is proposed by Pillay & Fissihi floating tablet which consists of a wire mesh which is put above the dosage form so that the floating tablet doesn't interfere with paddle.

h) Parenterals [46, 47]

Parenterals are the preparations which are given other than the oral route. Parenteral drug delivery systems include implants and depot injections .An implant is defined as the sterile solid dosage form in which drug is dispersed throughout the matrix to get controlled release. The invitro test method for the implants includes shaking flask

method and flow through cell method. In flow through cell method in order to mimic the invivo condition the flow rate of dissolution medium is kept very slow by the use of HPLC pumps and we have to satisfy the osmalarity and pH conditions.

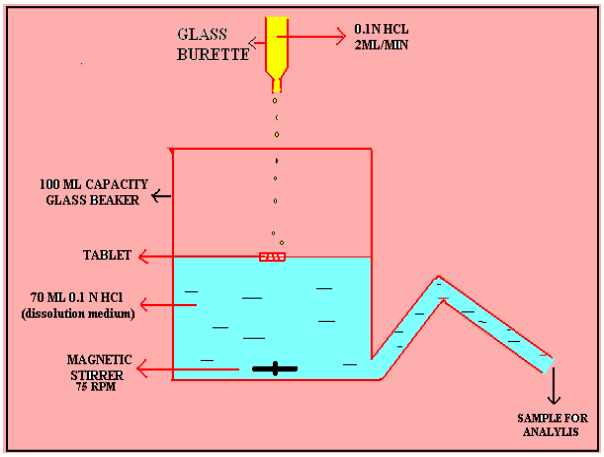

Figure 7: Modified Rosset-Rice Test Apparatus for Floating Drug Delivery Systems

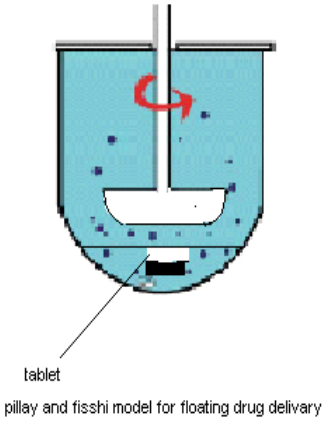

Figure 8: Pillay and Fisshi Model for Dissolution Testing of Floating Drug Delivery

Depot is another parenteral drug delivery system which is the suspension of poorly soluble salt of active drug in oil base for slow release of the drug. In vitro testing for depots include rotating dialysis cell with dialysis membrane to provide a well defined surface area and the dissolution medium is the buffer solutions pH 3 ± 0.01 (0.05 M phosphate buffer) pH 5 ± 0.01 (0.05 M Acetate buffer) pH 7 ± 0.01 (0.05 M phosphate buffer) which resembles the pH at the absorption site with respect to the nature of drug .Volume of the medium is 1000ml, stirring rate is 50 rpm and is maintained at 37 ± 0.5˚C.

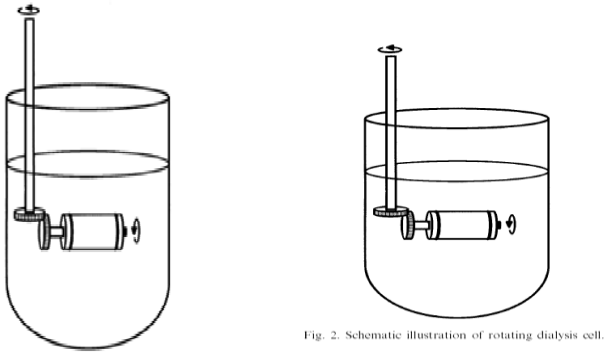

Figure 9: Rotating Dialysis Cell for Dissolution Testing of Parenterals

h) Microspheres [48]

Microspheres are defined as submicron particulate drug delivery systems. Though the number of microsphere-based products has been growing in the market, there is no specific in-vitro dissolution technique described in any pharmacopoeia or no specific guideline has been framed for the dissolution studies. The usage of these techniques depend upon their ability power to discriminate the release profiles of the dosage form tested and provide an in-vitro/in-vivo correlation (IVIVC) .Usually the drug release profiles are carried to determine the time period of drug release which in case of microspheres ranges from weeks to months so in such a situation performing drug release profiles for a long period of time is time consuming. In order to overcome such problems, in-vitro release is carried out under accelerated conditions where, only the drug release is accelerated without affecting the mechanism by which the drug is released. One of the in-vitro dissolution used is dialysis techniques which involves the usage of a dialysis membrane bag of certain molecular weight cut off (MWCO). The microsphere suspension is placed in the dialysis membrane bag, sealed from both ends and suspended in the buffer under constant agitation using a shaker or paddle. Sink conditions are maintained by reducing the volume of the micro particulate suspension to 5-10 times of that of bulk media. However, this technique cannot be used if the drug binds to the dialysis membrane. Nastruzzi et al. Studied the release of bromocriptine mesylate from microspheres using dialysis tubes and a flow-through cell method and compared the reproducibility between the two methods. Dialysis technique exhibited more drug release with longer time to plateau whereas with the flow-through cell, the time to reach the plateau was comparatively shorter, and lesser amount of drug was released. Another dissolution technique reported is modified flow through cell technique in which microspheres are mixed with glass beads in the cells which aids in preventing the aggregation of microparticles and increasing laminar flow in flow through cells.

CONCLUSION

Dissolution test is an excellent and powerful tool during the drug development process and monitors batch to batch quality and assist with the development of bioequivalence. It is important for characterization of dosage form performance invitro under standardize conditions which help us to understand the drug release behavior invivo. In general dissolution methods are recommended for solid oral dosage forms however these are extended to other dosage forms. Various dissolution techniques are proposed for novel drug delivery systems which include vertical diffusion cell for transdermal as well as semi solid dosage forms, dialysis cell for parenterals, 3 piston apparatus for chewing gum, multi compartment cells for poorly soluble compounds, modified Rosset-rice test for floating tablets and so on. Dissolution tests for novel drug delivery systems have been limited primarily to literature citation and are yet to find a place in pharmacopeia.

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