REVIEW

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RECENT REVIEW OF SMALL VOLUME DISSOLUTION TESTING METHODOLOGIES

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ABSTRACT:

Research into strategies for dissolution testing started around a century ago and dissolution methodology is currently the most widely used parameter to assure the quality of pharmaceuticals. World over, dissolution testing of non-liquid dosage forms are routinely carried out as a quality control measure. Dissolution testing plays a key role in optimizing new formulations as well as in evaluating marketed formulations. Several Pharmacopoeias have included dissolution testing in their monographs and have specified different types of test apparatus for carrying out the test. In order to overcome the limitations of classical dissolution testing, small volume dissolution testing was conceptualised. It has been found to be advantageous for evaluation of small quantities of API, powders as well as drugs for periodontal applications. Certain novel drug delivery systems have been evaluated using such specialized systems. This review discusses non-compendial small volume dissolution testing equipments, their principle and applications.

KEYWORDS: Compendial, rotating bottle, small volume dissolution, Micro DISS Profiler™, Transwell® apparatus

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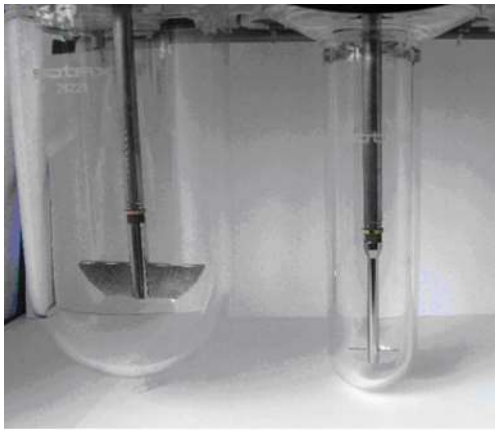
INTRODUCTION

When a drug is administered orally, it has to dissolve in the gastrointestinal fluid so as to be available for systemic absorption. This indicates that dissolution of the drug in biological fluids is an important prerequisite for its availability at the target site. Thus, dissolution testing is an important tool that can predict the pharmacokinetic behaviour of any administered drug. Therefore, general monographs on dissolution apparatus, protocols for dissolution testing and drug product monographs containing dissolution test have been included in several Pharmacopoeias[1-3]. Conventional dissolution testing involves carrying out the test in volumes of 500 to 1000 ml and the apparatus most commonly used is IP type I and IP type II apparatus. However, in certain situations such as limited API availability, low analytical sensitivity, lack of discrimination or biorelevance, the conventional techniques cannot be used. During drug discovery phase, drug candidates are screened using animal models. The developed drug dissolution models should ideally mimic the gastrointestinal conditions encountered in animals[4]. This gave rise to the concept of small volume dissolution (SVD) which offers the advantage of smaller sample sizes, smaller dissolution media volumes, lesser material consumption and results that have higher predictive value in animal models[5,6]. Another important area where SVD offers distinct advantage as compared to classical dissolution testing is inhalation products.

In this review, the authors have focussed on few of the non-compendial specialised SVDs that have been reported in literature.

1. Sotax AT7 smart apparatus

The Sotax small volume vessel is a single device that can be installed directly on existing compendial dissolution equipment[7]. A small paddle blade of 29 mm length fitted at 10 mm from bottom of the vessel is used (Figure 1). The volume of dissolution medium used can be varied from 50 to 200 ml while paddle speed of 50 to 150 rpm can be achieved. It uses standardized working conditions and can be set up to fit to the common one-litre vessel fittings. It potentially allows to expand the discriminating power of a method by applying gentle agitation and is useful in the evaluation of immediate release and disintegrating tablets.



Sotax small volume vessel

Figure 1:Conventional dissolution flask versus Sotax small volume vessel

2. ROTATING BOTTLE APPARATUS

An early drug release apparatus that allowed a dosage form to be exposed to various media in a rotating bottle apparatus was reported in The National Formulary in 1975. It consisted of a sealed tube rotating in a water bath (Figure 2). The medium and the dosage form is contained within the sealed bottle. This unofficial apparatus is still used for some implants and dosage forms that may take weeks or months to dissolve. In another modification, volumes as low as 3 ml have been achieved by introducing implants into 4-mL HPLC vials, which are placed in small holders on the rotating bottle apparatus[8].

