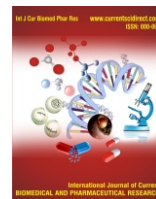




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Review Article

Dissolution and Dissolution Apparatus: A Review

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ABSTRACT

For orally administered non-solution dosage forms, in vitro performance test procedure such as dissolution test is performed for various purposes. It is one of the routinely performed quality control tests for the oral solid dosage forms. Dissolution research started to develop about 100 years ago as a field of physical chemistry and since then important progress has been made. Apart from its importance in the field of pharmaceutical analysis it is also important in pharmaceutical formulation technology and drug discovery. In this review paper we will focus on different mathematical aspects of dissolution process and different dissolution apparatuses are in use. We will discuss some non-conventional dissolution testing methods. The review will also focus on modernization of dissolution process and dissolution testing apparatuses including automation in dissolution testing and adoption of fiber optic technology.

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1. Introduction

The study of the dissolution process has been developing since the end of the 19th century by physical chemists. Therefore, most of the fundamental research in the field was not related to drugs at all, and the basic laws for the description of the dissolution process were already available when interest in drug dissolution started to rise. Despite the advances in in vitro dissolution in chemical engineering sciences, in the pharmaceutical sciences the concept was not used extensively until the early 1950s. Until then the in vivo availability of the drug was thought to be determined solely by the disintegration of the tablet, ignoring the dissolution process. [1]

For orally administered non-solution dosage forms, in vitro performance test procedures such as dissolution and disintegration are used to i) guide drug development and select formulations for further in vivo studies, ii) evaluate comparability between products before and after changes in formulation and/or

manufacturing; iii) serve as a surrogate for in vivo bioequivalence studies, with suitable in vitro/in vivo correlations and/or use of the Biopharmaceutics Classification System approach, and iv) ensure batch-to-batch consistency for product performance. [2] In pharmaceutical industry, in vitro dissolution test is performed early in order to validate initial screening among potential formulations to detect the influence of critical manufacturing variables and to help in the selection of the candidate formulation. [3-5] The use of dissolution test can speed up the formulation development, enabling a prompt identification of potential problems in drug release. [6] In vitro release testing is also a very important tool for batch to batch quality control. [7] In vitro dissolution tests are important in the development and ultimately in the quality control (QC) of a solid dosage form. [8] A dissolution test measures the rate of release of the drug. The objective is to develop a discriminatory method that is sensitive to variables that affect the dissolution rate. Such variables may include characteristics of the active pharmaceutical ingredient (API) (e.g., particle size, crystal form, bulk density), drug product composition (e.g., drug loading, and the identity, type, and levels of excipients), the drug product manufacturing process (e.g., compression forces, equipment), and the effects of stability storage conditions (e.g., temperature, humidity). [9] At early stages of formulation development, in vitro dissolution testing provides guidance on optimizing drug release from formulations. While at later stages, it

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may be employed as an indicator of the in vivo performance of drug products to potentially reduce the number of bioavailability/bioequivalence studies. [10] The connection between the dissolution test and in vivo performance is based on the fact that before an active pharmaceutical agent can be absorbed, it must first be dissolved in the aqueous contents of the gastrointestinal (GI) tract. Because there is no other in vitro performance test with such a close link to in vivo performance, dissolution and drug release studies are a regulatory requirement for the development, and ultimate approval, of all solid oral drug products. [11] It is evident that the release profile and thus absorption of drug may be influenced by design and operation of the apparatus, and the selection of medium, USP describes the various apparatuses used in dissolution studies, and has been recently harmonized with the European Pharmacopoeia and the Japanese Pharmacopoeia. [12] Several guidelines are available for the development and application of dissolution testing in various FIP position papers [13,14] and regulatory guidelines [11,15,16] are also available. Dissolution research started to develop about 100 years ago as a field of physical chemistry and since then important progress has been made (Table 1)

