Pion

Analytical Services

Pion Analytical Services can support your drug development challenges with tests, assays, analysis and interpretation.

DISCOVERY | PRE-FORMULATION | FORMULATION

Pion Analytical Services

Drug development can be a complex, multifaceted challenge – so finding effective scientific support can be critical to making progress. More and more organizations are turning to Pion Analytical Services, for the tests, assays, analysis and interpretation required at all the key phases of drug development.

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Discovery

Let Pion support you in establishing the primary characteristics of compounds under consideration, with high-throughput solubility assessment and excipient screening, permeability and all relevant PhysChem Analysis.

Pre-formulation

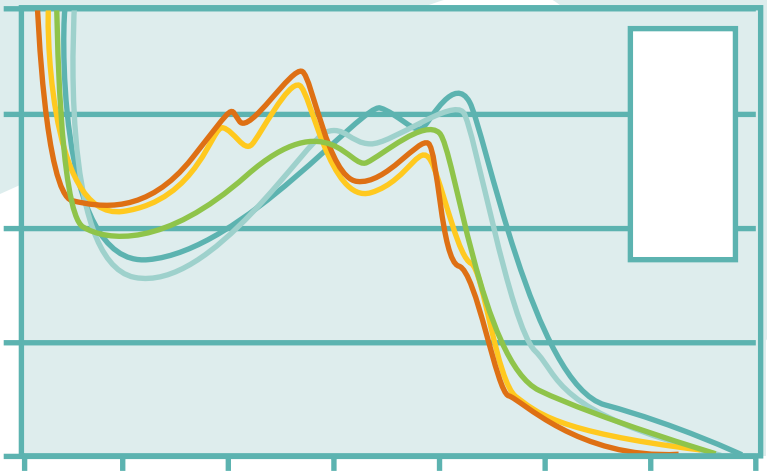
As you move into the second phase of drug development, Pion helps partners start to establish the behavioral characteristics of pipeline candidates, analyzing dissolution properties, supersaturation considerations, excipient selection and optimal PhysChem behavior.

Formulation

Once candidates reach the formulation stage, Pion offers a range of tests and expertise to help you characterize your formulations. We will work with you to ascertain levels of dissolution, absorption and biorelevancy, and even predict behavior in subcutaneous and intestinal environments.

Contents

Drug Discovery



pK_a Assays

Introduction

Many drugs are weak acids or weak bases and exist in solution as an equilibrium between unionised and ionised forms. The pK_a, also known as the acid dissociation constant, is an intrinsic property of such ionisable compounds and indicates the pH at which a functional group exists in solution as a 50:50 ratio of neutral : ionised species. If the pK_a of a molecule is known, the degree of ionisation of the molecule can be determined for other pH values.

The ionisation state of a compound affects the distribution of the drug in solution and affects the availability of the drug to enter into physical, chemical and biological reactions. Hence, the pK_a of a compound and the pH influences properties such as logD, permeability and solubility as well as the overall absorption, distribution, metabolism and elimination characteristics. In addition, it can have an impact on protein binding and *in vitro* potency of a drug candidate. Later on, in early development, knowledge of the pK_a can be used in salt selection strategies to select an appropriate salt counter-ion (e.g. hydrochloride salt of a free base) in order to optimise stability or delivery attributes.

Key Deliverable

A full study report is provided. Reports include; sample and customer details, table of pK_a results, distribution of species profile and statement of methodology.

Experiment Overview

pK_a measurements are performed using the SiriusT3 physchem platform. The SiriusT3 can utilise both spectrometric and potentiometric techniques in order to provide our customers with high quality, reliable results. Several assays are provided covering a high throughput rapid determination of pK_a through to co-solvent studies for poorly soluble samples over an increased pH range.