Literature survey revealed the use of several other non-compendial apparatus which involved shaker tables within an incubator or rotary mixers contained in temperature-controlled incubators. However, dissolution in such apparatus may lead to inconsistencies in dissolution rate due to battering and rough handling of the dosage form during the test[9].

Figure 2: Bottle rotating apparatus (Electrolab)

3. AGILENT 400-DS APPARATUS 7

Agilent 400-DS Apparatus 7 operates at significantly lower media volumes than compendial USP type 7 equipment. The dissolution cell consists of a glass tube that is open at both ends. Each tube is surrounded by a heating jacket. A sampling port is present at the bottom of the cell (Figure 3). This apparatus is suitable for dissolution tests lasting weeks, or even months. Dissolution testing can be carried out in volumes as less as 3 ml. This technique reduces evaporation, even when used with organic solvents. In addition, media may be partially or completely replaced at each time point for each vessel using a built-in fluidics module. As many as five different media may be used during a single method. The 400-DS dissolution apparatus can simultaneously test up to 12 samples and a control or standard, while giving users direct visibility of each dissolution cell[10]. Magnetically coupled agitators provide the reciprocating motion from the exterior of the chamber. It is useful in the testing of novel drug delivery systems and combination drug products.

Figure 3: Agilent 400-DS Apparatus 7

4. FLOW PERFUSION CELL

Eadara et al developed a modified dissolution apparatus that uses a small volume (25 µL) of stationary medium for in vitro dissolution testing of respirable drug particles[11]. A study to evaluate the dissolution profile of two anti-TB drugs, moxifloxacin and ethionamide was reported[12]. The apparatus consists of a flow perfusion cell connected to a syringe pump and an optical microscope connected to a digital camera (Fig 4a and Fig 4b).

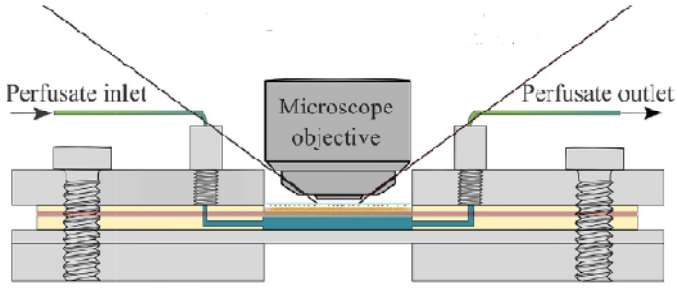


Figure 4a: Schematic representation of Flow perfusion cell

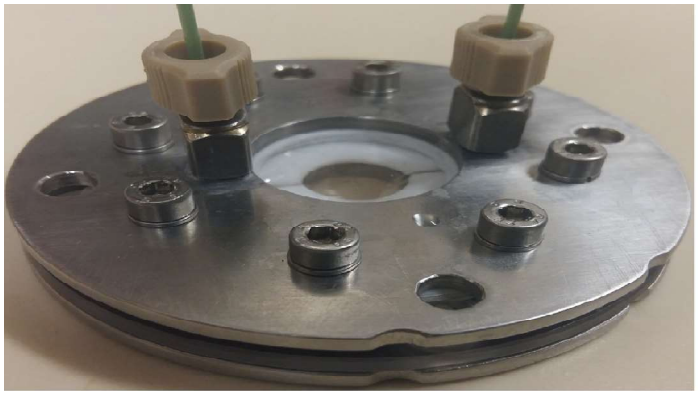


Figure 4b: Custom made Flow perfusion cell

For this study, a dialysis membrane was fitted in the flow perfusion cell and phosphate buffered saline was pumped on the luminal side of the membrane. The chamber is enclosed in a temperature-controlled jacket which was responsible for adjusting the inner temperature to 37°C.An aliquot (25 µL) of mucus simulant, polyethylene oxide (PEO) was uniformly spread over the membrane. The drug samples deposited were brought into contact with the mucus simulant applied on the membrane and particle disappearance observed using a recording optical microscope. This dissolution apparatus shows promise in understanding the dissolution behaviour of aerodynamically classified drug particles in small volumes of stationary fluid simulating the in vivo dissolution in the trachea-bronchial region of the lungs.

