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Review Article

DISSOLUTION: A PREDICTIVE TOOL FOR CONVENTIONAL AND NOVEL DOSAGE FORMS

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ABSTRACT

Dissolution 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. 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, Drug Release Testing and Novel Dosage forms.*

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 [1].

Dissolution testing is an official test used by pharmacopeia's for evaluating drug release of solid and semisolid dosage forms dissolution tests were first developed to quantify the amount and extent of drug release from solid oral dosage forms including immediate/sustained release tablets and capsules [2]. More recently, dissolution has become important in testing drug release of dosage forms such as, buccal and sublingual tablets, chewing gums, soft gelatine capsules, suppositories, transdermal patches, aerosols and semisolids the study of the dissolution process has been developing since the end of the 19th century by physical chemists. The goal is to have a fully functional set of USP performance tests for all kinds of dosage forms [3].

Table No. 1: List of the Official Dissolution Apparatus and their uses

S. No.	Official Name	Main features of the apparatus	Uses	Rot. speed
1	USP Apparatus 1	Basket	Tablets, capsules, Floating dosage forms	50-120 rpm
2	USP Apparatus 2	Paddle	Tablets, capsules, enteric forms	25-50 rpm
3	USP Apparatus 3	Reciprocating cylinder	Extended release drug product	6-35 rpm
4	USP Apparatus 4	Flow through cell	Implants, powders, suspensions	N/A
5	USP Apparatus 5	Paddle over disk	TDDS, Ointments	25-50 rpm
6	USP Apparatus 6	Cylinder 6	TDDS	N/A
7	USP Apparatus 7	Reciprocating disk	Extendedrelease drug product	30 rpm

Conditions (for all in general):

1. Temp. - 37±0.5oC
2. PH - ±0.05 unit in specified monograph
3. Capacity – 1000 ml
4. Distance between inside bottom of vessel and paddle/basket is maintained at 25±2 mm.
5. For enteric coated dosage form it is first dissolved in 0.1 N HCl & then in buffer of pH 6.8 to measure drug release. (Limit – NMT 10% of drug should dissolve in the acid after 2hr.and about 75% of it should dissolve in the buffer after 45 min.

The dissolution apparatus has evolved gradually & considerably from a simple beaker type to a highly versatile & fully automated instrument. Based on absence or presence of sink conditions, there are three principal types of dissolution apparatus [4-8]:

1. Closed-compartment- Basically a limited volume apparatus operating under non-sink conditions. E.g. App-I & II.
2. Open compartment- One in which dosage form is contained in a column which is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition)

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3. Dialysis type system- Used for very poorly aqueous soluble drug for which maintenance of sink conditions would otherwise require large volume of dissolution fluid.

I.P. and E.P:

Apparatus I – paddle apparatus
Apparatus II – basket apparatus

B.P. and U.S.P.:

Apparatus I – basket apparatus
Apparatus II – paddle apparatus

B.P. and E.P.:

Apparatus III – flow through cell apparatus

1) Apparatus I- Basket Apparatus:

- ✓ Unless otherwise specified in the individual monograph, use 40-mesh cloth.
- ✓ Useful for: Capsules, Beads, Delayed release / Enteric Coated dosage forms , Floating dosage forms
- ✓ Standard volume: 900/1000 ml

2) Apparatus-II - Paddle Apparatus

Method of first choice the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of no reactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.

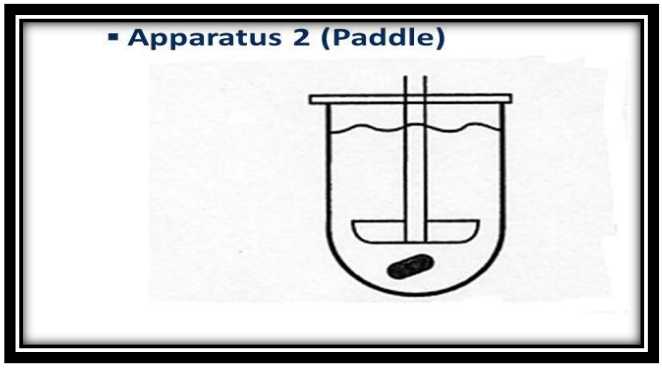

Fig. 1: Paddle

- ✓ Useful for: Tablets, Capsules, Beads, Delayed release, enteric coated dosage forms
- ✓ Standard volume: 900/1000 ml.

