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USE OF BEADS FOR ADDED MECHANICAL STRESS

The development of the Reciprocating Cylinder Apparatus arose from a need for an alternative drug release apparatus capable of providing pharmacokinetic and mechanical conditions that more closely represent the various regions throughout the gastrointestinal tract. While the traditional paddle and basket apparatus offered a convenient means to evaluate most oral drug formulations at single and multiple pH and over long periods, it was difficult to change pH during the test, and changes in agitation rates during the in vitro test were seldom noted as well.

A presentation at the 1980 Federation Internationale Pharmaceutique (FIP) drew attention to acute problems associated with USP Apparatus 1 and 2 dissolution results. The conference inspired the concept for the USP Apparatus 3. Also known as the Bio-Dis, USP Apparatus 3 is excellent for developing controlled-release products because it can quickly and easily expose products to mechanical and physiochemical conditions that may influence the release of the products in the GI tract. The Bio-Dis Extended Release Tester was designed to test the dissolution rates of extended-release products or any dosage form requiring release profiling at multiple pH levels. The ability to transfer the product from one pH to another makes it an excellent candidate for delayed- and modified-release products.

Apparatus 3 allows the dosage form to be placed inside an inner tube that is then dipped in an outer vessel at varying speeds in up to six different media simulating the pH changes that an orally ingested product would be exposed to in the GI tract (see figure).

By retaining the dosage form in the inner tube through the use of screens at the bottom (or top and bottom) of the inner tube, the vertical mixing action creates an environment where the dosage form constantly floats up and down inside the inner tube.

Figure 1. Theophylline Beads floating freely within the Reciprocating Cylinder exposing all surfaces to the media.

Case Studies with the Utilization of Beads: Chewable Tablets with Beads

Conventional Apparatus 1 (baskets) or 2 (paddles) do not allow simulation of this type of increased mechanical action except through increased rotational speed, and this is often accompanied by lower Q values to reflect the inability of USP 1 and 2 to break down the dosage form quickly enough.

The capabilities of the apparatus have stimulated discussion regarding the addition of beads to further increase the shear force applied to the dosage form. Workshops held by FIP and AAPS to outline guidelines for the dissolution and drug release testing of novel dosage forms indicated that the reciprocating cylinder apparatus could be suitable for testing chewable tablets. The addition of glass beads would be required to provide more intensive agitation to the in vitro dissolution test.[1]

Chewable tablets often contain highly soluble API, but they are very difficult to disintegrate and solubilize in traditional dissolution apparatus. For this reason, chewable formulations share a need for additional mechanical forces similar to poorly soluble compounds. Chewable tablets may be tested in the reciprocating cylinder apparatus with the addition of plastic beads, or possibly glass beads, to provide an intense contact with the dosage form through reciprocation and to break down the chewable tablet relatively quickly with mechanical shearing, which could simulate the mastication process required for disbursing chewable tablet formulations. The following figure shows chewable tablets reciprocated with beads of various sizes at 30 DPM.

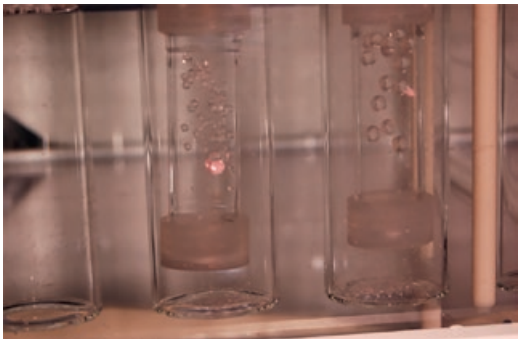

Figure 2. Chewable Aspirin tablets in the presence of 1.5 mm beads (left) and 6 mm beads (right).

