Dissolution Test

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In Vitro-In Vivo Correlations Springer Science & Business Media

Dissolution testing is a critical step in quality control of manufactured final products in the pharmaceutical industry. The United State Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle) is the most widely used dissolution test devices in the pharmaceutical industry to formulate solid drug dosage forms and to develop quality control specifications for its manufacturing process. Mini vessels and mini paddle dissolution testing systems are smaller versions of the USP 2 Apparatus. The concept of the mini paddle apparatus is similar to that of the USP 2 setup but it is scaled down about to 1/5 of the volume and 40% with respect to vessel and impeller sizes. Mini vessel systems, requiring a small volume (200 mL) and a mini paddle impeller, are becoming increasing common in the pharmaceutical industry to overcome the limitations associated with the USP 2 dissolution testing method, especially for dissolution testing involving very small tablets. Mini apparatuses can be useful tools in characterizing drug release profiles since smaller sample sizes and smaller volumes of media are needed, thus offering several advantages in terms of substance, analytical, and material cost savings when evaluating release properties of drug candidates.Despite their increasing importance in dissolution testing, little information is currently available on mini vessels, and especially on the agitation speed needed to prevent "coning" effects. Typically during dissolution testing, a disintegrating tablet becomes rapidly fragmented, and the resulting solid particles may or may not become suspended depending on the agitation speed of the paddle and other geometric and operating parameters "Coning" (the accumulation of particle fragments from a disintegrating tablet) often appears in dissolution testing but can be eliminated by increasing the agitation speed N. Therefore, it is important to be able to predict the minimum rotation speed at which coning phenomena disappears in a dissolution testing system and especially in mini vessels systems.The focus of this work was the determination of the minimum agitation speed, Njs, at which the just suspended state by dispersed particles is achieved in a mini paddle system (thus removing "coning" effects). In the past, Njs, has been experimentally obtained in mixing systems by determining the agitation speed at which no particles are visually observed to be at rest on the vessel bottom for more than one to two seconds. Therefore, the first objective of this work was to develop an observer-independent method to measure experimentally Njs. This was achieved by extending to mini vessel a method that was recently developed in our laboratory and that is based on the determination of the fraction of unsuspended solids in the vessel at different agitation speed (Njs-Ds method). The results of this method agree well the visually observable values of Njs(Njs-visual).Once new method was validated in mini vessels, Njs was experimentally measured using well characterized solid particles under a number of operating conditions, such as liquid level-to-vessel diameter ratio (H/T), particle size (dp), and paddle clearance-to-vessel diameter ratio Cb/T). The results could be interpreted using the Zwietering Equation originally developed for solids suspension in baffled stirred tanks. The Zwietering "S" parameter was obtained for the mini vessel system thus enabling the use of this equation to predict when "coning" effects can be eliminated in mini vessel systems during tablet dissolution testing.

Pharmaceutical Dissolution Testing Springer Science & Business Media

Introduction, Historical Highlights, and the Need for Dissolution Testing Theories of Dissolution Dissolution Testing Devices Automation in Dissolution Testing, by William A. Hanson and Albertha M. Paul Factors That Influence Dissolution Testing Interpretation of Dissolution Rate Data Techniques and of In Vivo Dissolution, by Umesh V. Banakar, Chetan D. Lathia, and John H. Wood Dissolution of Dosage Forms Dissolution of Modified-Release Dosage Forms Dissolution and Bioavailability Dissolution Testing and the Assessment of Bioavailability/Bioequivalence, by Santosh J. Vetticaden Dissolution Rediscovered, by John H. Wood Appendix: USP/NF Dissolution Test.

Improvements to biorelevant dissolution testing: lyophilized media, buffer alternatives and miniaturized apparatus Pragati Books Pvt. Ltd.

