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Flow through cell dissolution test apparatus : A Review and Update

Rohith S.[1], **Vasanth A.**[1], **Saba Maanvizhi** [2]*

1 Master of Pharmacy, Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Chennai, Tamil Nadu, India.
2 Professor, Department of Pharmaceutics, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (DU), Chennai, Tamil Nadu, India.

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***Corresponding author:**

Email : sabamaanvizhi@sriramachandra.edu.in
Phone : +91 - 98411 62130

ABSTRACT

The dissolution apparatus specified by the United States Pharmacopeia (USP) plays a crucial role in pharmaceutical development and quality control, notably in determining the release rate of active pharmaceutical ingredients (APIs) from solid dosage forms. This review provides an extensive account of the history, design concepts, operating parameters, and regulatory issues associated with USP Type 4 dissolution equipment. The key components of dissolution testing, including medium choice, temperature regulation, and sampling methods, are covered in this review. In addition, it focuses on the regulations established by the USP and other global regulatory bodies to guarantee the precision and uniformity of dissolution data produced using Type 4 equipment. Also, it describes the open loop, closed loop configurations, Pump and flow patterns, and types of cells for different dosage forms. Additionally, new developments and technology advancements targeted at enhancing the automation, precision, and efficiency of dissolution testing are discussed. This study provides useful details on the practical application of USP Type 4 dissolving equipment in pharmaceutical development and quality assurance by synthesizing current research and expert perspectives.

INTRODUCTION

Dissolution assessments are used in pharmacopeia to evaluate the release of drugs from both solid and semi-solid formulations. [1] For basic medications with low solubility, pH-dependent solubility is a major concern because the stomach's emptying process significantly reduces the drug's ability to dissolve. [2] The process of dissolving drugs establishes the rate and volume of drug release from a prescribed dose. It has various key functions that lead to the development of novel medicines, particularly in solid forms of oral administration. [3-5] Dissolution testing is an essential analytical procedure that needs to be incorporated into the final phase of release and evaluated for solid forms for oral administration to ensure the material's stability and consistency between batches. [6]

In addition, as an illustration, it's often employed as an approach to process control methods to guarantee uniformity. among batches, and integrity in the manufacturing of smaller therapeutic molecules. Additionally, it can offer informative data and direction for designing formulations and serves under physiological conditions for the replica of in-vitro bioequivalence examinations and *in-vivo* and *in-vitro* correlation (IVIVC) research, as well as offer insightful data and direction for formulation development.[7],[8] When developing, characterizing, and ensuring the quality of formulations for both regulated and fast release, this approach is crucial. [9]

Dissolution testing is a crucial Procedure for developing novel medications in many aspects. The solubility of chemicals and dosage forms is studied using a variety of instruments, both compendial and non-compendial. [10] The most popular procedures for dissolution testing, baskets and paddle in USP apparatus 1 and 2, ensure that the amount being administered, its breakdown, and solubility can all be evaluated in a thoroughly

mixed, buffer-enriched atmosphere. However, the rotating basket and paddle systems have apparent drawbacks, such as difficulties controlling sink conditions and low repeatability. [11]

A flow-through cell dissolving analyzer is frequently advised for medications that are very difficult to dissolve, variable, or prolonged discharge. USP device- 4 with relation to the creation of novel medications and their transportation techniques is the most suggested technique for researching dissolution characteristics of oral, non-oral as well as other medical devices including implants and stents.

Because of its highly adaptable design, ability to operate in a variety of dispersible environments, different cellular units and medication positioning, fluid mechanics, replacement of buffer, and rate of flow of the medium, USP device- 4 may proceed with the transition to meet the changing requirements of modern drug release and dissolution examinations. [12]

Due to its unique characteristics, which enable it to successfully address the issue of non-sink circumstances by providing an infinite supply of new dissolving medium with a simple pH change within one run, The flow-through cell (FTC) is gaining favor as a dissolving device. This method is very crucial to acquiring data from *in-vivo* findings, and this makes assessing sturdiness in formulation, also regards in alterations of the digestive system easier. The FTC also has the benefit of providing regulated hydrodynamics in a precisely specified cell shape that is unaffected by sampling and medium change. [11]