Case Studies with the Utilization of Beads: HPMC Matrix Tablets with Beads

Similar work has been performed with the reciprocating cylinder apparatus and plastic beads to provide a more discriminating dissolution method utilizing beads for testing extended release HPMC matrix tablets to predict in vivo performance, which enabled the development of Level A IVIVC for several formulations. It was noted that high mechanical forces were necessary in vitro to provide a satisfactory correlation with the in vivo data.

For the bead-based method, synthetic polymeric bead material from 1 to 8 mm with a density of about 1.1 g/cm were used, which allowed good interaction with the tablet. It was noted that glass beads are generally unsuitable because they usually stay on the bottom of the cylinder and do not exert any mechanical forces on the tablets even when agitating with a high dip rate. This testing summarized that the use of Apparatus 3 methods with beads of proper size and density supply additional mechanical stress that is advantageous for evaluating matrix tablets where erosion is involved in the release mechanism. Additionally, beads may be useful in future studies since robust matrix formulations that are bioequivalent to the reference product could be planned during early stages of the development.[2]

Further information on this topic may be obtained through The AAPS Journal: http://www.pharmagateway.net/ArticlePage.aspx?doi=10.1208/s12248-012-9422-x

In summary, the utility of the reciprocating cylinder apparatus has been used for obtaining more shear forces for a number of dosage forms, but the utilization of beads opens new doors for the apparatus to provide intense mechanical shear representative of the gastric region. For more information on the reciprocating cylinder apparatus contact your Agilent representative or visit our web site at www.agilent.com

References

1. Martin Siewert, Jennifer Dressman, Cynthia K. Brown, and Vinod P. Shah; FIP/AAPS Guidelines to Dissolution / In Vitro Release Testing of Novel / Special Dosage Forms; AAPS :PharmSciTech 2003; 4 (1) Article 7, January 2003
2. Uros Klancar, Bostjan Markun, Sasa Baumgartner, and Igor Legen; A Novel Beads-Based Dissolution Method for the In Vitro Evaluation of Extended Release HPMC Matrix Tablets and the Correlation with the In Vivo Data, The AAPS Journal, Vol. 15, No. 1, January 2013

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ADDRESSING DISSOLUTION COMPLIANCE THROUGH AGILENT LEARNING RESOURCES

Agilent remains committed to providing the highest quality analytical instrumentation to the pharmaceutical industry. Along with that commitment, we provide a range of information that is readily available to you through educational materials, seminars, and contact tools that keep scientists updated on Agilent products and applications as well as current compendial and regulatory requirements. Agilent's Dissolution Exchange (http://dissolution.chem.agilent.com/) provides numerous opportunities for learning, solving, and discussing dissolution-related issues. Here is a sampling of Agilent dissolution resources:

DISSOLUTION | EXCHANGE

- **Dissolution Discussion Group (DDG):** http://www.dissolution.com/ The DDG is an independent forum that gives you the opportunity to anonymously discuss issues that challenge the industry and affect the day-to-day task of developing, performing, and validating dissolution tests and related chemical analysis.

- **DDG Online WebEx:** http://www.dissolution.com/ See recordings on DDG homepage. Conducted quarterly, our online meetings concern hot topics in dissolution and drug release testing. These one-hour meetings feature experts in the dissolution industry discussing challenges in dissolution testing.

- **Dissolution 1-on-1:** http://dissolution.chem.agilent.com/learn/dissolution-1-on-1/ Agilent's free dissolution course is a self-paced training resource that provides theoretical knowledge of how and why dissolution testing is performed.

- **Dissolution Hotline:** dissolution.hotline@agilent.com Our team of dissolution experts is ready to assist with questions ranging from Agilent dissolution products and components to application issues and parts.

Agilent also offers numerous dissolution seminars including one-hour sessions on various topics, **Dissolution Compliance Workshops**, and full-day seminars on **Fundamentals of Dissolution** and **Method Development.**

Several titles and abstracts from our ongoing Dissolution Compliance Workshops are provided to give a flavor of our offerings being presented worldwide.