Eight samples of heel solids from tank 241-C-109 were delivered to the 222-S Laboratory for characterization and dissolution testing. After being drained thoroughly, one-half to two-thirds of the solids were off-white to tan solids that, visually, were fairly evenly graded in size from coarse silt (30-60 [mu]m) to medium pebbles (8-16 mm). The remaining solids were mostly strongly cemented aggregates ranging from coarse pebbles (16-32 mm) to fine cobbles (6-15 cm) in size. Solid phase characterization and chemical analysis indicated that the air-dry heel solids contained H"8 wt% gibbsite [Al(OH)3] and H"7 wt% natrophosphate [Na--F(PO4)2·19H2O]. The strongly cemented aggregates were mostly fine-grained gibbsite cemented with additional gibbsite. Dissolution testing was performed on two test samples. One set of tests was performed on large pieces of aggregate solids removed from the heel solids samples. The other set of dissolution tests was performed on a composite sample prepared from well-drained, air-dry heel solids that were crushed to pass a 1/4-in. sieve. The bulk density of the composite sample was 2.04 g/mL. The dissolution tests included water dissolution followed by caustic dissolution testing. In each step of the three-step water dissolution tests, a volume of water approximately equal to 3 times the initial volume of the test solids was added. In each step, the test samples were gently but thoroughly mixed for approximately 2 days at an average ambient temperature of 25 °C. The caustic dissolution tests began with the addition of sufficient 49.6 wt% NaOH to the water dissolution residues to provide H".1 moles of OH for each mole of Al estimated to have been present in the starting composite sample and H".6 moles of OH for each mole of Al potentially present in the starting aggregate sample. Metathesis of gibbsite to sodium aluminate was then allowed to proceed over 10 days of gentle mixing of the test samples at temperatures ranging from 26-30 °C. The metathesized sodium aluminate was then dissolved by addition of volumes of water approximately equal to 1.3 times the volumes of caustic added to the test slurries. Aluminate dissolution was allowed to proceed for 2 days at ambient temperatures of H"9 °C. Overall, the sequential water and caustic dissolution tests dissolved and removed 80.0 wt% of the tank 241-C-109 crushed heel solids composite test sample. The 20 wt% of solids remaining after the dissolution tests were 85-88 wt% gibbsite. If the density of the residual solids was approximately equal to that of gibbsite, they represented H"7 vol% of the initial crushed solids composite test sample. In the water dissolution tests, addition of a volume of water H".9 times the initial volume of the crushed solids composite was sufficient to dissolve and recover essentially all of the natrophosphate present. The ratio of the weight of water required to dissolve the natrophosphate solids to the estimated weight of natrophosphate present was 8.51. The Environmental Simulation Program (OLI Systems, Inc., Morris Plains, New Jersey) predicts that an 8.36 w/w ratio would be required to dissolve the estimated weight of natrophosphate present in the absence of other components of the heel solids. Only minor amounts of Al-bearing solids were removed from the composite solids in the water dissolution tests. The caustic metathesis/aluminate dissolution test sequence, executed at temperatures ranging from 27-30 °C, dissolved and recovered H"9 wt% of the gibbsite estimated to have been present in the initial crushed heel solids composite. This level of gibbsite recovery is consistent with that measured in previous scoping tests on the dissolution of gibbsite in strong caustic solutions. Overall, the sequential water and caustic dissolution tests dissolved and removed 80.3 wt% of the tank 241-C-109 aggregate solids test sample. The residual solids were 92-95 wt% gibbsite. Only a minor ...

In-vitro In-vivo Correlation Developed Using a Biorelevant In-vitro Dissolution Test in the Prediction of In-vivo Pharmacokinetic Parameters for the Treatment of Multiple Sclerosis United Nations

Dissolution testing is routinely used in the pharmaceutical industry to provide in vitro drug release information for drug development and quality control purposes. The USP Testing Apparatus 2 is the most common dissolution testing system for solid dosage forms. Usually, sampling cannulas are used to take samples manually from the dissolution medium. However, the inserted cannula can alter the normal fluid flow within the vessel and produce different dissolution testing results. The hydrodynamic effects introduced by a permanently inserted cannula in a USP Dissolution Testing Apparatus 2 were evaluated by two approaches. Firstly, the dissolution tests were conducted with two dissolution systems, the testing system (with cannula) and the standard system (without cannula), for nine different tablet positions using non-disintegrating salicylic acid calibrator tablets. The dissolution profiles at each tablet location in the two systems were compared using statistical tools. Secondly, Particle Image Velocimetry (PIV) was used to obtain experimentally velocity vector maps and velocity profiles in the vessel for the two systems and to quantify changes in the velocities on selected horizontal so-surfaces. The results show that the system with the cannula produced higher dissolution profiles than that without the cannula and that the magnitude of the difference between dissolution profiles in the two systems depended on tablet location. However, in most dissolution tests, the changes in dissolution profile due to the cannula were small enough to satisfy the FDA criteria for similarity between dissolution profiles (f1 and f2 values). PIV measurements showed slightly changes in the velocities of the fluid flow in the vessel where the cannula was inserted. The most significant velocity changes were observed closest to the cannula. However, generally the hydrodynamic effect generated by the cannula did not appear to be particularly strong, which was consistent to dissolution test results. It can be concluded that the hydrodynamic effects generated by the inserted cannula are real and observable. Such effects result in slightly mod fications of the fluid flow in the dissolution vessel and in detectable differences in the dissolution profiles, which, although limited, can introduce variations in test results possibly leading to failure of routine dissolution tests.