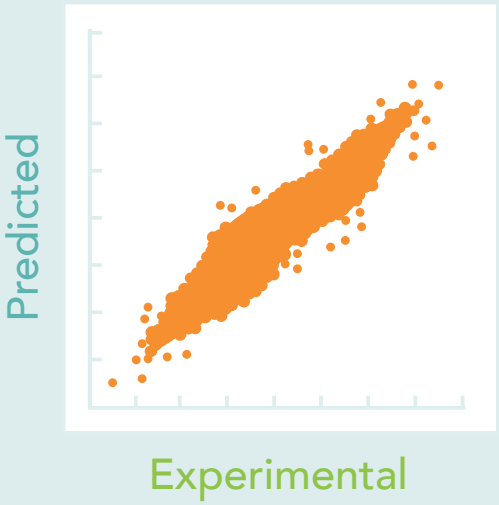
The Fast-UV (screening) method measures UV absorbance at multiple wavelengths in an acid-base triple titration. Results are obtained from changes in UV-spectra as a compound alters its ionisation state. Hence, the Fast-UV method provides pK_a results for samples with chromophores whose UV absorbance changes as a function of pH. The UV-metric method carefully records UV data and extends the pH range for samples with UV chromophores. Results are obtained from changes in UV-spectra as a compound alters its ionisation state.

pH-metric methods are based on potentiometric acid-base titration. Results are obtained by fitting the pH of each point in the titration curve using mass and charge balance equations that contain the pK_a of the compound. The pK_a that provides the best fit of calculated titration data to the measured titration data is taken to be the measured pK_a value. pH-metric methods can measure all pK_as between pH 2 and 12, provided the sample remains in solution throughout the experiment.

Sample Submission Details

200 µL of 10mM DMSO stock solution required for pK_a screening assays.

10 mg of dry compound required for Gold Standard pK_a assays based on a sample with a formula weight approximately 400 g/mol.



LogP/D Assays

Introduction

LogP and logD are measures of lipophilicity. Lipophilicity is a key parameter in understanding the pharmacokinetic behaviour of drugs and can influence distribution into tissues, absorption and protein binding characteristics of a drug. It is also an important factor in determining the solubility of a compound. In particular, drugs designed for oral administration require a good balance between lipophilicity and solubility in order to achieve adequate *in vivo* absorption.

The partition coefficient logP is a constant which describes the equilibrium distribution of a neutral molecule between an aqueous medium layer and a lipid medium layer, which may indicate the compound's ability to absorb across lipid bilayers *in vivo*.

Many drugs are weak acids or weak bases and exist in solution as an equilibrium between unionised and ionised. The ionisation state (pK_a) of a compound affects the distribution of the drug in aqueous solution at a given pH. The distribution coefficient logD accounts for the distribution of all neutral and charged forms of the molecule between aqueous and lipid medium layers, at the pH of interest.

LogP and logD are usually measured in the octanol-water system (where the octanol is a simple representation of a biological membrane).

Key Deliverable

A full study report is provided. Reports include; sample and customer details, presentation of logP/D results, lipophilicity profile (where appropriate) and statement of methodology.

Experiment Overview

We offer two methods for the determination of the logP/D. In order to determine the logP, the pK_a of the compound is required.

Our potentiometric (pH-metric) logP method determines the logP of a compound from the measurement of the apparent ionisation constant in the presence of octanol/water (p_oK_a). The shift in the apparent ionisation constant relative to the aqueous ionisation constant is measured at different volume ratios of octanol/water and is then used to calculate the logP.

Our shake-flask (HPLC) logP/D technique will be performed using the shake-flask (with HPLC quantification) methodology at a given pH specified by the customer (pH 1– pH 13). It can be used for both ionisable and nonionisable compounds. The compound is prepared at different partition ratios of octanol/aqueous buffer tailored to its estimated logP value. These systems are then shaken for a period of 24 hours before being centrifuged and analysed by HPLC. The concentration of compound in each aqueous layer is compared to a known standard to determine the partitioned sample quantity. Submitted samples should exhibit absorbance in the UV region in order to be effectively quantified by HPLC.