2. Different Mathematical Aspects

2.1. Dissolution of particles

The modified Noyes-Whitney equation [17] offers a rationale base to describe the dissolution process of a particle:

$$\frac{d_m}{d_t} = AD \frac{C_s - C}{h}$$

Where C is the instantaneous concentration of drug in the medium, A is the surface area available for dissolution, D is the diffusion coefficient of the molecule, C_s is its solubility in the dissolution medium and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. From this simple mass balance equation one can infer that to enhance the dissolution rate dm/dt it is possible to increase the total drug surface area A by micronization and/or by optimizing its wetting characteristics, to promote perfect sink conditions (C→0), to reduce the thickness of the boundary layer or by increasing the apparent drug solubility C_s. [18] The parameter D is a function of the diffusion coefficient of the solute molecules. Maximum dissolution rates are predicted when C=0. Consequently, as C increase, the dissolution rate decreases. The parameter D is also dependent on C_s-C. Such conditions, where dissolution is followed by absorption of the drug, as in the in vivo situation, are described as sink condition. In-vitro systems should ideally maintain a sink condition and the dissolving solid should be tested in fresh solvent, where there is no build up of dissolved drug in the dissolution medium. Such a situation is only actually achieved in flow-through type apparatus e.g., USP Apparatus 4, whilst Apparatus 1 and 2 there is a gradual increase in C during the test.

Table 1. Major contributions and events in the development of dissolution testing [1]

Year	Contributor (s)	Major contribution
1897	Noyes AN and Whitney WR	Conducted the first dissolution experiments and published an article entitled "the rate of solution of solid substances in their own solutions". Noyes-Whitney equation
1900	Brunner E and von Tolloczko S	Showed that the rate of dissolution depends on the exposed surface, the rate of stirring, temperature, structure of the surface and the arrangement of the apparatus.
1904	Nernst W and Brunner E	Nernst-Brunner equation based on the diffusion layer concept and Fick's second law.
1931	Hixson AW and Crowell JH	Dependence of reaction velocity upon surface and agitation. Hixson and Crowell reported that the Noyes-Whitney equation in its original form and without any details about the mechanism of the process had been sufficiently validated with a wide range of experiments, as opposed to the various mechanistic explanations that had appeared, none of which was entirely satisfactory.
1951	Edwards LJ	First to appreciate that following the oral administration of solid dosage forms, if the absorption process of drug from the gastrointestinal tract is rapid, then the rate of dissolution of that drug can be the step which controls its appearance in the body.
1957	Nelson E	First to explicitly relate the blood levels of orally administered drugs (theophylline salts) to their in vitro dissolution rates.
1961	Higuchi T	Reviewed the interfacial barrier model proposed by Wilderman in 1909 and Danckwerts model (1951).
1962	Levich VG	Improved the theoretical model of the dissolution experiment using rotating disks, taking into account the centrifugal force on diffusion.
1970		The basket-stirred-flask test (USP apparatus 1) was adopted as an official dissolution test in 6 monographs of the United States Pharmacopoeia (USP) and National Formulary (NF).
1978		Adoption of the paddle method (USP apparatus 2).
1981		The first guidelines for dissolution testing of solid dosage forms were published as a joint report of the Section for Official Laboratories and Medicines Control Services and the Section of Industrial Pharmacists of the FIP.
1991		Adoption of the reciprocating cylinder (USP apparatus 3) for extended-release products.
1995		Adoption of the flow-through cell in (USP apparatus 4) for extended-release products.

2.2. Dissolution of mono-dispersed powder

Dissolution processes of multiparticulate systems where the specific surface area decreases during the dissolution, may be described by the Hixson and Crowell cube root law [19] in the following equation-

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

Where, W_o = the original mass of drug, W = amount of remaining drug at time t , and K = dissolution rate constant. There are several factors assumed in cube root law, such as, constant diffusion layer thickness, isotropicity of the sample, an independence of solubility from particle size, smooth surfaces, and sink conditions. For non-sink conditions and polydispersed systems modifications of the equation was required. Lai and Carstensen [20] derived shape factors to modify cube root behavior. [21]

2.3. Dissolution of disintegrating tablets and capsules

Disintegration produces vast changes in surface area. As a result the development of theories of dissolution from disintegrating tablets and capsules becomes very difficult. Attempts have been made to develop models to describe dissolution rates from tablets using complex mathematical approaches. [21]

2.4. Dissolution of non-disintegrating tablets

For systems where drug release involves the dissolution of a soluble drug at high concentrations from an insoluble matrix, the Higuchi equation [22] adequately describes release rates.

$$\frac{W_r}{t^{1/2}} = 2W_o \frac{S}{V} (D/\pi\tau)^{1/2}$$

Where, W_r = amount of drug dissolved in time t , W_o = dose of the drug, S = effective diffusional area, V = volume of the hydrated matrix, D = diffusion coefficient of the drug in the hydrated matrix, τ = tortuosity of the matrix. An analogous equation was developed for drugs of limited water solubility. [23]