Media for in Vitro Dissolution Testing of Polysaccharide Based CDDS John Wiley & Sons

Dissolution tests are routinely carried out in the pharmaceutical industry to determine the dissolution rate of solid dosage forms. Dissolution testing serves as a surrogate for drug bioavailability through in vitro – in vivo correlation (IVIVR), and it additionally helps in guiding the development of new formulations and in assessing lot-to-lot consistency, thus ensuring product quality. The United States Pharmacopoeia (USP) Dissolution Testing Apparatus 2 is the device most commonly used for this purpose. Despite its widespread use, dissolution testing using this apparatus remains susceptible to significant error and test failures. There is documented evidence that this apparatus is sensitive to several geometric variables that can affect the release profile of oral dosage forms, including tablet location during the dissolution process. In this work, the dissolution profiles of disintegrating calibrator tablets containing Prednisone were experimentally determined using two systems, i.e., a Standard USP Dissolution Testing Apparatus 2 (Standard System) and a Modified Standard USP Dissolution Testing Apparatus 2 (Modified System) in which the impeller was located 8 mm off the vessel centerline. The dissolving tablets were located at different off-center positions on the vessel bottom to test the effect of tablet location in these two systems. Tablet dissolution in the Standard System was found to be strongly dependent on tablet location, as previously reported by this and other research groups. This apparatus appears to generate variable results that may not be associated with the tablets undergoing testing but with the hydrodynamic characteristics of the apparatus itself and the location of the tablet on the vessel bottom. However, when the same experiments were conducted in the Modified System, the dissolution profiles for the same tablets were found to be nearly completely insensitive to tablet location. The dissolution process in the Modified System was faster than that in the Standard System because of the improved mixing performance of the Modified System resulting from the non-symmetrical placement of the impeller. However, when the Modified System was operated at 35 rpm, the dissolution profiles for centrally located tablets were found to be very similar to those for the Standard System operating at 50 rpm. Unlike the Standard System however, the dissolution profiles obtained at 35 rpm in the Modified System were found to be insensitive to tablet location. It can be concluded that the newly proposed Modified System for dissolution testing is a simple and yet robust and valid alternative to the current dissolution testing practice using the Standard USP Dissolution Testing Apparatus.

The Modification of an Automated Dissolution Test Apparatus for the Rotating Disk Method of Intrinsic Dissolution Rate Measurement, Its Validation and Use in Evaluating Tablet Diluents Pharmaceutical Dissolution Testing

A potential scenario for retrieving saltcake from single shell tanks is the "Rainbird{reg_sign} sprinkler" method. Water is distributed evenly across the surface of the saltcake and allowed to percolate by gravity through the waste. The salt dissolves in the water, forming a saturated solution. The saturated liquid is removed by a saltwell pump situated near the bottom of the tank. By this method, there is never a large inventory of liquid in the tank that could pose a threat of leakage. There are many variables or factors that can influence the hydrodynamics of this retrieval process. They include saltcake porosity; saltwell pumping rate; salt dissolution chemistry; factors that could promote flow channeling (e.g. tank walls, dry wells, inclusions or discontinuities in the saltcake); method of

water distribution; plug formation due to crystal formations or accumulation of insoluble solids. A brief literature search indicates that very little experimental data exist on these aspects of saltcake dissolution (Wiersma 1996, 1997). The tests reported here were planned (Herting, 2000) to provide preliminary data and information for planning future, scaled-up tests of the sprinkler method.

Pharmaceutical Dissolution Testing CRC Press

An expertly written source on the devices, systems, and technologies used in the dissolution testing of oral pharmaceutical dosage forms, this reference provides reader-friendly chapters on currently utilized equipment, equipment qualification, consideration of the gastrointestinal physiology in test design, the analysis and interpretation of data and procedure automation -laying the foundation for the creation of appropriate and useful dissolution tests according to the anticipated location and duration of drug release from the dosage form within the gastrointestinal tract.

K Basin Sludge Conditioning Testing CRC Press

Dieser erste Titel einer ganzen Serie von anwendungsbezogenen Handb ü chern zur Kapillarelektrophorese besch ä ftigt sich mit der Analytik von pharmazeutischen Substanzen. Dabei werden verschiedene Techniken praxisnah erl ä utert. Jeder, der im Labor - ob wissenschaftlich oder praxisnah - mit der Analyse von oft chiralen Pharmazeutika konfrontiert ist, wird viele Hinweise und Tips f ü r seine Arbeit finden.USP: Einzige Monographie zur Analyse von Pharmazeutika mit CE This book describes the current state of the art for the analysis of pharmaceuticals by capillary electrophoresis and contains several hundred references to specific applications and methods. The main purpose of the book is to present the application possibilities of CE an therefore tabulated application data are provided. Chapters of the book are devoted to providing details of individual application areas such as chiral analysis, determination of drug related impurities, determination of drug counter-ions, drug residue monitoring and main component assay. An introductory chapter provides theoretical background to CE an related techniques. A chapter is dedicated to capillary electrochromatography which highlights the importance this technique currently possesses. Successful regulatory acceptance of CE methods is also described. A comprehensive chapter covers method validation aspects. Other chapters include discrete areas such as the use of non-aqueous solvents, forensic applications of CE, the application of experimental designs, determination of drugs in biofluids, and the analysis of vitamins by CE.