The device known as the FTC, Generally represented as a Type-4 device in USP, has acquired growing popularity recently in the dissolution industry because of its flexibility in assessing novel medications in situations when the dissolving equipment is currently in usage to meet current trends in pharmacy and its procedures failed to succeed. [13] The first approved application for commercially available stents that releases therapeutic materials made use of FTC is currently advised for most innovative medications. [14]

HISTORY OF DRUG DISSOLUTION TECHNIQUES

The first dissolving investigations were carried out in 1897 and documented by Noyes and Whitney in the scientific journal looked at the breakdown of the lead chloride and benzoic acid, two chemicals that are only sparingly soluble.[15] Pharmaceutical professionals began to understand the effect of solubility on medication intake absorption when oral medication was provided in the early 1950s. In 1951, Edward proposed the theory that the breakdown of aspirin was the rate-limiting stage in its bloodstream absorption. [16] Nelson was the first scientist to distinctly link theophylline's dissolution and blood levels after it was taken orally in 1957. [17] The effect of dissolving on gastrointestinal medication's therapeutic action was first recognized in the middle of the 1960s, indenbaum revealed in 1971 that the various digoxin formulations had differences in serum digoxin levels that were seven times larger. The FDA investigated the disintegration of 44 batches of digoxin from 32 different producers as a result of this discovery. [18]

The USP Apparatus 1, served as a representative dissolving test in 6 monographs in 1971. The USP Device - 2 originally emerged in 1978, and in 1985 USP 21 published an extensive chapter on drug release. In 1981, The DT working committee of the International Pharmaceutical Federation (F.I.P.) suggested the flow-through cell as a substitute for kinetics of *invitro* assessments of medication release. [19] United States pharmacopeia adopted the USP Device - 3 in 1991 regarding altered release formulations, and the flow-through cell (USP Apparatus 4) for expandable-release formulations in 1995. This technique was then included in several pharmacopeias. [20]

FDA published four guidance in 1997 that addressed Regulatory perspectives on *in-vitro* dissolution and its use, signaling a revolution in the dissolution area. The Food Drug Administration's broad expectations for the dissolving of IR dosage forms are outlined in the first guidance, along with the methods for analyzing the similarities and differences between two dissolution patterns using statistics. [21] The Food Drug Administration published guidelines on IVIVC for altered-release medication in September 1997. These guidelines provided a basic overview of expectations for the creation, assessment, and use of IVIVC. [22] The FDA published two guidelines on post-approval modifications and scale-up for both IR [23] and MR formulations. [24]

A VARIETY OF DISSOLUTION TESTING APPARATUS

The USP offers seven alternative apparatus that were applied for dissolving testing- the majority of tablets and capsules employ USP Apparatuses - 1 or 2, popularly denoted by basket and paddle. Throughout the 1960s, both devices were created, and in the 1970s, the USP accepted them. [1]

VARIOUS FORMS OF TABLET DISSOLUTION DEVICES [25]

As per USP, a variety of tablet-dissolving devices include:

1. Basket
2. Paddle
3. Reciprocating cylinder
4. Flow through cell
5. Paddle over disc
6. Rotating cylinder
7. Reciprocating disc

USP 4 - APPARATUS DESCRIPTION

The system is made up of a device known as a pump that propels the buffer to pass through the upwards-positioned flow cell, an immersion tank to regulate the thermal reading of the unit, and a dissolvent agent holding on to the storage tank. [10]

METHODOLOGY

Vertically oriented FTC and Analytical compounds inside the device are used to pump the medium at the appropriate temperature (37°C) and flow rate. The eluate is collected manually or by a sample collector after being filtered at the unit's ridge. To determine, the proportion of release kinetics, The samples undergo additional analysis utilizing suitable analytical techniques.[12],[26]

USP APPARATUS 4: WHY WAS IT CHOSEN

- When it comes to weakly dissolving medications, USP device - 4 is an excellent approach.
- To achieve the infinite sink condition, the USP 4 apparatus is the optimal approach for dissolving tremendous

quantities of media.