3. Different Dissolution Testing Apparatus

The USP has 7 different apparatus that can be used for dissolution testing although most tablets and capsules use Apparatus 1 or 2 also known as basket and paddle. These two apparatus were developed through the 1960s and adopted by the USP in the 1970s. [24]

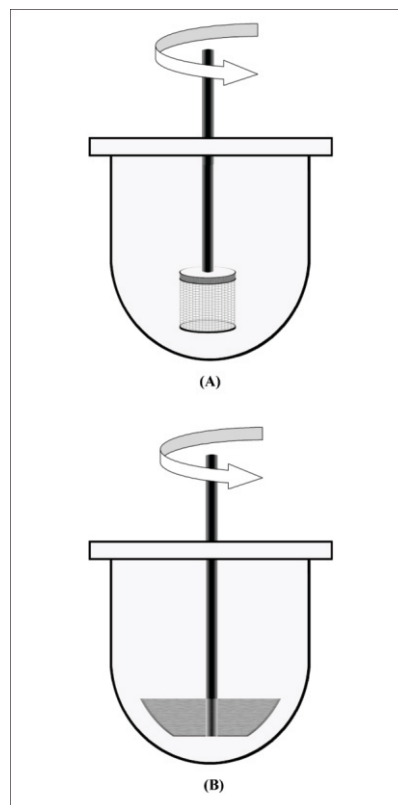
3.1. USP Apparatus 1 (Basket Apparatus)

The basket method was first described in 1968 by Pernarowski and his co-workers. [25] The most commonly used methods for evaluating dissolution first appeared in the 13th edition of the U.S. Pharmacopeia in early 1970. These methods are known as the USP basket (method I) and paddle (method II) methods and are referred to as "closed-system" methods because a fixed volume of dissolution medium is used. [26]

In practice a rotating basket method provides a steady stirring motion in a large vessel with 500 to 1000 mL of fluid that is immersed in a temperature -controlled water bath. Basket method is very simple, robust, and easily standardized. The USP basket method is the method of choice for dissolution testing of immediate-release oral solid dosage forms. [27]

This apparatus is useful for tablets, capsules, beads and floaters. Solids (mostly floating), monodisperse (tablets) and polydisperse (encapsulated beads) drug products are commonly tested using USP Apparatus 1 (Figure 1).

Figure 1. Schematic diagram of (A) USP Apparatus 1 and (B) USP Apparatus 2



3.2. USP Apparatus 2 (Paddle Apparatus)

An apparatus described by Levy and Hayes [28] may be considered the forerunner of the beaker method. It consisted of a 400 ml beaker and a three-blade, centrally placed polyethylene stirrer (5 cm diameter) rotated at 59 rpm in 250 ml of dissolution fluid (0.1N HCl). The tablet was placed down the side of the beaker and samples were removed periodically. In the Apparatus 2, (the paddle apparatus method) a paddle replaces the basket as the source of agitation. As with the basket apparatus, the shaft should position no more than 2mm at any point from the vertical axis of the vessel and rotate without significant wobble. [21]

The apparatus is useful for tablets, capsules and suspensions. Like USP Apparatus 1 solids (mostly floating), monodisperse (tablets) and polydisperse (encapsulated beads) drug products are commonly tested using USP Apparatus 2. But floating dosage forms require sinker which could be considered as a disadvantage of the apparatus. Moreover cone formation and positioning of tablet during the test is sometimes hard to maintain. [29]

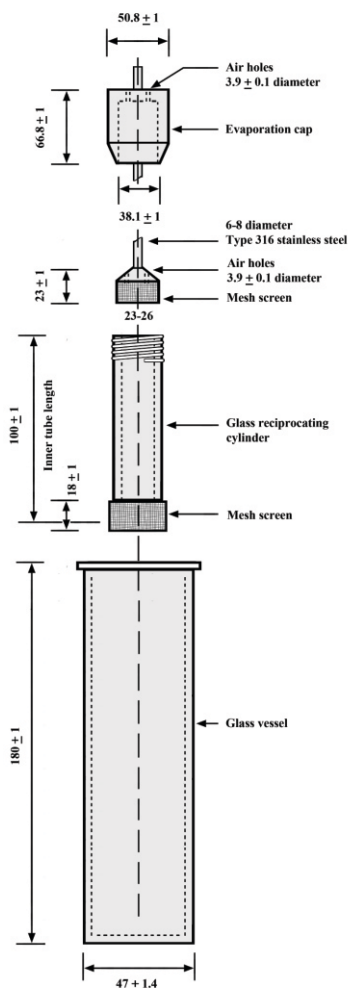
Both the USP Apparatus 1 and 2 share some common advantages and disadvantages. Advantages include: i) widely accepted apparatus for dissolution test, ii) apparatus of first choice for solid

oral dosage forms, iii) standardized, iv) easy to operate, v) robust and vi) broad experience. Disadvantages include: i) limited volume of the dissolution media, ii) simulation of the gastrointestinal transit is not possible and iii) hydrodynamic conditions are not known. Dissolution results obtained with USP Apparatus 1 and 2 may be significantly affected by shaft wobble, location, centering, and coning [29]. Schematic diagram of Apparatus 2 is shown in Figure 1+