3) Apparatus III – Reciprocating cylinder:

The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and screens that are made of suitable nonsorbing and nonreactive material (polypropelene) and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels.

The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5 during the test.

The dosage unit is placed in reciprocating cylinder & the cylinder is allowed to move in upward and downward direction constantly. Release of drug into solvent within the cylinder measured.

- ✓ Useful for: Tablets, Beads, controlled release formulations.
- ✓ Standard volume: 200-250 ml/station.

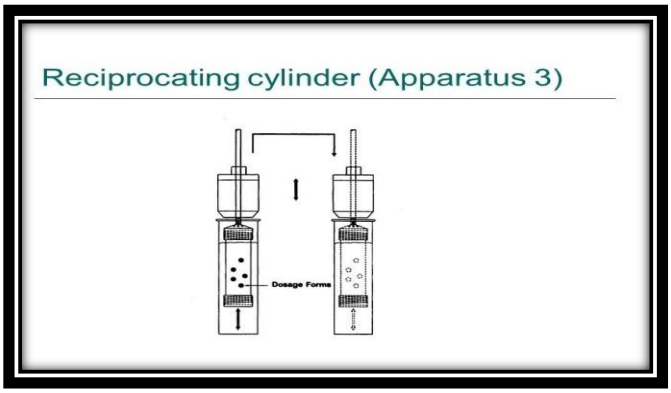

Fig. 2: Reciprocating Cylinder

4) Apparatus IV – flow through cell

The assembly consists of a reservoir and a pump for the Dissolution Medium; a flowthrough cell; a water bath that maintains the Dissolution Medium at 37 ± 0.5. The cell size is specified in the individual monograph.

The pump forces the Dissolution Medium upwards through the flow-through cell. Place the glass beads into the cell specified in the monograph, Place 1 dosage unit on top of the beads or, if specified in the monograph, on a wire carrier and then assemble the filter head, and fix the parts together by means of a suitable clamping device.

By introducing the pump the Dissolution Medium warmed to 37 ± 0.5 through the bottom of the cell to obtain the flow rate specified in the individual monograph. Collect the elute by fractions at each of the times stated, Perform the analysis as directed in the individual monograph.

- ✓ Useful for: Low solubility drugs, Micro particulates, Implants, Suppositories, Controlled release formulations
- ✓ Variations: (A) Open system & (B) Closed system

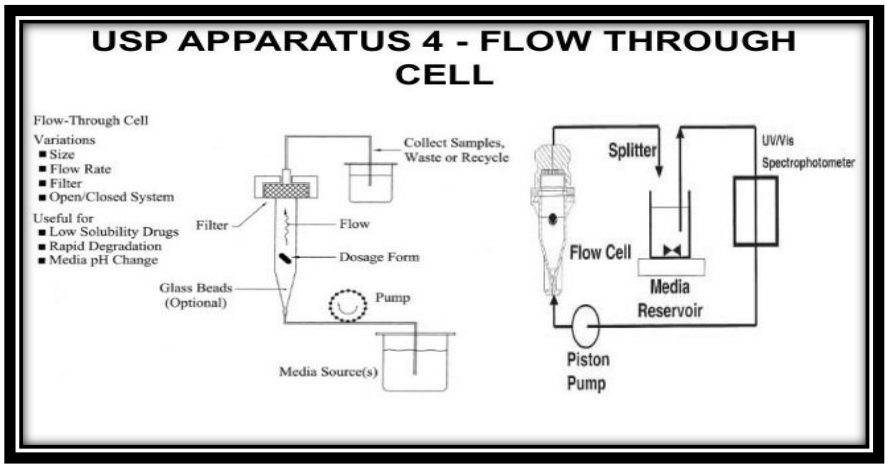

Fig. 3: Flow through Cell (USP)

5)ApparatusV–Paddleoverdisk:

Use the paddle and vessel assembly from Apparatus 2 with the addition of a stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel. Other appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being tested. The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel, the disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade, the vessel may be covered during the test to minimize evaporation.

- ✓ Useful for: Transdermal patches
- ✓ Standard volume: 900 ml.