Pharmaceutics OECD Publishing

Dissolution testing is routinely conducted in the pharmaceutical industry to provide in vitro drug release information for quality control purposes. The most common dissolution testing system for solid dosage forms is the United States Pharmacopeia (USP) Dissolution Testing Apparatus 2. In this work, a modified Apparatus 2, termed "OPI" System for "off-center paddle impeller," in which the impeller is placed 8 mm off center in the vessel is tested to determine its sensitivity to differentiate between the dissolution profiles of differently formulated and manufactured tablets. Dissolution tests are conducted with both the OPI System and the Standard System using three different brands of aspirin at nine different tablet positions. The OPI system produces dissolution profiles that are highly dependent on the different brands of aspirin used, similarly to those generates in the Standard System. However, the dissolution profiles obtained with the OPI apparatus are found to be largely independent of the tablet location at the vessel bottom, whereas those obtained in the Standard System generates statistically different profiles depending on tablet location. It can be concluded that the newly proposed OPI system can effectively eliminate artifacts generated by random settling of the tablet at the vessel bottom, thus making the test more robust, while at the same time being just as sensitive as the Standard System to actual differences in differently manufactured tablets having intrinsically different dissolution profiles.

Dissolution Testing of Prednisone and Salicylic Acid Calibrator Tablets at Different Tablet Locations John Wiley & Sons

In the pharmaceutical industry, dissolution testing is routinely carried out to determine the dissolution rate of oral solid dosage forms. Among several testing devices, the USP Dissolution Apparatus 2 is the device most commonly used. However, despite its widespread use, this apparatus has been shown to produce test failures and to be very sensitive to a number of small geometry changes. The objective of this study was to determine whether a novel dissolution system termed "OPI" for "off-center paddle impeller" was sensitive enough to determine differences in tablet dissolution profiles caused by different compression pressure during the tablet manufacturing process. The OPI Dissolution System simply consists of a modified Apparatus 2 in which the impeller is placed 8mm off center in the vessel. In this work, aspirin tablets were manufactured from powder with a manual tablet press using three different compression pressures. The dissolution profiles of these tablets were then obtained in both the OPI system and the standard USP Apparatus 2 system. Tests were conducted by dropping the tablets in the vessels at the beginning of an experiment, and, in separate experiments, by initially immobilizing the tablets on the vessel bottom at nine different locations. This approach has been used in the past by our group to determine the sensitivity of the dissolution apparatus to minor changes in the geometry of the dissolution system. All dissolution profiles were found to be affected by the compression pressure. Faster dissolution profiles were obtained at lower compression pressures. When tablets were dropped in the vessel, a comparison of the dissolution profiles obtained in the standard Apparatus 2 system and in the OPI system showed that similarly manufactured tablets produced statistically similar dissolution profiles in both systems, i.e., that the OPI system was just as sensitive as the standard system to variations in the tablet manufacturing process. However, when the tablets were immobilized during the dissolution process, the standard system generated very different dissolution profiles even for tablets manufactured at the same compression pressure. By contrast, the dissolution profiles in the OPI system for tablets manufactured at different pressure but located at different positions were very similar. It can be concluded that the OPI system is sensitive enough to detect differences in intrinsic tablet dissolution rates (such as those caused, as in this case, by changes in the manufacturing process), while being unaffected by small changes in the system geometry that instead caused the standard system to fail. Therefore, the OPI system appears to be a more reliable dissolution testing apparatus than the current apparatus.