3.3. USP Apparatus 3 (Reciprocating Cylinder Apparatus)

The design of USP apparatus 3 is based on the disintegration tester. The assembly of USP apparatus 3 consists of a set of cylindrical, flat-bottomed glass outer vessels; a set of glass reciprocating inner cylinders; and stainless steel fittings and screens that are made of suitable material and that are designed to fit the tops and bottoms of the reciprocating cylinders. Operation involves programming the agitation rate, in dpm, of the up and down for the inner tube inside the outer tube. On the up stroke, the bottom mesh in the inner tube moves upward to contact the product and on the down stroke the product leaves the mesh and floats freely within the inner tube. Thus the action produced carries the product being tested through a moving medium. [29]

Figure 2. Schematic diagram of USP Apparatus 3 (Reciprocating Cylinder Apparatus)



The USP Apparatus 3, a Reciprocating Cylinder, dips a transparent cylinder containing the dosage form at a rate determined by operator. The tubes have mesh base to allow the medium to drain into a sampling reservoir as the tube moves up and down, thus creating convective forces for dissolution. The cylinders can also be transfer to different media at specified time automatically. A second design is the rotating bottle apparatus, which also allow for changing of medium to simulate a pH gradient or fed and fasted conditions. [26] It allows automated testing for up to six days and the manufacturers advocate its use in the testing of extended-release dosage forms. It became official in USP 22 as Apparatus 3 and is prescribed for the testing of extended-release articles. [30]

This apparatus is originally used for extended release products, bead type modified release dosage form, [27] particularly beads in capsules. It is also useful for solids which are mostly non-disintegrating (Figure 2).

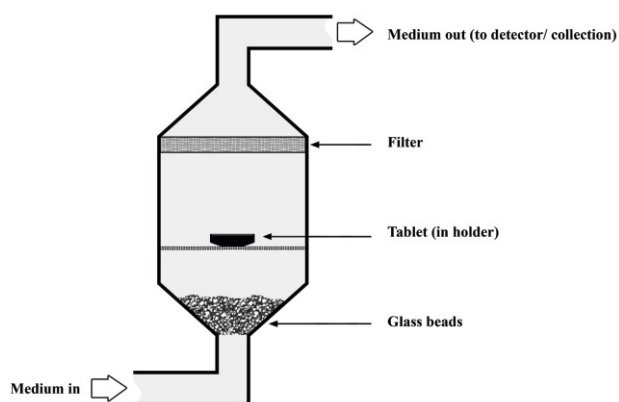
USP Apparatus 3 offers advantages like i) programmed for dissolution in various media for various time, ii) the media can be changed easily, iii) may start at pH 1 and then pH 4.5 and then at pH 6.8 and iv) attempts to mirror pH changes and transit times in the GI tract. But it has got some disadvantages too, i.e. i) disintegrating dosage forms show too low results, ii) surfactants cause foaming and iii) volume of dissolution media is too small.

3.4. USP Apparatus 4 (Flow-Through Cell Apparatus)

The history of the flow through cell methodology in drug release testing of oral dosage forms begins in the 1950's. The first attempt for the development of the flow-cell method was probably made in the laboratories of the U.S. Food and Drug Administration in 1957. Since then, various flow-cell devices have been described. The flow through cell was recommended as an alternative in vitro drug release testing apparatus by the Dissolution Tests working group of the Fédération Internationale Pharmaceutique (F.I.P.) in 1981. [11] Afterwards, the method was incorporated in various pharmacopoeias. [31] USP Apparatus 4 can be operated under different conditions such as open or closed system mode, different flow rates and temperatures. The diversity of available cell types allows the application of this apparatus for testing of a wide range of dosage forms including tablets, powders, suppositories or hard and soft gelatin capsules. It is the method of choice for extended release and poorly soluble products. [32,33] USP Apparatus 4 requires the sampling pump to be on continuously throughout the analysis, as the dissolution rate is directly proportional to the flow rate of the medium that is pumped into the flow through cell. Sampling for this technique therefore requires that continuous collection or measurement of the eluted sample be maintained. As the dissolution time increases, large sample storage may be required, which may not be practical. Fraction collectors have a finite number of positions that are reduced as the volume of samples to be collected increases, which can limit the number of time points that can be collected. Sample splitters can also be used to divert the sample sequentially between collection and waste, thus reducing the volume of sample to be collected. More recently a dual sampling rack has been designed to allow samples to be collected while simultaneously diluting, if required, and injecting into either an HPLC system or a UV spectrophotometer. [34]