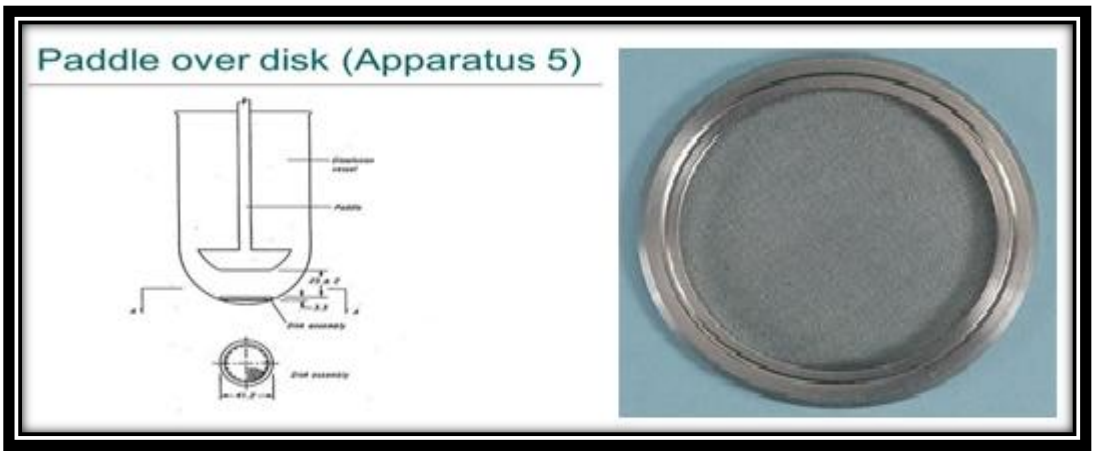

Fig. 4: Paddle over Disk

6)Apparatus VI–cylinder:

Use the vessel assembly from Apparatus 1 except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5 during the test. The dosage unit is placed on the cylinder at the beginning of each test, to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder & removes trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph.

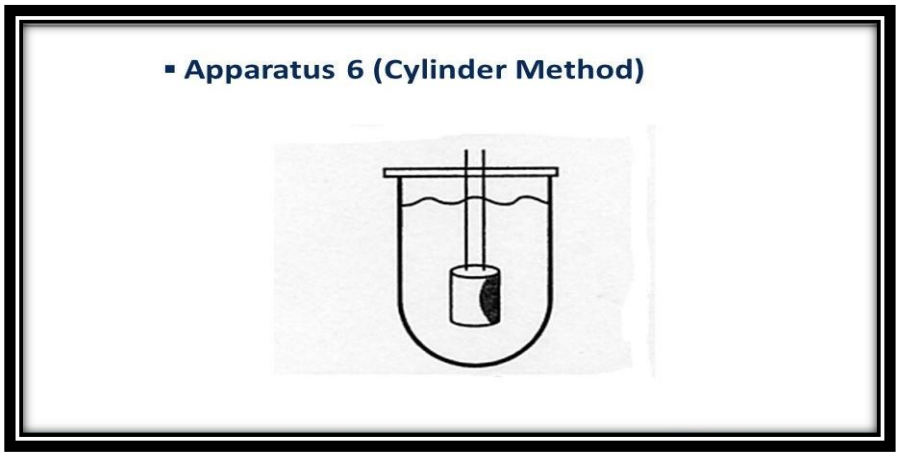

Fig. 5: Cylinder Method

7) Apparatus VII – Reciprocating Holder:

The assembly consists of a set of volumetrically 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 solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, inside the containers at 32 ± 0.5. For Coated tablet drug delivery system attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the end of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

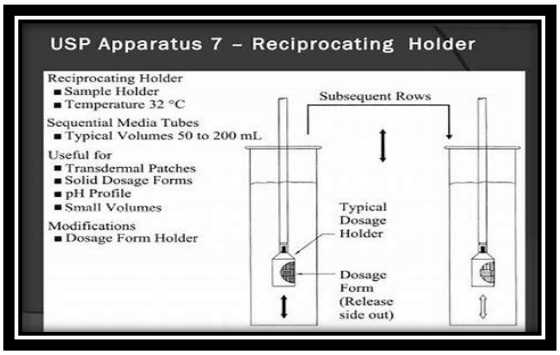

Fig. 6: Reciprocating Holder

For Transdermal drug delivery system attach the system to a suitable sized sample holder with a suitable O-ring such that the back of

the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder, trim the excess substrate with a sharp blade for Other drug delivery systems attach each system to be tested to a suitable holder as described in the individual monograph.

Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of Dissolution Medium within a calibrated container reciprocate at a frequency of about 30 cycles per minute with amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Perform the analysis as directed in the individual monograph.