5. MICRODISS PROFILER™

The Micro DISS Profiler™ is an innovative in situ fibre optic UV monitoring system, specifically designed to monitor concentration in real-time from small volume dissolution assays[13]. The specialised dissolution apparatus consists of eight dissolution chambers whose capacity is 1 to 20 ml (Figure 5). Dissolution behaviour is studied by means of dip probes.

Figure 5: micro DISS Profiler™ based small volume dissolution apparatus

The advantages of such a system include:

- Near zero operating cost
- Simultaneously running 8 parallel experiments
- Acquire data for all 8 channels in 1 second
- Use 1000 times less material
- Sample volume as low as 1mL
- Greater accuracy in data monitoring

This system has great applications in tablet as well as powder dissolution, Intrinsic Dissolution Rate (IDR), solubility determination, nanoparticle dissolution, non-aqueous solubility, excipient screening, salt selection, simulated intestinal/gastric fluid concentration monitoring and stability monitoring[14].

6. CONTINUOUS FLOW THROUGH FILTRATION CELL

This apparatus consists of a single stirred, continuous flow-through filtration cell fitted with a dip tube for removal of undissolved solid particles (Figure 6). Around 10 ml of the dissolution medium is pumped into the cell at a rate such that the medium is completely replaced in about 8 minutes. Once the cell is filled with the medium and flow rate is adjusted to achieve steady state, the dosage form is introduced. The sample is filtered and analysed in line by UV flow through cell. This apparatus can be used to accurately determine the rate of drug release from sublingual/buccal medications[15].

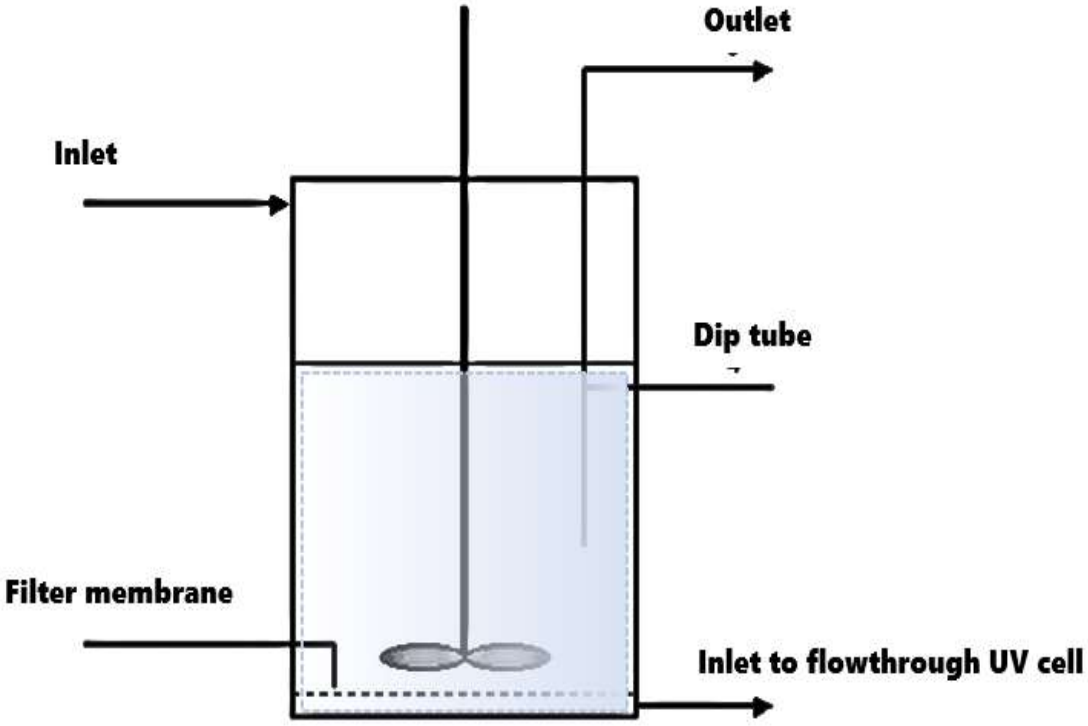


Figure 6: Continuous flow through filtration cell apparatus.