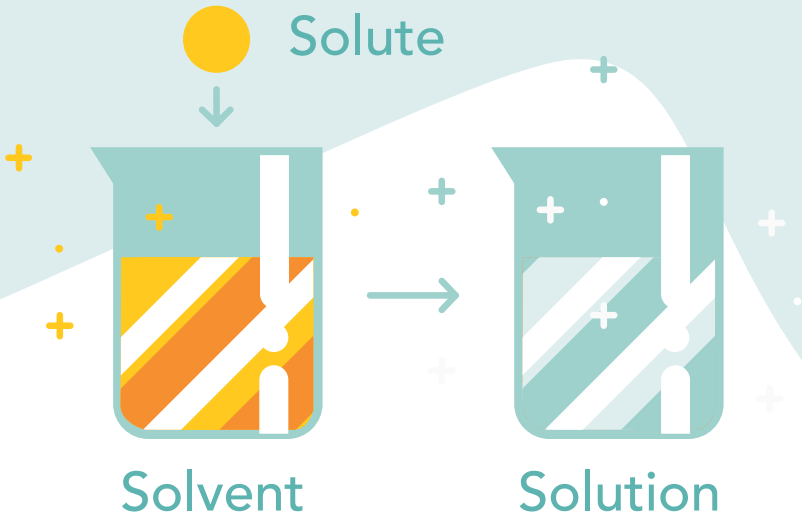
Sample Submission Details

200 µL of 10mM DMSO stock solution required for logD screening assays.

5 mg dry compound required for Gold Standard pH-metric logP/D assays based on a sample with a formula weight of approximately 400 g/mol.

20 – 50 mg dry compound required for Gold Standard shake-flask logP/D assays based on a sample with a formula weight approximately 400 g/mol.

Drug Discovery



Solubility Assays

Introduction

Determining compound solubility is an essential tool for understanding drug compound behaviour. Poor solubility can lead to unreliable results, erratic absorption and poor bioavailability, as well as increased costs during development. Solubility studies in the presence of buffers are used to rank order discovery compounds or inform on progress and select drug candidates during lead optimisation stages of drug discovery.

Experiment Overview

For screening determination we offer the miniaturised Shake-Flask Method of Solubility Assay (MicroSOL) using a UV 96-well microtitre plate. The reference standard solutions are pre-dissolved in organic solvent and the samples are prepared at the required pH values. The samples are agitated on an electronic shake-plate for 9 hours and left to settle for a further 9 hours before filtering and quantification. The determination of the solubility is obtained using a UV Plate Reader.

The shake-flask (HPLC) protocol is used to determine the solubility of a compound in the presence of selected aqueous buffers. The compounds (prepared from solid) are shaken in the selected medium for a period of 24 hours, followed by a further 24 hours for the sedimentation period prior to vacuum filtration and quantitation by HPLC. *See also pages 10-12.*

The potentiometric solubility assay (CheqSol) is used for ionisable compounds where the pK_a has previously been determined. The sample could be titrated in water or in a minimum of three titrations under co-solvent conditions when the sample is poorly soluble. The CheqSol method determines the intrinsic solubility from the measurement of the apparent solubility under precipitation conditions relative to the aqueous ionisation constant (where the sample is fully dissolved). The kinetic solubility and the possible metastable forms solubility could also be determined. *See also page 11.*

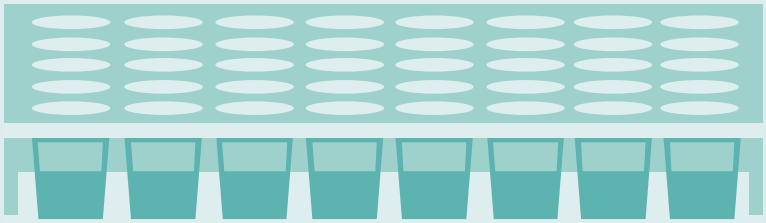
Key Deliverable

A full study report is provided. Reports include: sample and customer details, solubility results, a logS profile and table *versus* pH (for potentiometric assays) and statement of methodology.

Sample Submission Details

250 µL of 10mM DMSO stock solution required for solubility screening (or 3 mg for free-DMSO protocol).

20 – 50 mg dry compound required for shake-flask (HPLC) and potentiometric (CheqSol) solubility analysis based on a sample with a formula weight approximately 400 g/mol.



Parallel Artificial Membrane Permeability Assay (PAMPA)

Introduction

The Parallel Artificial Membrane Permeability Assay (PAMPA) is used to determine passive diffusion across an artificial lipid membrane impregnated onto a porous filter support. Passive diffusion is an important factor in determining absorption of orally administered compounds in the gastrointestinal tract (GIT), penetration of the blood-brain barrier (BBB), as well as general transport across cell membranes. Depending upon the type of lipid and the setup used, the PAMPA assay can be predictive of gastrointestinal tract absorption (PAMPA-GIT), blood-brain barrier permeability (PAMPA-BBB) or transdermal penetration (Skin-PAMPA). Typically, PAMPA experiments are carried out in the early drug discovery phase to select lead compounds with promising oral bioavailability or brain penetration potential by cost-efficiently ranking candidates within large compound sets. The data generated by PAMPA can be used by medicinal chemists to guide structural modifications of discovery compounds to improve their *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the apparent permeability coefficient for each compound (P_{app}) and statement of methodology.