Drug products like solids (tablets, capsules, implants, powder, and granules), semisolids (suppositories, soft gelatin capsules, ointments) and liquids (suspensions) are usually tested using this apparatus (Figure 3).

Figure 3. Schematic diagram of USP Apparatus 4 (Flow-Through Cell Apparatus)



Advantages of the apparatus include: i) no limitation regarding the volume of media used for the dissolution test, ii) suitable for low soluble drugs, iii) gentle hydrodynamic conditions, iii) simulation of the gastrointestinal transit and iv) suitable for special dosage forms such as powder and granules, implants. But the apparatus has got limited experience; pump precision may influence the results and fractioned primary data lead to greater experimental error when computed to cumulative profiles.

3.5. USP Apparatus 5 (Paddle-over-Disk Apparatus)

In Paddle-over-Disk method 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. The temperature is maintained at $32^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade. [35] The apparatus is used to test transdermal patches. [7]

3.6. USP Apparatus 6 (Cylinder Apparatus)

This is a modification of the basket apparatus (USP Apparatus 1). It uses the vessel assembly from Apparatus 1 except to replace the basket and shaft with a stainless steel cylinder stirring element. [35] The apparatus is used to test transdermal patches. [7]

3.7. USP Apparatus 7 (Reciprocating Holder Apparatus)

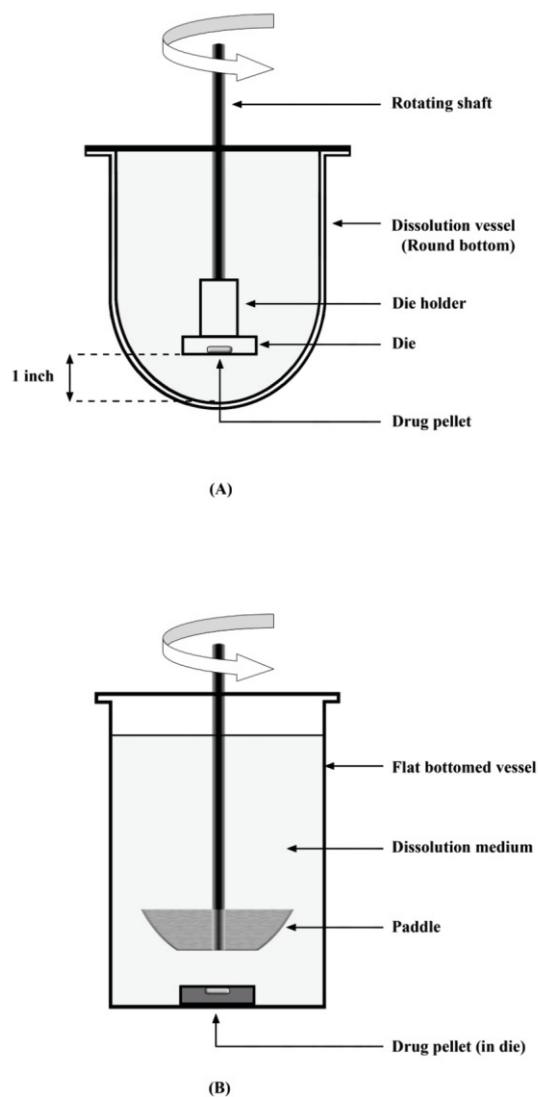
Originally introduced in the USP as a small-volume option for small transdermal patches, the reciprocating disk apparatus was later renamed the reciprocating holder apparatus with the adoption of four additional holders for transdermal systems, osmotic pumps, and other low-dose delivery systems. [36] The apparatus is used to test transdermal patches. [7]

4. Intrinsic dissolution method

The intrinsic dissolution rate is defined as the rate of dissolution of a pure pharmaceutical active ingredient when conditions such as surface area, temperature, agitation or stirring speed, pH, and ionic

strength of the dissolution medium are kept constant. Determining this parameter allows the screening of drug candidates and aids in understanding their solution behavior under various biophysiological conditions. [37,38]

Figure 4. Schematic diagram of (A) the rotating disk apparatus (Wood Apparatus) and (B) the stationary disk apparatus



Two variations of the IDR apparatus exists i) the rotating disk apparatus (Wood Apparatus) and ii) The stationary disk apparatus (Figure 4).