7. MINI VESSEL DISSOLUTION SYSTEM

The mini vessel dissolution system consists of a cylindrical glass tube with a closed hemispherical bottom (Figure6). It has a capacity of 100 ml and is fitted with a mini paddle impeller. This vessel can be mounted in a commercial USP dissolution apparatus using a round mounting plate with a central opening to accommodate the mini vessel. In order to minimize optical distortion effects during the velocity measurements, the mini vessel can be suspended in a Plexiglas box filled with water placed under the mounting plate of the dissolution testing system. This system has been developed for the estimation of drug release from low dosage strength systems[16].

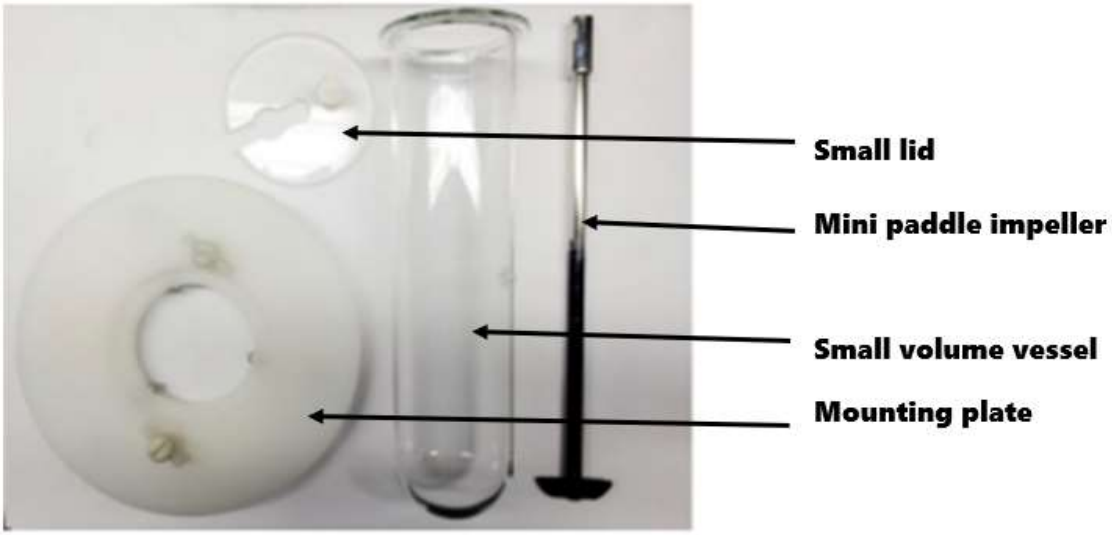


Figure 7: Mini vessel apparatus.

8. FLOW THROUGH DISSOLUTION CHAMBER

A physiologically relevant, dissolution chamber for investigating the release of drugs from periodontal drug delivery was constructed using 3D printing technology[17]. The apparatus is rectangular in shape with a chamber volume of 0.03 to 0.24 ml and is made up of photo initiated acrylic polymer clear resin (Figure 7). The dissolution chamber is connected to a syringe pump which provides a continuous flow of fresh medium. The formulation is placed in the chamber and the medium is continuously circulated by the syringe pump. Samples are collected at predetermined intervals through the sample collecting tube.