Analysis of Pharmaceuticals by Capillary Electrophoresis Cuvillier Verlag

Dissolution in different steps of pharmaceutical drug development was considered in this work. Dissolution is used as informative tool throughout the entire development process: After identification of a possible drug candidate, intrinsic dissolution in different buffer media is tested for physicochemical characterization. In galenics dissolution is used to develop and optimize formulations by comparative release studies. During scale-up dissolution testing is used to observe influence of process or parameter changes. For regulatory affairs all of these dissolution studies are of interest and many have to be presented to the authorities. Most of the dissolution testing designs in pharmaceutical development are following pharmacopoeial monographs or general chapters and official guidelines. In addition these “ official ” dissolution testing setups, a progression of more innovative dissolution methods closer to physiological conditions are used. Devices simulating movement and flow of the GIT combined with media simulating the gastrointestinal fluids are often used. Disadvantages of these methods are that they are time-consuming and expensive, both of which limit throughput. The aims of this thesis were to (a) reduce time consumption regarding preparation of biorelevant dissolution, (b) increase biorelevance of the media FaSSIF and FeSSIF by substituting the non-physiological buffer systems for bicarbonate and (c) to increase throughput by miniaturization of dissolution devices. To meet the first goal a novel preparation method for the biorelevant media FaSSIF and FeSSIF was established. The conventional method uses chlorinated organic solvent, is time-consuming in preparation (approx. 2 hours) and needs to be done daily. The investigated method uses freeze-drying for the preparation of instant biorelevant media. The instant media only consist of bile salt and lecithin in mixed micelles. In situ preparation is done by simply adding blank buffer to the rapidly dissolving lyophilisate. Freeze-dried product gave comparable results to freshly prepared media and improved reproducibility. Comparison to commercial available instant media indicated superiority of the freeze-drying method. Next, a buffer system based on the more physiological bicarbonate buffer was investigated. A method to maintain a stable buffer system throughout the dissolution testing. The buffer therefore was created by sparging carbon dioxide into alkali saline solution to forming carbonate and bicarbonate as buffer system. At equilibrium the media was transferred to the vessels and supply of carbon dioxide continued by sparging the gas above the solution. Therewith bubble formation could be minimized, although not excluded. Only a small range of buffer strength and pH combinations was possible. The lowest pH still providing effective buffer capacity (5 mmol/l/ Δ pH) was 5.5. Physiologically relevant buffer capacities of 10 and 30 mmol/l/ Δ pH were tested at pH 6.5. The buffer turned out to be very sensitive against pH modifying agents by loosening its buffer capacity and strength. Standard deviations were generally higher. No superiority over conventional buffer systems like phosphate or acetate buffer regarding IVIVC was given. Therefore it is concluded that bicarbonate buffer is not a suitable medium for in vitro dissolution testing. Subsequently methods for small scale dissolution testing were established. Improvement of throughput in dissolution testing was achieved. The investigated BI miniDiss method can be used to test release profiles of small particulate formulations or intermediates. High throughput excipient screening for early formulation is possible by using the well-plate method. In the first series of tests, downscaling by factor 10 was conducted by miniaturizing and automating standard dissolution apparatus. Small vessels of 20 ml volume and paddles of about 8 mm diameter were used. Automating was done by sampling through paddle hollow shafts and online UV/VIS measurement. Since no filtration was possible due to the small sample volume, the true % dissolved was calculated using mathematical scatter correction of spectra from turbid solutions. In this way, release profiles comparable to standard dissolution testing were obtained. Cleaning and restart is accelerated and therewith throughput increased. The 10fold reduced consumption of drug formulation reduces API consumption, so that a larger variety of formulations can be prepared and tested with the same amount of API. The BI miniDiss is limited to multiparticulates like pellets, extrudates, minitablets, granules or intermediates. Downscaling of matrix or IR tablets will likely result in different results due to changed surface to volume ratio. The well-plate method offers a miniaturization of factor 100. Dissolution of multiparticulates showed significant differences compared to standard methods. However, ranking of formulations was possible in several cases. The well-plate method is not suitable for conducting comparative release profiles. However, it can be used for selection of excipients by supersaturation testing. It is an informative tool in early formulation screening helping to optimize formulation of poorly soluble compounds. As last part of the work, the BI miniDiss was used to screen various buffers to finding the best media for IVIVC, retrospectively. The BI miniDiss proved to be useful as a fast and cost and effective screening method. In summary, several improvements in dissolution for pharmaceutical development purposes have been developed regarding consumption of API, costs and efficiency. An easy and rapid preparation of biorelevant media was established making their use in pharmaceutical development and routine quality control more feasible. The miniaturized dissolution methods and the improved high-throughput fulfil demands from pharmaceutical industries to facilitate API-saving methods in development.

Oral Drug Delivery for Modified Release Formulations John Wiley & Sons

Introduction to Pharmaceutics and its Scope - Development of a New Drug - Introduction to Dosage Forms of Drugs - History and Development of Profession of Pharmacy - Introduction to Pre-formulation - Biopharmaceutics - Good Manufacturing Practices - Introduction to Pre-formulation - Biopharmaceutics - Good Manufacturing Practices - Introduction to Alternative Systems of Medicines - Drug Delivery Systems - Biological Products - Packaging of Pharmaceuticals - Bibliography - Index

Dissolution of Different Commercial Aspirin Tablets Using a Novel Off-center Paddle Impeller (OPI) Dissolution Testing System CRC Press