5. Unconventional methods

Pillay and Fassihi described various new or alternative methods for both qualitative and quantitative in vitro dissolution analysis, [39] including intervention with the ring/mesh assembly, application of two-phase dissolution media systems, use of reverse binding technique, chemical stabilization via constant nitrogen gas purge into aqueous dissolution media, and chemical complexation/interaction outside the dissolution vessel as a colorimetric tool for analytical measurements, emphasize the potential of:

1. Application of ring/mesh assembly for determination of release profiles from swellable low and high-density matrices. Pillay and Fassihi have used a new device (ring/mesh assembly) in conjunction with the paddle method to study the influence of the position of various dosage forms on release behavior and evaluated the release profiles obtained with such modification with those derived under standard dissolution conditions including the USP 23- recommended helical wire sinker used for swellable floatable delivery systems.
2. Evaluation of drug release from lipid-filled hardshell or softgel capsules. In a recent report a method which encompasses the development, design, and use of a modified two-phase dissolution media system by a novel approach for testing of either soft or hard shell lipid-filled gelatin capsules was proposed.
3. Determination of dissolution profile under nitrogen blanket for oxidizable or unstable substances.
4. Glucosamine release study from swellable hydrophilic matrix system.
5. Use of reverse-binding technique for evaluation of dmp 504, a water-insoluble bile acid Sequestrant.

6. Modernization in Dissolution Testing

6.1. Automation in dissolution testing

Laboratories automate dissolution tests to increase capacity, improve accuracy and reduce costs per test. These factors lead one to consider automation as a method of choice for a quality-control laboratory as well as for a research laboratory. In addition, the emerge of service laboratories testing samples outsourced from pharmaceutical companies calls for automation to offer clients an economic service. [40] With the widespread acceptance of dissolution testing in pharmaceutical industry various automated procedures have been developed. [41]

6.1.1. Fiber optics technology

Proposals for a new general chapter on dissolution in the USP [42] have highlighted the use of this technology and a regulatory perspective has also been published. [43] These developments suggest that fiber optic technology is likely to emerge as a common analytical tool in future. Bynum et al reported of the development of a UV Fiber Optic Probe Dissolution System for the analysis of solid dosage forms. The system uses 12 dip-type fiber optic probes coupled to 12 separate PDA spectrophotometers to acquire continuous dissolution curves in real time. The system is applicable to the analysis of both immediate and controlled release formulations. The system is accurate, quicker, and easier to set up when compared with conventional HPLC or UV-sipper systems. [44] Zolnik et al and his co-workers [45] reported that fiber optic UV probes can be used in conjunction with USP apparatus 4 to monitor the release from dispersed systems, such as microspheres, since the dispersed system is in an isolated chamber (flow through cell) and therefore does not interfere with UV analysis. The fiber optic probes allow ease of collection of multiple data points and therefore can be useful to achieve a comprehensive characterization of the release profile.

7. Conclusion

Dissolution research started to develop in 1897 when Noyes and Whitney derived their equation in the course of their dissolution studies on benzoic acid and lead chloride. Thus, dissolution started as a topic in physical chemistry, and is still an important subject of research in various sections of physical sciences. [1,46] The goal of dissolution testing is to assure the pharmaceutical quality of the product which includes not only ability to manufacture the product reproducibly and the drug to maintain its release properly throughout its self life but also that the product's biopharmaceutical characteristics, such as 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. [47] Dissolution testing is a routine work for pharmaceutical quality control for oral solid dosage forms like tablets, capsules. It is also essential for the transdermal drug delivery systems. The science of dissolution testing is developing every day. Advancement in technology makes the procedure easy, fast and reliable through scientific experiments worldwide. It is an essential tool for pharmaceutical analysis and drug development.