Experiment Overview

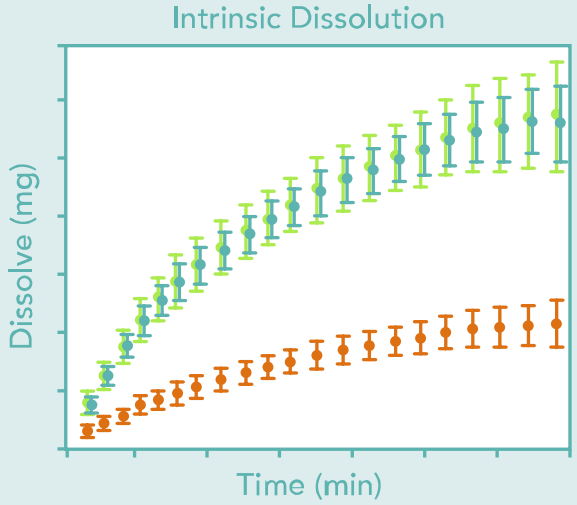
PAMPA uses two disposable 96-well plates that are assembled into a "PAMPA sandwich". The top plate (acceptor plate) contains a porous filter at the bottom of each well which is placed on top of a second, donor plate. The filter is coated with a solution of lipid material to prepare the artificial membrane layer. The test compound solutions are added to pH-adjusted buffer in the wells of the donor plate and acceptor buffer solution is added to each well of the acceptor plate. The acceptor plate is placed on top of the donor plate allowing the donor solution to come into contact with the filter support. The plates are then incubated at room temperature, in a humid environment, for up to 4 hours depending on the assay conditions. Each donor well can be individually stirred using magnetic stir discs. Standards solutions are prepared for each test compound in order to calculate the permeability. The donor and acceptor samples are quantified by UV plate reader. The experimental analyte recovery is calculated using both donor and acceptor compartment concentrations and can also be used to determine membrane retention percentage. *See also page 18.*

Sample Submission Details

400 µL 10mM stock solution required for GIT and BBB aqueous screenings.

For Skin-PAMPA analysis, the amount of sample required will be determined upon enquiry.

Pre-formulation



Disc Intrinsic Dissolution Rate Assay

Introduction

The Intrinsic Dissolution Rate (IDR) is a measure of the rate of dissolution of a pure active pharmaceutical ingredient (API) where the conditions of surface area, temperature, agitation/stirring speed, medium pH and ionic strength are all kept constant. A well-defined surface area is presented to the dissolution medium by preparing a flat tablet disc of specific size. IDR is important during the development of new drug molecules as it is possible to predict potential problems using small quantities of material. It has applications in evaluating drug solubility in accordance with the biopharmaceutics classification system (BCS), comparison of the dissolution rate during salt selection or polymorph screening to choose the best candidate, and setting specifications for particle size in order to achieve complete dissolution of the required dose within the typical gastrointestinal transfer time. Disc IDR screening can be applied to promising drug candidates to guide early development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the IDR (mass/time/area) for each sample for the chosen buffer system and statement of methodology.

Experiment Overview

In the disc method, the drug powder is compressed into discs of fixed diameter. Theoretically, this results in an exact and constant surface area that is in contact with the dissolution medium during the full time of the experiment, and this is the major advantage of this method. The IDR (μg/min/cm^2) is measured using the MicroDISS™ and inForm.

In the MicroDISS™, as little as 5 mg of compound is compressed in a Mini-IDR compression system. The discs are fixed into a cylindrical Teflon rotating disk carrier, placed in a glass vial containing dissolution medium where drug concentration over time is monitored *in situ* using fibre-optic UV probes.