This book represents the invited presentations and some of the posters presented at the conference entitled "In Vitro-In Vivo Relationship (IVIVR) Workshop" held in Sep tember, 1996. The workshop was organized by the IVIVR Cooperative Working Group which has drawn together scientists from a number of organizations and institutions, both academic and industrial. In addition to Elan Corporation, which is a drug delivery com pany specializing in the development of ER (Extended Release) dosage forms, the IVIVR Cooperative Working Group consists of collaborators from the University of Maryland at Baltimore, University College Dublin, Trinity College Dublin, and the University of Not tingham in the UK. The principal collaborators are: Dr. Jackie Butler, Elan Corporation Prof. Owen Corrigan, Trinity College Dublin Dr. lain Cumming, Elan Corporation Dr. John Devane, Elan Corporation Dr. Adrian Dunne, University College Dublin Dr. Stuart Madden, Elan Corporation Dr. Colin Melia, University of Nottingham Mr. Tom O'Hara, Elan Corporation Dr. Deborah Piscitelli, University of Maryland at Baltimore Dr. Araz Raoof, Elan Corporation Mr. Paul Stark, Elan Corporation Dr. David Young, University of Maryland at Baltimore The purpose of the workshop was to discuss new concepts and methods in the devel opment of in vitro-in vivo relationships for ER products. The original idea went back ap proximately 15 months prior to the workshop itself. For some time, the principal collaborators had been working together on various aspects of dosage form development.

OECD Guidelines for the Testing of Chemicals / OECD Series on Testing and Assessment Guidance Document on Transformation/Dissolution of Metals and Metal Compounds in Aqueous Media Cuvillier Verlag

Dissolution testing is routinely carried out in the pharmaceutical industry to determine the rate of dissolution of solid dosage forms. This test is one of the several tests that pharmaceutical companies typically conduct on oral dosage formulations (e.g., tablets) to determine compliance. The USP Dissolution Testing Apparatus 2 is the most common of the apparatuses listed in the USP. However, it has been shown previously that the dissolution profile of a tablet undergoing dissolution in the USP Dissolution Apparatus 2 can be affected by the tablet location in the apparatus. In this work, the dissolution rates of both non-disintegrating tablets (salicylic acid) and disintegrating tablets (Prednisone) were experimentally determined for many different tablet locations, both centered on the vessel bottom and off-center. The location of the tablet was experimentally varied in very small increments in order to determine the exact location where a transition in the dissolution profile occurred. It was found that in a small region (2-4 mm in radius) centered around the vessel centerline just below the impeller the dissolution profiles were similar to those observed with a centered tablet. However, outside this region the dissolution profiles were found to be significantly different, as indicated by the values of the Similarity Factor f1 and the Difference Factor f2. These finding are consistent with previous hydrodynamic investigations that showed the existence of a poorly mixed zone below the USP Apparatus 2 impeller. The results of this work can guide the practitioner on when to accept dissolution testing results based on tablet location.

Initial Results from Dissolution Testing of Various Air-oxidized Spent Fuels

The oral bioavailability of a drug substance is strongly related to its aqueous solubility. Only complete dissolution during the GI-passage can maintain an optimal bioavailability. Poor aqueous drug solubility results, according to the Nernst-Brunner equation into a slow dissolution rate, sometimes too slow for complete dissolution in the GI tract. The dissolution rate increases with decreasing particle size and therefore increasing surface area of the drug particles. In consequence,, micronization of the drug is applied to increase oral bioavailability, but often meets with modest success. Recently developed techniques were applied to decrease the particle size into the nanometer range. For some substances, pharmacokinetic parameters could be influenced decisively, e.g. the obviation of a food effect for the drugs aprepitant and fenofibrate. The assessment of a dosage form is investigated by dissolution testing. For a reasonable assessment of such tests, a separation of solid and liquids has to be ensured within an appropriate time frame. For particle sizes of about 150 nm it appears questionable whether such separation can be succeeded by classical techniques, e.g. the use of syringe filters with a pore size of 0.45 µ m. The aims of this thesis were to investigate the suitability of various analytical techniques in analysis of dissolution tests containing nanosized drug substance. Furthermore, a suitable analytical tool is applied to establish an in vitro – in vivo correlation of the nanosized drug fenofibrate. At first, several techniques were investigated in theory to assess their ability to ensure a rapid and complete separation of solids and liquids. The classical dialysis, turbidity