Compendial Updates Pertaining to Dissolution

Novel dosage forms and issues with crosslinking have required a change in standard procedures to accommodate a more accurate and precise determination of drug product performance. Of the several chapters we will discuss, we will initially review the proposal to introduce new enzymes in <711> to address crosslinking in gelatin capsules between

the pH range of about 4.0–6.5. This has presented issues in the past where the activity of the present enzymes, pepsin and pancreatin, have not possessed sufficient activity in this pH range to deal with crosslinking issues. We will also discuss changes in the USP <1092> chapter on dissolution method development and validation to cover the reorganization of the chapter, as well as the additions and clarifications that address automated dissolution sampling. Lastly, we will evaluate <1724> for the performance testing of ointments, creams, and gels with the immersion cell method, which utilizes traditional dissolution apparatus modified for small volume with the addition of the Enhancer Cell.

FDA Draft Guidance for Industry: Dissolution Testing and Specification Setting for BCS Class 1 and 3 Drugs

Although presented in draft form, this guidance provided clear insight into the agency's thinking on standardizing the testing of drug products that are not rate limited in terms of solubility. We will review the proposed standard test methods for BCS Class 1 and Class 3, high solubility dosage forms for the paddle and basket methods, along with the rationale for the individual parameters. We will also address the possibility of utilizing the disintegration test for some products where greater than 85% release is achieved in 85 minutes or less.

Implementation of Enhanced Mechanical Qualification (eMQ) of Dissolution Apparatus 1 and 2

Whether apparatus calibration is performed in-house by analysts and metrologists or it is outsourced, the spirit of the alternative approach to dissolution apparatus periodic qualification is to maintain the apparatus in top condition and alignment, which is seen by industry and regulatory as an improvement over the USP Performance Verification Test. We will discuss the five steps of implementation in detail: certification of components, periodic maintenance, measurements, evaluation of components at time of use, and the laboratory procedures required to control significant sources of variability due to vessel quality, de-aeration, and vibration. Although the eMQ is becoming widely accepted, shortcomings in implementation have caused warning letters for omitting portions of the implementation, not thoroughly documenting the frequency of parameter measurement, or failing to properly evaluate the apparatus and components on an ongoing basis.

DAN SPISAK, DISSOLUTION PRODUCT MANAGER, AGILENT TECHNOLOGIES INC.

AGILENT 850-DS SAMPLING STATION – FIRMWARE 2.0

Figure 3. Agilent 850-DS Sampling Station

You talked. We listened.

And we have new firmware to prove it.

The feedback received since the release of the **850-DS Sampling Station** has been overwhelmingly positive. But we're always trying to improve and, as part of this process, have incorporated many of the suggested improvements collected from our users worldwide. Key features contained in this release include:

- Doubling method storage capacity from 20 to 40
- Enabling ejection of the tray during a test to remove samples for analysis
- Prefill of test tubes or vials prior to the beginning of the test

Along with pump optimization and hardware improvements along the way, the 850-DS is now better than ever and continues to lead the way to dependable dissolution automation. Find out what makes the Agilent solution your best option for an improved workflow and why your automated system validation is more likely to pass with the 850-DS!

Contact your Agilent representative for more information or request your own demonstration – email us at dissolution.hotline@agilent.com

KAREN KRAUEL-GÖLLNER, DISSOLUTION PRODUCT SUPPORT, AGILENT TECHNOLOGIES INC.

850-DS 8-CHANNEL FILTER PLATES – 0.2 µm NOW AVAILABLE

Figure 4. New 0.2 µm Filter Plates Loaded in the 850-DS Filter Module

GE Whatman has increased their offering of 8-channel filter plates for use in the Agilent 850-DS Sampling Station and now offers additional membrane options including those with a pore size of 0.2 µm.