For the inForm platform, samples can similarly be prepared as tablet discs but with 3 mm, 6 mm or 8 mm diameters. The reverse side of the tablet discs are sealed with a rubber bung to prevent exposure of the reverse side of the tablet to the dissolution medium. The tablet discs are automatically placed into the dissolution vial using a robotic arm once the dissolution medium has been prepared by the inForm platform. Drug concentration over time is also monitored *in situ* using a fibre-optic UV probe.

Sample Submission Details

200 mg dry compound required based on a sample with a formula weight approximately 400 g/mol.

Surface Dissolution Imaging Assay (Compact Flow Cell) Assay

Introduction

The miniaturized SDi2 (Surface Dissolution Imaging) platform, is used to record images of the dissolution process at the surface of the compact and is able to rank-order IDR (µg/min/cm^2) and visualise the dissolution of APIs and salts during early development.

The Intrinsic Dissolution Rate (IDR) is a measure of the rate of dissolution of a pure active pharmaceutical ingredient (API) where the conditions of surface area, temperature, agitation/stirring speed, medium pH and ionic strength are all kept constant. A well-defined surface area is presented to the dissolution medium by preparing a flat tablet disc of specific size. IDR is important during the development of new drug molecules as it is possible to predict potential problems using small quantities of material. It has applications in evaluating drug solubility in accordance with the biopharmaceutics classification system (BCS), comparison of the dissolution rate during salt selection or polymorph screening to choose the best candidate, and setting specifications for particle size in order to achieve complete dissolution of the required dose within the typical gastrointestinal transfer time. IDR imaging can be applied to promising drug candidates to guide early development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the IDR (mass/time/area) for each sample for the chosen buffer system, images of the dissolution process and statement of methodology.

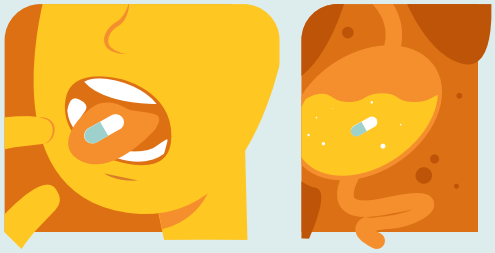
Experiment Overview

Samples are prepared by compressing small amounts of sample powder (~5 mg) into a sample cup with a fixed surface area exposed to the dissolution medium. The Surface Dissolution Imaging IDR measurement is based on flow-through dissolution and direct UV imaging of the flow-cell. The technique records the release of material directly from the surface of a 3mm compacted disc of API and from near downstream to calculate IDRs. The instrument comprises a sample flow cell, pump system, light source and ActiPix detector, and control and data analysis software. The transmitted light in the presence of flowing medium is captured by the detector during the sample run and the light intensity at each pixel is converted into an absolute absorbance. The images collected for the duration of the experiment are used to create a movie that provides a detailed view of the dissolution process at the solid–liquid interface and downstream of the compact. Applying proprietary software tools then allows extraction of standard intrinsic dissolution rate values of (mass/time/area) which are easily calculated from the volumetric flow rate and the absorbance values downstream of the compact. *See also page 22.*

Sample Submission Details

100 mg dry compound required for compact flow-cell analysis based on a sample with a formula weight approximately 400 g/mol

Pre-formulation



Solubility – Impact of Biorelevant Media

Introduction

Determining compound solubility is an essential tool for understanding drug compound behaviour. Solubility studies in the presence of biorelevant media are used to further understand the sensitivity of APIs (Active Pharmaceutical Ingredients) to be influenced by components found in the gastrointestinal tract and is an especially important consideration for poorly soluble drugs. The composition of intestinal fluids (e.g. bile acids and phospholipids) can have a significant impact on enhancing solubility. Higher drug concentrations for solubility limited BCS Class II drugs can lead to increased flux across biological membranes and increase overall drug absorption. Solubility-SIF (simulated intestinal fluids) studies can be used to understand the impact of biorelevant media on compound solubility behaviour and guide early development efforts to assess a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided showing the impact of SIF on the solubility behavior drug.

Reports include: sample and customer details, the equilibrium solubility for each compound in the presence of SIF (e.g. FaSSIF) or various SIF (bile acid and lecithin) compositions, and statement of methodology.