measurement and UV-measurement via fiber optics were excluded from further investigation due to various reasons, e.g. the speed of separation for dyialisis. The asymmetrical flow field-flow fractionation appeared to be a promising tool, but lack of equipment precluded further investigation. The ultrasonic resonance technology (ResoScan), the microdialysis and the use of centrifugal filter devices have shown to be inappropriate for the analytics of nanosized drugs in dissolution test. The use of syringe filters with various pore sizes and the ionselective electrode (ISE) was promising, so these techniques were examined more intensively. The syringe filters with various filter pore sizes were investigated for their ability to hold back colloidal drug. Fenofibrate was chosen as model drug, since this is commercially available both as micronized and nanosized formulation (Lipidil TerR and Lipidil 145 ONER), enabling direct comparison. The experiments with micronized fenofibrate which contains little or no colloidal fenofibrate yielded similar dissolution profiles, irrespective of filter pore size; f2 was always greater than 65, indicating less than 5% difference between the dissolution profiles in any medium. Using a pore size of 0.1 μm or less, the maximum concentration of drug achieved in solution from the nanosized formulation was commensurate with the saturation solubility of fenofibrate in all tested media. Filtration with a pore size of 0.2 μm or 0.45 μm generated concentrations exceeding the saturation solubility. These results, in combination with higher standard deviations of the analytical results, indicate that the apparent “supersaturation” is caused by colloidal fenofibrate, which is too fine to be held back by these filters. The f2-value of less than 50 when comparing the profiles obtained from 0.1 μm and 0.2 μm filter pore size indicates that the choice of filter pore size is crucial to the interpretation of the dissolution profiles. To separate nanosized drug from molecularly dissolved fenofibrate in Lipidil 145 ONER, a filter pore size of 0.1 μm or less appears to be appropriate. It was observed that the experimental increase of dissolution rate is not congruent with common hypothesis regarding the boundary layer h for decreasing particle sizes and subsequent application of the Nernst-Brunner equation. The initial dissolution rates of both formulations were investigated by using a filter pore size of 0.1 μm. The results were utilized in an in silico model (STELLAc) to correlate the in vitro results with in vivo data (Model A). In the preprandial state a good in correlation was established for the micronized fenofibrate, while for the nanosized fenofibrate the plasma levels were overpredicted. The model was expanded to investigate the impact of an absorption step at the intestinal membrane on the in vitro – in vivo correlation. It was found that even a minor deceleration of absorption results in varied plasma profiles caused by a lagged appearance of drug in the blood. For both formulations the rate determining step was identified: When changing from the micronized to the nanosized formulation, the rate-determining step for absorption may change from completely dissolution-controlled to at least partly permeationcontrolled in the fasted state. In the fed state, gastric emptying appears to be rate-determining for absorption of fenofibrate from both the micronized and the nanosized formulation. Another technique appears to be suitable for analysis of nanosized drugs in dissolution testing. The Ion-selective electrode (ISE) is a recently developed analytical system measuring the changes of the electrochemical potential in solutions. A transformation via the Nikolski – Eisenmann equation results into the concentration of the respective drug in solution. Since only dissolved drug is detected, obviating the need for separation of dissolved from undissolved drug, this system appears to be very promising in the analytics of nanocrystalline drugs. Diphenhydramine_HCl was chosen as model substance for the ISE studies. It was the goal of investigation to test compatibility of the ISE with complex media, e.g. all biorelevant dissolution media. This is done in advance of application of the ISE in these media for nanocrystalline drug substance. The results were compared to manual sampling, filtration and subsequent HPLC-UV analysis. The results demonstrate that the ion-selective electrode is suitable for measurements of diphenhydramine HCl in fasted state biorelevant media (FaSSGF, FaSSIF, FaSSIF-V2) as both a stand-alone system (Method A) and in conjunction with a single point conventional assay (Method B). The results acquired are similar to those obtained by manual sampling and subsequent HPLC-UV analysis. The ISE also delivers satisfactory results in a milk-based medium (FeSSGF), in which it has distinct advantages over manual sampling with HPLC-UV analysis by obviating the need for sample preparation. The application of the ISE in FeSSIF type media will need further study. Finally, as an on-line technology, ISE offers more efficient generation of dissolution profiles than conventional sample-based methods.

Dissolution of Disintegrating Solid Dosage Forms in a Modified Dissolution Testing Apparatus 2

A human, regional absorption study was undertaken, in-vivo data for the systemic exposure of Firategrast, a multiple sclerosis treatment was obtained. Immediate release, Modified release over 3, 6 and 9 hour solid oral tablet formulations in the fasted state, alongside the modified release 6 hour formulation administered with food were administered. As part of pharmaceutical development, understanding the release profile of the formulation is critical to understanding the bioavailability the product. A theory in understanding Firategrast bioavailability was tasked; could in-vitro dissolution be used to understand the bioavailability at the time of 'gastric emptying' and be used to predict in-vivo absorption of Firategrast. In order to investigate bioavailability, a range of biorelevant in-vitro dissolution tests were developed, with the aim of developing an IVIVC. The biorelevant dissolution test focussed on mimicking two key areas of in-vivo gastro-intestinal transit that are critical to bioavailability; gastric media and gastric agitation. The dissolution tests developed were validated for use with an analytical HPLC method. No trends were observed in using fasted and fed media or using the peristaltic pump to mimic the gastric hydrodynamics. The data was then applied to the 'gastric emptying window' theory for bioavailability. The percentage in-vitro dissolution at 1 hour (fasted gastric emptying time), 3 and 4 hours (fed gastric emptying times) were correlated with the in-vivo pharmacokinetic data parameters such as AUC and plasma concentration (ng/mL). A multiple level C correlation was observed according to FDA guidelines. Correlations show weaknesses in the form of variable dissolution data and potentially skewed in-vivo data. Further work is recommended to increase the statistical power of the correlations.