- Automated media changes for both liquid and solid dose forms in IVIVC trials are achievable with ease.
- "Accelerated" test investigations are possible with the ease of changing flow rates.
- Numerous issues, such as tablets floating and sticking, are resolved. [13]

GLOBAL REGULATORY AUTHORITIES' ACCEPTANCE

The "Flow-Through" Method didn't start to gain traction until the FIP suggested it in 1981 as a substitute for the basket and paddle methods for dosage forms with protracted release and poor solubility. After being approved by the USP and Ph. Eur., in 1990 and the JP in 1996, the technique was officially recognized as a compendial apparatus. In the twenty-first century, several monographs and NDAs were officially granted on behalf of regulatory bodies. [14]

SYSTEM REQUIREMENTS UNDER USP GUIDELINES

The most important component of USP apparatus 4 is ensured by the pump unit, which is in charge of

- Rate of flow of media.
- The recommended temperature as per USP is ±0.5.
- Even when these filters are creating back pressure, the flow rate needs to remain constant during the test.
- Under United States Pharmacopoeia regulation, the sinusoidal pulse rate in the flow profile should be 120 ± 10 pulses/min.
- The United States Pharmacopoeia suggests that 37°C be the ideal medium temperature. [27]

DISSOLUTION AND RELEASE MEDIA

The use of relevant media, pharmacopoeia-recommended media, and conventional buffers are all possible. Throughout the experiment, media can be switched out (a medium choosing can be employed). Deaeration may be required for dissolving medium. [10]

FLOW THROUGH CELL

The FTC dissolving device was commonly suggested for weakly dissolving, altered-release, and prolonged-release formulations. [28] As novel approaches of drug release in pharmaceutical formulations have emerged, FTC was put to work on *In- vitro In - vivo* correlation studies, suspensions, injectables, drug-coated medical devices, parenteral formulations, implants, gels, ointments, creams, liquids, ophthalmic solutions and lenses, suppositories, soft gelatin capsules, beads, granules, APIs, microspheres and many more. [29] FTC was utilized in the first approved application for a drug-eluting stent to be released into the market, and it is currently advised for the majority of innovative dosage formulations. [30]

PUMP AND FLOW PATTERNS

The most crucial element of the Flow-Through Method is the rate of flow of media, which the pump is in charge of maintaining. The flow rate may be contrasted with USP 1 and 2's RPM speed or USP 3's RPM. Even when filter resistance produces back pressure, this flow rate must remain constant throughout every phase of the test. [10] The SOTAX CP 7 Digital Piston Pump was designed particularly for the USP- 4 procedure.

With its seven pump heads made of ceramic that are valveless, this pump offers a high elevated level of uniformity and repeatability. There was a substantial decline in maintenance. One may adjust the flow rate between 1.5 and 35 milliliters per minute. which fulfills 4, 8, and 16 milliliters per minute, according to USP standard flow-rate guidelines. WinSOTAX software and the pump's firmware both allow for automated flow rate adjustment. The pump's ability to have distinct rates of flow for every media outlet makes it a useful tool for creating procedures for experimentation. [14]

OPEN LOOP CONFIGURATION

The dissolving profile of not well-dissolved medications can be examined using USP apparatuses - one, two, and three, although it does not offer the perfect sink conditions required for this task. USP-4, on the other hand, has historically been connected to "ideal environments", since this device provides flexibility about the necessary medium volume. An "open-loop" design allows for an infinite total media volume to be used because new media is continuously flowing across the form of medication. This indicates that utilizing higher quantities of media without the use of solubilizing agents can prevent the negative effects of subpar sink conditions on the test. [13]

Samples can be gathered in fractions over a predetermined period, and then appropriately examined by utilizing analytical methods. The flow rate determines the overall volume of fluid going through the dosage form. In an open-loop system, outcomes are computed as a differential curve, which represents the drug release rate over time. Obtaining a sample at each of the fourteen-time frames (twenty-one-time frames according to user's requirements) with a capacity of 75 ml is possible when EFD-07 is combined with a sample collector with a splitter in an open loop configuration. Test volume is automatically divided into collection and waste sections by a separator and collection device, based on the required capacity. [10], [31]