Analysis of dissolution samples is increasingly carried out by HPLC and UHPLC. To protect highly sensitive UHPLC columns from potential blockage with undissolved particles – and in reponse to customer requests – Agilent and GE Whatman have collaborated to develop filter plates with this finer pore size. The following table shows the pore size and membrane options available for use with the 850-DS filter module.

GE Part Number	Pore Size (µm)	Membrane Material
7707-3000	0.45	Polytetrafluoroethylene (PTFE)
7707-3100	0.45	Nylon
7707-3200	0.45	Polyethersulfone (PES)
7707-3300	0.7	Glass Microfiber (GMF)
7707-3400	0.2	Polytetraflouroethylene (PTFE)
7707-3500	0.2	Nylon
7707-3600	0.2	Polyethersulfone (PES)

Visit www.gelifesciences.com for more information, especially regarding the chemical resistance and recommended applications of the specific filter material.

Dissolution filter selection is dependent on the specific method and the drug formulation under test. The volumetric accuracy of the 850-DS is dependent on the membrane type, the pore size, and the cannula filter (Full Flow Filter) being used. The accuracy is also dependent on the drug product and its concentration, the excipient load, and the dissolution media; other factors that can impact the volume accuracy are the prime volume, pumping speed, and dwell time (all flexible parameters of the 850-DS). Due to high pressures encountered with the use of sub-micron filters, the accuracy specifications for the 850-DS may not be guaranteed for all filter types and drug products under certain conditions.

The filter plates are designed to group the filters in a single manageable plate for ease of use and automated exchange. Only the outer physical appearance was modified to a plate design – the internal product and contact components of the 25 mm disc filters remain unchanged. Whatman filters and filter plates are supplied by authorized GE Healthcare representatives as well as the Fisher Scientific and VWR network worldwide. Each filter plate consists of eight individual 25 mm filters configured for use with the Agilent 850-DS filter changer option. Agilent recommends using each filter plate for a single timepoint to avoid clogging and potential carryover issues.

A useful guide for validating your choice of filters is available from Agilent at the following link:
www.agilent.com/lifesciences/filter_validation

For questions related to the use of these filter plates, please feel free to contact Agilent Technologies Dissolution Hotline at dissolution.hotline@agilent.com. Agilent is happy to assist in resolving problems you may encounter with the 850-DS, the filter module, the filter plates, or any dissolution questions in general.

QUESTIONS YOU ASKED

We are routinely asked for input on applications or our instruments. The following are excerpts we thought you'd find interesting.

Question: My customer is getting low dissolution results on a sugar coating dosage form using Apparatus 2. Do you have any dissolution experience with sugar coating tablet? If not, where can I find the proper method?
Answer: There are a large number of sugar coated tablets on the market, many of which use Apparatus 2. To evaluate whether the proper method is being used, if the product is generic, they may wish to compare the method to the established method for a particular generic product.
I would suggest that the customer consult the FDA dissolution data base:
http://www.accessdata.fda.gov/scripts/cder/dissolution/
Secondly, there is a new Dissolution Method Database that has just been offered by USP:
http://www.usp.org/usp-nf/overview/compendial-tools/usp-dissolution-methods-database
By the way, sugar coating is sometimes problematic for the formulators, as the thickness of the applied coating can drastically change dissolution results. Also, please evaluate the physical parameters of the apparatus generating the results to ensure vessel temperature and rotational speed are accurate, since these are often implicated in low test results. Lastly, filter validation and not wasting enough sample to properly condition a filter may also contribute to low results.

Question: How can I deal with foaming in Apparatus 3 when using surfactants?
Answer: Surfactants can be very challenging to deal with for Apparatus 3 since the dipping will create foaming very quickly and can even result in the media foaming over the vessels. The best way to handle foaming is to add an anti-foaming agent such as simethicone to the dissolution media. Antifoaming agents can usually be used in very low concentrations (0.1–0.5%) and generally do not impact the chromatography or the dissolution itself.

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