Effects of Operating and Geometric Variables on Hydrodynamics and Tablet Dissolution in Standard and Modified Dissolution Testing Apparatuses 2

This publication addresses classification and labeling of chemicals by types of hazards. It provides the basis for worldwide harmonization of rules and regulations on chemicals and aims at enhancing the protection of human health and the environment during their handling, transport and use by ensuring that the information about their physical, health and environmental hazards is available.

Analytics of dissolution testing of products containing nanosized drugs with a view to predicting plasma profiles

This report describes tests performed by Pacific Northwest National Laboratory (PNNL) for Numatec Hanford Corporation (NHC) as part of the overall activities for the development of the K Basin Sludge Treatment System. These tests were conducted to examine the dissolution behavior of a K East Basin canister sludge composite in nitric acid at the following concentrations: 2 M, 4 M, 6 M, 7.8 M and 10 M and temperatures of 25 C and boiling. Assuming that the sludge was 100% uranium metal, a 4X stoichiometric excess of nitric acid was used for all testing, except that conducted at 4 M. In the 4 M nitric acid dissolution test, 50% excess nitric acid was used resulting in a dissolver solution with a significantly higher solids loading. The boiling tests were conducted for 11 hr, the 25 C dissolution tests were conducted from 24 hr to 2 weeks. For the 25 C dissolution testing, the weight percent residual solids was determined, however, chemical and radiochemical analyses were not performed.

Hydrodynamic Effects of a Cannula in a USP Dissolution Testing Apparatus 2

Explore the cutting-edge of dissolution testing in an authoritative, one-stop resource In Pharmaceutical Dissolution Testing, Bioavailability, and Bioequivalence: Science, Applications, and Beyond, distinguished pharmaceutical advisor and consultant Dr. Umesh Banakar delivers a comprehensive and up-to-date reference covering the established and emerging roles of dissolution testing in pharmaceutical drug development. After discussing the fundamentals of the subject, the included resources go on to explore common testing practices and methods, along with their associated challenges and issues, in the drug development life cycle. Over 19 chapters and 1100 references allow practicing scientists to fully understand the role of dissolution, apart from mere quality control. Readers will discover a wide range of topics, including automation, generic and biosimilar drug development, patents, and clinical safety. This volume offers a one-stop resource for information otherwise scattered amongst several different regulatory regimes. It also includes: A thorough introduction to the fundamentals and essential applications of pharmaceutical dissolution testing Comprehensive explorations of the foundations and drug development applications of bioavailability and bioequivalence Practical discussions about solubility, dissolution, permeability, and classification systems in drug development In-depth examinations of the mechanics of dissolution, including mathematical models and simulations An elaborate assessment of biophysiologically relevant dissolution testing and IVIVCs, and their unique applications A complete understanding of the methods, requirements, and global regulatory expectations pertaining to dissolution testing of generic drug products Ideal for drug product development and formulation scientists, quality control and assurance professionals, and regulators, Pharmaceutical Dissolution Testing, Bioavailability, and Bioequivalence is also the perfect resource for intellectual property assessors.

Development and Characterization of a Novel Drug Dissolution Test Method Using a Quartz Crystal Microbalance

Guides readers on the proper use of in vitro drug release methodologies in order to evaluate the performance of special dosage forms In the last decade, the application of drug release testing has widened to a variety of novel/special dosage forms. In order to predict the in vivo behavior of such dosage forms, the design and development of the in vitro test methods need to take into account various aspects, including the dosage form design and the conditions at the site of application and the site of drug release. This unique book is the first to cover the field of in vitro release testing of special dosage forms in one volume. Featuring contributions from an international team of experts, it presents the state of the art of the use of in vitro drug release methodologies for assessing special dosage forms ’ performances and describes the different techniques required for each one. In Vitro Drug Release Testing of Special Dosage Forms covers the in vitro release testing of: lipid based oral formulations; chewable oral drug products; injectables; drug eluting stents; inhalation products; transdermal formulations; topical formulations; vaginal and rectal delivery systems and ophthalmics. The book concludes with a look at regulatory aspects. Covers both oral and non-oral dosage forms Describes current regulatory conditions for in vitro drug release testing Features contributions from well respected global experts in dissolution testing In Vitro Drug Release Testing of Special Dosage Forms will find a place on the bookshelves of anyone working with special dosage forms, dissolution testing, drug formulation and delivery, pharmaceutics, and regulatory affairs.