AUTOMATED MEDIA CHANGE OVER

Samples can be taken in fractions over a predetermined period, and the appropriate analytical method can be used to examine them. The flow rate determines the overall volume of fluid going through the dosage form. Improved correlations have been shown in studies, partially because of the Flow-Through Cell's enhanced hydrodynamics and maintenance of sink conditions. Modified release, prolonged release, and enteric-coated medications can also benefit from it. In contrast to the laborious and time-consuming process of physically removing the dose and switching to a fresh medium in the USP Apparatus 1, 2, and 3 procedures, USP 4 preserves dosage integrity and temperature control even for dissolving Photo-sensitive dosage forms. FTC is a sole technique that permits a buffer transfer of suspensions and powders.

CALCULATIONS IN OPEN LOOP CONFIGURATION

A portion of the samples are collected and removed over a predetermined period. The first step is to figure out how much drug is in each sample that was taken. Subsequently, employing the subsequent formula, ascertain the dosage inside every fraction interval:

$$\text{AMOUNT DISSOLVED} = \frac{\text{CONCENTRATION SAMPLE} * (\text{Flow rate} * \text{time interval})}{1000}$$

CLOSED LOOP CONFIGURATION

The FTC uses a Standard quantity of solvent to flow over the medications in a closed system that is comparable to USP Apparatus One and Two. Test solutions can be collected automatically using an autosampler, and they can be read using a fiber optic probe or an online UV. A cumulative dissolution curve is used to represent medication dissolving results. Closed systems are the greatest solution for medications with optimal soluble matter and sink conditions in volumes ranging from fifty milliliters to two Liters. Another option for comparing outcomes with the conventional two hundred and fifty, five hundred, nine hundred milliliters, one Liter, and two liters paddle, baskets, and USP - 3 procedures is provided by USP 4. Additionally, this approach has benefits over previous USP methods in that it eliminates coning or dead zones, addresses sample difficulties, and has distinct hydrodynamic and mixing effects than USP 1 and 2. [32]

TYPES OF FLOW

Laminar Flow (Vs) Turbulent Flow

Within an FTC, there exist two distinct forms of fluid mechanics: laminar flow and turbulent flow. One hundred and twenty pulses per minute are produced by the pump, creating the first more turbulent flow channel. In cases when dose medicaments necessitate a greater rate of mixing to release their therapeutic ingredients, this type is more advantageous. We refer to another kind of flow as laminar. This was done by loading the unit with the one-millimeter beads made of glass that are listed in the USP. When the flow crosses the medicament, it becomes more regulated. In certain instances, the dose form may rest on the beads, be positioned between them, or even combine with them.[33],[14].

DIFFERENTIAL DOSAGE FORMS USING FLOW-THROUGH CELLS [12],[14],[34]

Tablet cell 12 mm:

According to the USP, Ph. Eur., and JP, this cell is tiny and intended for oral solid medicaments. Additionally, a removable tablet tray was available under the specifications. Furthermore, it was specifically utilized by stents, parenteral, tiny health-related gadgets, and suspensions.

Tablet cell 22.6 mm:

Among all the flow-through cells, this one is the most frequently utilized. For tablets and capsules, it is defined as a big cell in the USP, Ph. Eur., and JP. There's also an optional detachable tablet holder, per the specifications. Moreover, higher dosages of suspensions and microspheres can be employed with it. This cell has a range of holders designed to store various dosage forms.

Cell for powders and granules:

The Unit's geometry was designed in Ph. Eur., according to a 12 mm cell. This serves as an assessment of the pace through which dissolution-active ingredients in medicines are employed as powders, granules, and bead formulations, as well as pure solid substances.

Dialysis adapter in 22.6 mm cell:

The dissolving profile of injectables, microspheres, nanoparticles, and micro-suspensions, among other materials, is studied employing this cell which is derived from the 22.6-millimetre cell. Testing on these dosage forms is made possible by a dialysis membrane inside the cell and an adaptor for dialysis. There is also an adapter available that fits the 1 mL Float-A-Lyzer.