Theories of Dissolution: [9]

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)

Diffusion Layer Model (Film Theory): It is a simplest model where dissolution of crystal, immersed in liquid takes place without involving reactive or electrical forces.Consist of two consecutive steps:

Solution of the solid to form a thin film or layer at the solid / liquid interface called as stagnant film or diffusion layer which is saturated with the drug this step is usually rapid (instantaneous).

Diffusion of the soluble solute from the stagnant layer to the bulk of the solution this step is slower and is therefore the rate determining step in the drug dissolution. Fick's law covers only diffusions under steady state conditions, modifying it Noyes & Whitney established another equation

$$dc/dt=k(c_s-c_b)$$

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

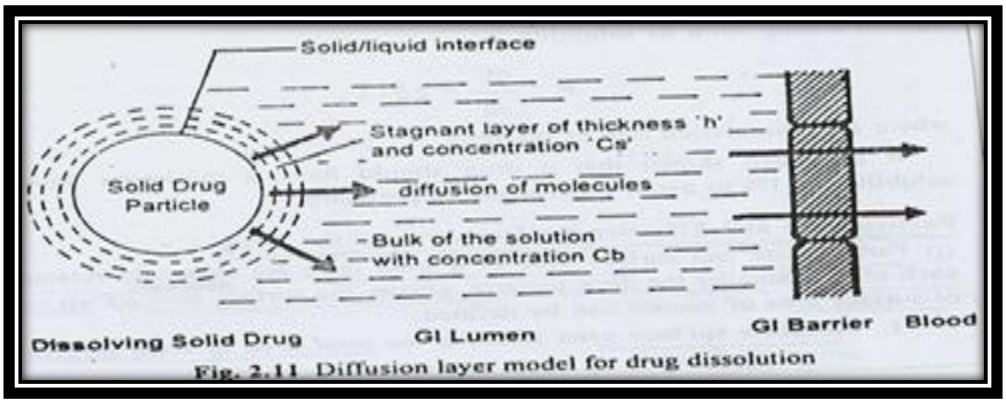

Fig. 7: Diffusion layer model for drug dissolution

Modified Noyes-Whitney's Equation:

$$dc/dt=DAKw/o(c_s-c_b)/vh$$

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.
$(C_s - C_b)$= conc. gradient for diffusion of drug.

Hixon-Crowell's cubic root law of dissolution takes into account the particle size decrease and change in surface area,

$$W_0^{1/3} - W^{1/3} = K_t$$

Where,
W_0=original mass of the drug
W=mass of drug remaining to dissolve at time t
K_t=dissolution rate constant.

Danckwert's Model (Penetration or Surface Renewal Theory):

This theory assumes that solid-soln equilibrium is achieved at interface and mass transport is slow step in dissoln process. The model could be visualized as a very thin film having a conc Ci which is less than saturation, as it is constantly being exposed to fresh surfaces of liquid having a conc much less than Ci, According to model, the agitated fluid consist of mass of eddies or packets that are continuously being exposed to new surfaces of solid and then carried back to bulk of liquid.

Diffusion occurs into each of these packets during short time in which the packet is in contact with surface of solid. Since turbulence actually extends to surface, there is no laminar boundary layer and so no stagnant film exists. Instead, surface continually being replaced with fresh liquid.

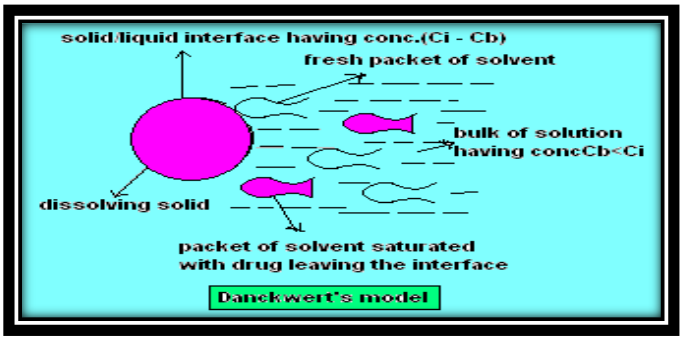

Fig. 8: Danckwert's model

The Danckwert's model is expressed by equation:

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

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

Interfacial Barrier Model (Double Barrier or Limited Solvation Theory):

The Diffusion layer model and the Dankwert's model were based on two assumptions:

1) The rate determining step that controls dissolution is the mass transport.
2) Solid solution equilibrium is achieved at the solid/liquid interface.