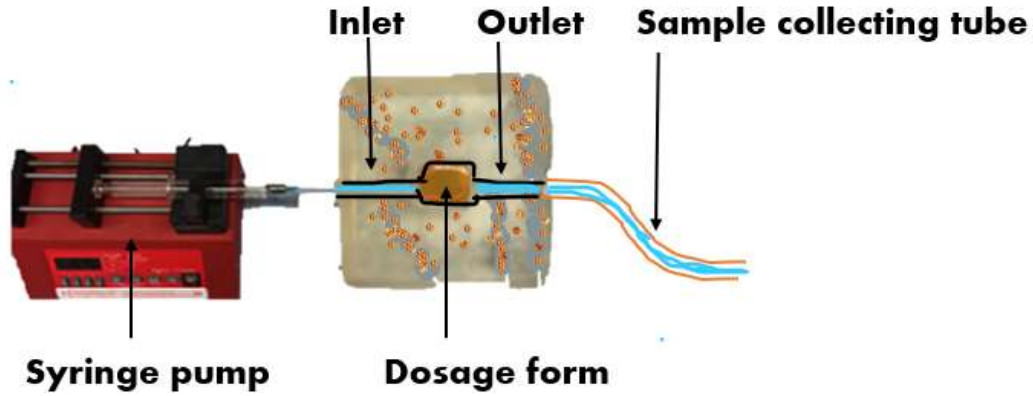


Figure 8: Flow through dissolution chamber

9. TRANSWELL® DISSOLUTION APPARATUS

The Transwell® apparatus is a specialised small volume system that can be used to conduct in vitro dissolution studies on orally inhaled drug products[18]. It consists of a Transwell® insert that separates the donor compartment from the receptor compartment by a membrane. The drug particles are introduced into the donor side of the insert and the medium is agitated by means of a stirring bar. The dissolved drug diffuses across a semi-permeable membrane and is monitored in the receptor compartment (Figure 8). The volume of the donor chamber is low compared to the receptor chamber, which offers the potential of generating sink conditions relatively easily. The low volume donor chamber mimics the limited lung lining volume and provides fluid-restricted dissolution conditions[19].

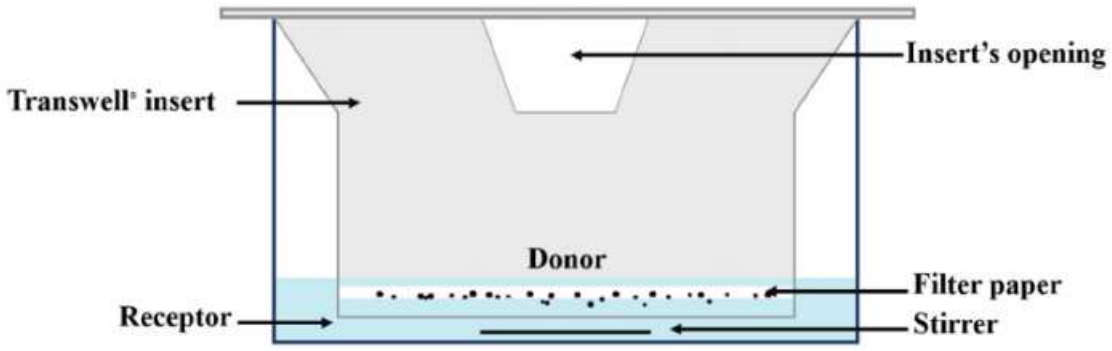


Figure 9: Schematic representation of Transwell® dissolution apparatus

CONCLUSION

Dissolution testing has contributed significantly not only to drug testing but also to the drug discovery program. As newer drugs and technologies emerge, conventional and compendial dissolution methodologies are unable to overcome the challenges posed such as limited availability of drug, need for high throughput screening, rapid in vitro testing, formulations designed to release drug in small volumes of physiological fluids. Also, specialized drug delivery systems have resulted in the exploration of small volume dissolution technology for the in vitro dissolution studies of drug substances as well as drug products. While most of these techniques are not official in any Pharmacopoeia, they have slowly gained regulatory acceptance and are being increasingly relied upon for in vitro characterization as well as prediction of in vivo behaviour of the drug.

In conclusion, development of custom-made systems is beneficial to the new drug discovery program. However, these systems need to be validated using them as analytical or discriminatory tools. Small volume dissolution apparatus must undergo design qualification, installation qualification, operational and performance qualification. Additionally, the developed method must be validated for accuracy, precision, specificity, limit of detection, limit of quantitation, linearity, robustness, and transferability. In vitro in vivo correlation must be established using standard drugs. The manufacturer specifications and tolerances should be used as the basis for mechanical verification of components. This review is an attempt to create awareness of small volume dissolution technology and the types of equipment that are currently described in literature.