8. References

- [1] Dokoumetzidis A, Macheras PA. Century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. *Int J Phar*. 2006; 321: 1-11.
- [2] Hauck WW, Foster T, Sheinin E, Cecil T, Brown W, Marques M, Williams RL. Oral Dosage Form Performance Tests: New Dissolution Approaches. *Pharm Res*. 2005; 22(2): 182-187.
- [3] Chevalier E, Viana M, Artaud A, Chomette L, Haddouchi S, Devidts G, Chulia D. Comparison of Three Dissolution Apparatuses for Testing Calcium Phosphate Pellets used as Ibuprofen Delivery Systems. *AAPS PharmSciTech*. 2009; 10(2):597-605.
- [4] Pillay V, Fassihi R. Evaluation and comparison of dissolution data derived from different modified release dosage forms: an alternative method. *J Contr Rel*. 1998; 55:45-55.
- [5] Missaghi S, Fassihi R. Release characterization of dimehydrinate from an eroding and swelling matrix: selection of appropriate dissolution apparatus. *Int J Pharm*. 2005; 293:35-42.
- [6] Joshi A, Pund S, Nivsarkar M, Vasu K, Shishoo C. Dissolution test for site-specific release isomiazid pellets in USP apparatus 3 (reciprocating cylinder): optimization using response surface methodology. *Eur J Pharm Biopharm*. 2008; 69:769-75.
- [7] Siewert M, Dressman J, Brown CK, Shah VP. FIP/AAPS Guidelines to dissolution in vitro release testing of novel/special dosage forms. *AAPS PharmSciTech*. 2003; 4:1-10.
- [8] Mehta AC. Dissolution testing of tablet and capsule dosage forms. *J Clin Pharm Ther*. 1993; 18:415-420.
- [9] Brown CK, Chokshi HP, Nickerson B, Reed RA, Rohrs BR, Shah PA. Acceptable Analytical Practices for Dissolution Testing of Poorly Soluble Compounds. *Pharmaceutical Technology*. 2004; 28(12): 56-65.
- [10] Prabhu NB, Marathe AS, Jain SK, Singh PP, Sawant K, Rao L, Amin PD. Comparison of Dissolution Profiles for Sustained Release Resinates of BCS Class I Drugs Using USP Apparatus 2 and 4: A Technical Note. *AAPS PharmSciTech*. 2008; 9(3): 769-773.
- [11] USP 30 and NF 25. US Pharmacopeial Convention. 2007; Rockville, MD.
- [12] Long M, Chen Y. Dissolution Testing of Solid Products. In: *Developing solid oral dosage forms, pharmaceutical theory and practice*. Qui Y, Chen Y, Zhang GGZ (eds). Burlington, Elsevier Inc, 2009, pp 319-340.