According to interfacial barrier model, an intermediate conc can exist at the interface as a result of solvation mechanism and is a function of solubility rather than diffusion. When considering the

dissolution of the crystal will have a different interfacial barrier given by following equation,

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

Where

G = dissolution per unit area

Ki = effective interfacial transport constant

In this theory, the diffusivity D may not be independent of saturation conc Cs.

The interfacial barrier model can be extended to both Diffusion layer model and the Dankwert's model.

Concept of Dissolution / Drug Release Testing:

In the pharmaceutical industry, dissolution testing is an important tool in both drug development and quality control. Although initially developed for immediate release (IR) solid oral dosage forms and then for modified release solid oral dosage forms, the application of dissolution testing has expanded to a variety of "novel" or "special" dosage forms. As these formulations have become more prevalent due to complexities of drug delivery, there has been an increased development of modified testing methods to characterize the in vitro release of these dosage forms.

Immediate releases tablet:

Immediate release dosage forms are intended for the rapid delivery of drug into 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 [11, 12]. Newer design for the testing of these dosage forms include mini paddle apparatus. 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 [13]. 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 [14-16]. 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 [17].

Transdermal Patches:

Although several apparatus and procedures have been utilized to study in vitro release characteristics of transdermal patches, it is desirable to avoid unnecessary proliferation of dissolution/drug release test equipment. Current compendial apparatus include the paddle over disk/disk assembly method, the rotating cylinder, the reciprocating disk, and a paddle over extraction cell method. The paddle over disk procedure with a watch glass– patch–screen sandwich assembly could be a suitable method as it has been shown experimentally that this procedure results in almost the same release profile as other, more complicated apparatus for all US marketed transdermal patches [18].

The configuration of this assembly ensures that the patch is prevented from floating during the entire testing period. Alternatively, the patch can be fixed to the supporting disk (e.g., by double-sided adhesive), superseding the use of a screen for fixation. Special attention needs to be given to the proper positioning of the patch so that the drug-loaded surface is exposed to the medium. The pH of the medium ideally should be adjusted to pH 5–6, reflecting physiological skin conditions. For the same reason, the test temperature is typically set at 32°C (even though the temperature may be higher when the skin is covered). One hundred revolutions per minute is considered a typical agitation rate and testing time should take into account the amount of drug administered to the body during the application time of the patch. In cases where drug release cannot be achieved in an appropriate time by using standard aqueous dissolution media, aqueous–organic solvent mixtures can also be used [18].

Soft gelatine capsules:

Soft gelatine capsules can be composed of either hydrophilic or hydrophobic components. In the case of hydrophilic capsules dissolution tests can be performed quite easily using USP apparatus 2 but this becomes more difficult for hydrophobic medication. However, it is speculated that exposure of the gelatine shell to such media may induce physical and/ or chemical changes of the drug, arising either through complex formation or crosslinking reactions. The official methods have the serious disadvantage that the dissolution condition for lipophilic floating materials is poorly. It is not suitable for lipid filled soft gelatine capsules, because after capsule rupture, the oil phase is quickly drawn into the filter on the top of the cell, which can clog the filter, or the oil is forced through the filter.

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. The results of their study showed that, after 6 hrs of dissolution, most of the viscous oily vehicle still remained entrapped within the basket; hence failure to release drug into the aqueous phase. It appears that the standard dissolution basket pores (40 meshes) and lack of appropriate hydrodynamic conditions within the basket had a significant limiting effect on drug release from the oleaginous formulation. The study showed that the most reproducible results can be obtained when the paddle is positioned in aqueous medium and the capsule is below the mesh assembly [19].

Suppositories:

Drug release mechanisms of suppositories primarily follow either erosional or melting processes depending on whether the matrix is soluble or dispersible in aqueous physiological media or if it melts at body temperature [20, 21].

The partition of compound from the water immiscible fatty base to body fluids may have an influence on the bio performance [22]. A paddle method or continuous flow method are favored for the hydrophilic suppositories with product specific adjustment of parameters such as paddle rotating speed or flow rate of the medium. Sink conditions should be taken into consideration in designing such a drug release testing method [23]. A rotation speed of 50 rpm in the paddle method and a flow rate of 16 ml/min in the continuous flow method using a phosphate buffer pH 7.4 at 37°C can be used as a starting point in method development for such suppositories. Lipophilic suppositories may undergo several phases before the release of the API such as softening, deformation melting, or disintegration accompanied by spreading [24, 25].