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REFERENCES

1 Indian Pharmacopoeia. Vol. 2. Government of India Ghaziabad: The Indian Pharmacopoeia Commission; 2010. p. 1269-72.

2 EP. European Pharmacopoeia. 2.9.3: Dissolution for solid oral dosage forms. The Council of Europe (European Directorate for the Quality of Medicines & Healthcare): Strasbourg, France, 2009.

3 Dissolution <711>. In United States Pharmacopeiaand National Formulary USP 31–NF 26; The UnitedStates Pharmacopeial Convention, Inc.: Rockville, MD,2008.

4 Gu CH, Gandhi RB, Tay LK, Zhou S, Raghavan K., Importance of using physiologicallyrelevant volume of dissolution medium to correlate the oral exposure of formulations of BMS-480188 mesylate., Int J Pharm., 2004; 269:195-202.

5 Klein S, Shah V., The Mini Paddle Apparatus a Useful Tool in the Early Developmental Stage?Experiences with Immediate-Release Dosage Forms., Dissolution Technol., 2006;13: 6-11.

6 Wyttenbach N, Alker A, Grassmann O, Scheubel E., Tenoxicam-Methylparaben cocrystal formation in aqueous suspension formulation., In Proceedings of 2009 AAPS Annual Meeting and Exposition,

Los Angeles, CA, USA, October 7, 2009.

7 Scheubel E, Marc L,Eric, B, Jean-Michel C., Small Volume Dissolution Testing as a Powerful Method during Pharmaceutical Development., Pharmaceutics., 2010; 2: 351-363.

8 Bryan G., Trends in Small-Volume Dissolution Apparatus for Low-Dose Compounds., Dissolution Technologies., February2009; 19-22

9 http://www.electrolabindia.com/ProductDetails.aspx?CType=ZgDIC937E8s%3d&CID=YT3rE99rPxE%3d&Counter=1&SEOType=BSuwhmB9Ll4%3d&PID=H1Hw1g7nXuo%3d

10 Varian 400-DS Automated Apparatus 7 Operator's Manual P/N 70-9051 Revision B

11 Eadara BB, Ian GT, Das SC., In vitro dissolution testing of respirable size anti-tubercular drug particles using a small volume dissolution apparatus., Int J Pharm., 2019; 559: 235-244.

12 Eedara BB, Rangnekar B, Sinha S, Doyle C, Cavallaro A, Das SC., Development and characterization of high payload combination dry powders of antituberculardrugs for treating pulmonary tuberculosis., Eur J Pharm Sci., 2018; 118:216–226.

13 Kogermann KA,Penkina K,Predbannikova K,Jeeger P,Veski J,Rantanen K, Dissolution testing of amorphous solid dispersions., Int J Pharm., 2013; 444(1–2): 40-46.

14 https://www.americanpharmaceuticalreview.com/25255-Dissolution-Testing-Analysis-Equipment/5821863--DISS-Profiler-Small-Volume-Dissolution-and-Solubility-Apparatus/

15 Hughes L., Tightening up buccal testing., Manuf Chem., 2003; 74: 28–30.

16 Wang B,Armenante PM., Experimental and computational determination of the hydrodynamics of mini vessel dissolution testing systems., Int J Pharm.,2016; 510(1): 336-349.

17 Ren W, Murawsky M, La Count T, Wanasathop A, Hao X, Kelm GR, Kozak D, Qin B, Li SK., Dissolution Chamber for small drug delivery system in the periodontal pocket., AAPS J., 2019., 10;21(3):51.

18 Sabine M, Saskia K, Birte J, Markus W, Schneider M, Lehr C., Miniature In Vitro Dissolution Testing of Powders for Inhalation.,Dissolution Technologies., August 2015; 40-51

19 Forbes B, Richer NH,Buttini F. Dissolution: A Critical Performance Characteristic of Inhaled Products?.in Pulmonary Drug Delivery, eds. NokhodchiA, MartinGP,Wiley Online, 2015 p 223-240.

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