Cell for suppositories and soft gelatin capsules:

The unique two-chambered architecture of this cell, which is detailed in the Ph. Eur., only allows the dissolving medium to pass through the mesh, while keeping the lipidic additives from the suppository or soft capsules of gelatin from flowing through.

Aerosol/inhaler cell:

A stainless-steel cell was created especially for investigating the rates of nebulizer medication flow.

Cell for drug-eluting stents:

Drug-eluting stents and other medical devices utilize this cell. It is essential to customize the inner diameter to suit the healthcare equipment precisely.

Cell for large medical devices:

This specific unit possesses a large dimension - eighty millimeters and can fit wider healthcare devices.

Cell for implants:

For smaller implantation, this cell is utilized; it features a tiny chamber to hold the dose.

Customized flow through cells:

Additional holders have been created specifically to accommodate different dosage forms, using the aforementioned cells as the primary models. Customization can be done according to holding devices, inner diameters, dose forms, media, and cell length, among other factors.

APPLICATIONS [12],[13],[35]

USP equipment 4 makes it easier to test for dissolution of:

1. Tablets
2. Capsules
3. Powder / Granules / APIs / Bead formulation
4. Injectable suspensions, Ophthalmic lenses
5. Suppositories / Soft gelatin capsules
6. Microspheres / Liposomes / Nanoparticles
7. Inhaler drugs
8. Drug-eluting stents / Implants
9. Ointment / Creams / Gels
10. Ophthalmic suspensions

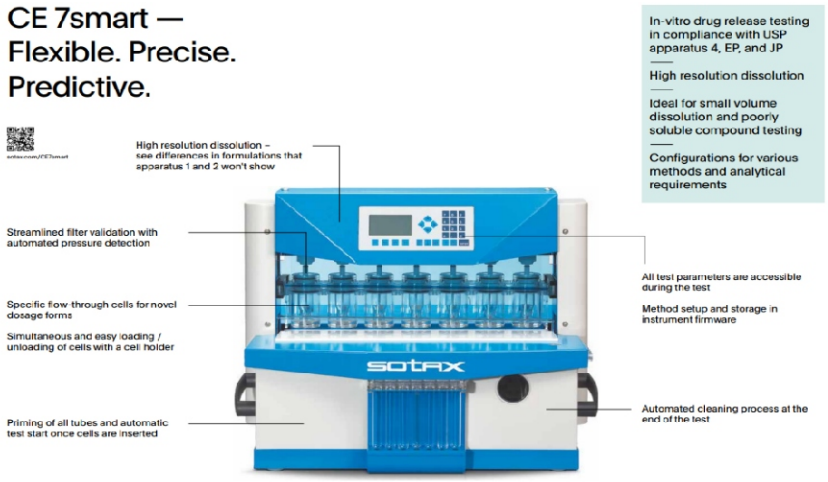

Figure 1 : Sotax Flow Through Cell [14] (at full page width)

CONCLUSION

The Flow-through cell USP dissolution test apparatus has been thoroughly reviewed in this study, which also offers insights into its design, uses, and latest developments. We have emphasized the apparatus's importance in pharmaceutical research, development, and quality control by exploring its distinctive features, such as its continuous flow system and real-time monitoring capabilities. To ensure the accuracy and repeatability of dissolution test findings, regulatory concerns, and new trends highlight how important it is to follow protocols and adopt modern technology. The flow-through cell dissolution equipment is expected to be one of the most important tools for accelerated drug development procedures and ensuring product quality as the pharmaceutical industry expands, with an increasing focus on personalized medicine and formulation optimization.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

USP: United States pharmacopeia; **API:** Active pharmaceutical ingredients; **pH:** Potential of Hydrogen; **IVIVC:** *Invitro In vivo* correlation; **FTC:** Flow through cell; **FDA:** Food and Drug Administration; **DT:** Dissolution testing; **FIP:** International Pharmaceutical Federation; **IR:** Immediate release; **MR:** Modified release; **Ph.Eur.:** European pharmacopeia; **JP:** Japanese pharmacopeia; **NDA:** New drug application; **RPM:** Revolutions per minute; **UV:** Ultraviolet

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