Microspheres:

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 [26].

Floating tablets:

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 [27]. 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 [28].

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 [29]. 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 [30].

Niosomes:

The in- vitro drug release of niosomal formulations was performed by using dialysis method [31]. dialysis bag which was fitted in a USP Drug Dissolution Apparatus II (paddle type) , Niosomal Formulation was added in to the dialysis tube and aliquots (5ml) were withdrawn each hour and replaced by the same amount of fresh buffer to maintain sink condition.

The dialysis bag (cut off of membrane 70 nm) could retain niosomal dispersion and allow the diffusion of free drug into dissolution medium. The bags were soaked in distilled water for 24 hrs before being used. The two ends fixed by strings and 50 rpm rotation speed.

The drug content was determined by HPLC method every one hour for a total period of 7 hrs. All the operations were carried out in triplicate.

The in-vitro drug release study was conducted in pH progression medium at 37°C ± 0.5°C [31]. The steps of using dissolution media at different pH was as follows: - 1st 2hours: 900 ml of hydrochloric acid aqueous solution at pH 1.2. - 3rd - 7th hours: 900 ml of phosphate buffer solution at pH 6.8.

Resealed Erythrocytes:

In vitro leakage of the drug from loaded erythrocytes is tested using autologous plasma or an isosmotic buffer at 370°Cwith a hematocrit adjusted between 0.5% and 50%.

The supernatant is removed at previously programmed time intervals and replaced by an equal volume of autologous plasma or buffer.Some authors recommended performing in vitro release studies from loaded erythrocytes using a dialysis bag [32].

Liposomes:

Membrane dialysis methods, such as dialysis sac and reverse dialysis sac, are conventionally used for performance testing of liposomes. These methods are needed for separating liposomes from the release media.

USP Apparatus 4, using a flow-through cell fitted with a dialysis adapter, may be used for performance testing of liposome formulations. An adapter has been designed for the 22.6-mm diameter flow-through cell. A dialysis membrane is placed over the adapter, and this assembly is then placed over the conical part of the flow-through cell. The method has been shown to be superior to dialysis and reverse dialysis sac methods for liposomes containing the hydrophobic drug dexamethasone in terms of reproducibility and discriminatory ability [33].

The flow-through cell (USP Apparatus 4), fitted with a dialysis adapter, may be used for performance testing of liposome formulations. However, if placed directly in the flow-through cell, the liposomes (nanometer size range) may either block the filter or pass through it. The dialysis adapter may be used with 12- or 22.6-mm diameter flowthrough cells. Flow-through cell size may be selected based upon the drug concentration in the formulation and the volume of formulation to be used for release testing. Higher volumes can be used with the 22.6-mm diameter flow-through cell.

The dialysis adapter framework consists of a circular top and bottom supported by three wires of a suitable material (such as peek, metal, or others). The circular top has an opening for sample introduction, and this opening can be closed with a leak-proof screw. A dialysis membrane/ bag is placed over this adapter frame and sealed with "O" rings. This assembly is then placed over the conical part of the flow-through cell. The standard tablet cells, 12.0 and 22.6 mm, may be used without the tablet clip present, and the unit may be operated in the open- or closed-system configuration. Appropriate flow rates can be selected, depending on the formulation and application. The temperature of the cells is usually maintained at 37 ± 2 °C. A set of six cells may be used for each test [33].

Implants:

The flow-through cell (USP Apparatus 4) may be used for release testing of implant formulations. The implants may be held in the flow-through cell with a special holder. The standard tablet cells, 12.0 and 22.6 mm, may be used without the tablet clip when the unit is operated in the closed-system configuration or in the open configuration. Appropriate flow rates can be selected, depending on the formulation and application. The temperature of the cells is usually maintained at 37 ± 2 °C. For accelerated testing, higher temperatures can be used. A set of six cells is used for each test [34].

Table No. 2: Acceptance criteria [35]

Stage	Number units	Acceptance criteria
S_1	6	Each unit is not less than Q* +5%
S_2	6	Average of the 12 (S1+S2) units is ≥ Q and no unit is less than Q−15%
S_3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q−15% and no unit is less than Q−25%

Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

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