- [13] FIP: Federation International Pharmaceutique. FIP guidelines for dissolution testing of solid oral products. *Die Pharmazeutische Industrie*. 1981; 42: 334–343.
- [14] FIP: Federation International Pharmaceutique. FIP guidelines for dissolution testing of solid oral products, Final draft, 1995. *Drug Information Journal*. 1996; 30: 1071–1084.
- [15] FDA: FDA Guidance for Industry. (1997a). Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070239.pdf> [Accessed on: September 2, 2011]
- [16] FDA: FDA Guidance for Industry. (1997b). Dissolution Testing Of Immediate Release Solid Oral Dosage Forms. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070237.pdf> [Accessed on: September 2, 2011]
- [17] Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. *J Am Chem Soc*. 1897; 19: 930–934.
- [18] Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Biopharm*. 2000; 50: 47–60.
- [19] Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. *Ind Eng Chem*. 1931; 23, 923–931.
- [20] Laia TY, Carstensen JT. Effect of shape factor on cube root dissolution behavior. *Int J Pharm*. 1978; 1(1): 33–40.
- [21] Dyas AM, Shah UU. Dissolution and dissolution testing. In: *Encyclopedia of Pharmaceutical Technology*. Swarbrick J (ed). USA. Informa Healthcare USA Inc., 2007, pp 908–928.
- [22] Higuchi WI. Analysis of data on the medicament release from ointments. *J Pharm Sci*. 1962; 51: 802–804.
- [23] Higuchi T. Mechanism of sustained action medication: Theoretical analysis of rate of solid drugs dispersed through solid matrices. *J Pharm Sci*. 1963; 52: 1145–1149.
- [24] FDA: Dissolution Apparatus – History and Sources of Variability. Available at: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4137b1_05_dissolution-summary.htm [Accessed on: September 3, 2011]
- [25] Pernarowski M, Woo W, Searl RO. Continuous flow apparatus for the determination of the dissolution characteristics of tablets and capsules. *J Pharma Sci*. 1968; 57: 1419–1421.
- [26] Sinko PJ. *Martin's physical Pharmacy and Pharmaceutical Sciences*. 6th edition. USA, Lippincott, Williams & Wilkins, 2010, pp 351–353.
- [27] Vaghela B, Kayastha R, Bhatt N, Pathak N, Rathod D. Development and validation of dissolution procedures. *Journal of Applied Pharmaceutical Science*. 2011; 01(03): 50–56.
- [28] Levy G, Hayes BA. Physicochemical basis of the buffered acetylsalicylic acid controversy. *New Engl J Med*. 1960; 262: 1053–1058.
- [29] Yu LX, Wang JT, Hussain AS. Evaluation of USP Apparatus 3 for Dissolution Testing of Immediate-Release Products. *AAPS PharmSci*. 2002; 4 (1): article 1. Available at: <http://www.aapsj.org/view.asp?art=ps040101> [Accessed on: September 3, 2011]
- [30] USP 22. The US Pharmacopeial Convention: Rockville, MD, 1990.
- [31] Fotaki N, Reppas C. The Flow Through Cell Methodology in the Evaluation of Intraluminal Drug Release Characteristics. *Dissolution Technologies*. 2005; 12(2): 17–21.
- [32] Möller H. Dissolution testing of different dosage forms using the flow through method. *Pharm Ind*. 1983; 45: 617–622.
- [33] Bhattachar SN, Wesley JA, Fioritto A, Martin PJ, Babu SR. Dissolution testing of a poorly soluble compound using the flow through cell dissolution apparatus. *Int J Pharm*. 2002; 236: 135–143.
- [34] Hodson A, Wilkinson KA. Simultaneous Sampling and HPLC Injection from USP Apparatus 4 using a Dual Sampling Rack. *Dissolution Technologies*. 2005; 12(2): 44–45.
- [35] USP: The Topical/Transdermal Ad Hoc Advisory Panel for the USP Performance Tests of Topical and Transdermal Dosage Forms. *Topical and Transdermal Drug Products*. *Dissolution Technologies*. 2010; 17(4): 12–25.
- [36] Crist GB. Trends in Small-Volume Dissolution Apparatus for Low-Dose Compounds. *Dissolution Technologies*. 2009; 16(1): 19–22.
- [37] Abdou HM. *Dissolution, Bioavailability and Bioequivalence*. Easton, PA, Mack Publishing, 1989, pp 11–36.
- [38] Viegas TX, Curatella RU, Van Winkle LL, Brinker G. Measurement of Intrinsic Drug Dissolution Rates Using Two Types of Apparatus. *Pharmaceutical Technology*. 2001; 25(6): 44–53.
- [39] Pillay V, Fassih R. Unconventional Dissolution Methodologies. *J Pharm Sci*. 1999; 88 (9): 843–851
- [40] Rolli R. Automation of dissolution tests. *J Autom Methods Manag Chem*. 2003; 25(1): 7–15
- [41] Dunkle JD, Gleason DJ, Hokanson GC. A Flexible Automated Dissolution Testing System for Use with Either USP Apparatus 1 or USP Apparatus 2. *Pharm Res* 1992; 9(4): 578–581
- [42] Gray VA, Brown CK, Dressman JB, Leeson LJ. A new general information chapter on dissolution. *Pharmacopeial Forum*. 2001; 27 (6): 3432–3439.
- [43] Gray VA. Dissolution testing using fiber optics—a regulatory perspective. *American Pharmaceutical Review*. 2003; 6 (2): 26–30.
- [44] Bynum K, Roinestad K, Kassia A, Pocreva J, Gehrlein L, Cheng F, Palermo P. Analytical Performance of a Fiber Optic Probe Dissolution System; *Dissolution Technologies*. 2001; 8(4): 1–8.
- [45] Zolnik BS, Raton JL, Burgess DJ. Application of USP Apparatus 4 and In Situ Fiber Optic Analysis to Microsphere Release Testing; *Dissolution Technologies*. 2005; 12(2): 11–14.
- [46] Avnir D. *The Fractal Approach to Heterogeneous Chemistry*. Chichester, NY, John Wiley & Sons Ltd. 1989.
- [47] Dressman JB. Dissolution Testing of Immediate-Release Products and Its Application to Forecasting In vivo Performance. In: *Oral Drug Absorption: Prediction and Assessment*. Dressman JB, Lennernäs H. (eds). New York, Marcel Dekker, Inc., 2000, pp 155–181.