Experiment Overview

The shake-flask (quantification by HPLC) protocol is used to determine the solubility of a compound in the presence of various biorelevant media (e.g. FaSSIF-v1, FaSSIF-v2, FeSSIF-v1, FeSSIF-v2, FaSSCoF, FeSSCoF, or other compositions). Typical assay conditions will involve an incubation period of 24 hours in the biorelevant medium, followed by a further 24 hours sedimentation period prior to vacuum filtration and quantitation by HPLC.

These experiments will determine the equilibrium solubility in biorelevant media and allow a comparison of the ability of SIF components to enhance solubility. Please contact Pion for more details on SIF recipes that can be used.

Sample Submission Details

20 – 50 mg dry compound required for Gold Standard solubility analysis based on a sample with a formula weight approximately 400 g/mol.

Solubility – Impact of Excipients

Introduction

Determining compound solubility is an essential tool for understanding drug compound behaviour. Solubility studies in the presence of excipients are used to understand the capacity of APIs (Active Pharmaceutical Ingredients) to be solubilised by ingredients commonly used in the pharmaceutical industry and is an important consideration for poorly soluble drugs. Solubility enhancing ingredients can lead to higher drug concentrations in the gastrointestinal tract for solubility limited BCS Class II drugs and can lead to increased flux across biological membranes and increase overall drug absorption. These solubility-excipient studies are used to understand the impact of common pharmaceutical excipients on compound solubility behaviour and can guide early development efforts as part of a solubility enhancement strategy.

Key Deliverable

A full study report is provided showing the impact of excipient on the solubility behaviour of the drug.

Reports include: sample and customer details, the equilibrium solubility for each compound in the presence of different levels of various excipients, and statement of methodology.

Experiment Overview

The shake-flask (quantification by HPLC) protocol is used to determine the solubility of a compound in the presence of various pharmaceutical grade excipients. Typical assay conditions will involve an incubation period of 24 hours in the assay media containing different levels of excipients, followed by a further 24 hours sedimentation period prior to vacuum filtration and quantitation by HPLC.

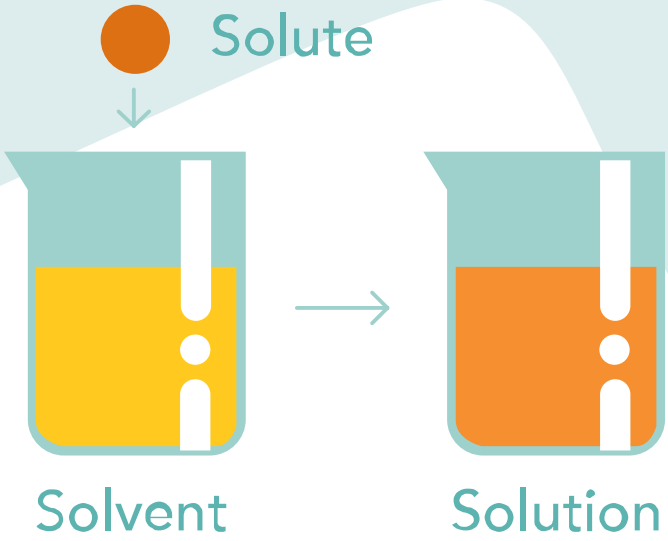
The potentiometric solubility assay (CheqSol) is used for ionisable compounds where the pK_a has been previously determined. The sample can be titrated in the present of different levels of excipients to study their effect on the solubility enhancement or inhibition of the drug.

These experiments will determine the equilibrium solubility in the presence of selected pharmaceutical excipients. Please contact Pion for more details on the types of excipients that can be used.

Sample Submission Details

20 – 50 mg dry compound required for Gold Standard solubility analysis based on a sample with a formula weight approximately 400 g/mol.

Pre-formulation



Solubility – Impact of Solvents

Introduction

Determining compound solubility is an essential tool for understanding drug compound behaviour. Solubility studies in the presence of solvents are used to understand the solubilisation capacity of APIs (Active Pharmaceutical Ingredients) and intermediates in solvents commonly used in the pharmaceutical industry. Solubility-solvent studies can guide development efforts for optimising and achieving sufficient yields during synthesis and process scale-up.

Key Deliverable

A full study report is provided showing the impact of solvent on the solubility behaviour of the drug.

Reports include: sample and customer details, the equilibrium solubility for each compound in the presence of various pure solvents at pre-selected temperatures, and statement of methodology.

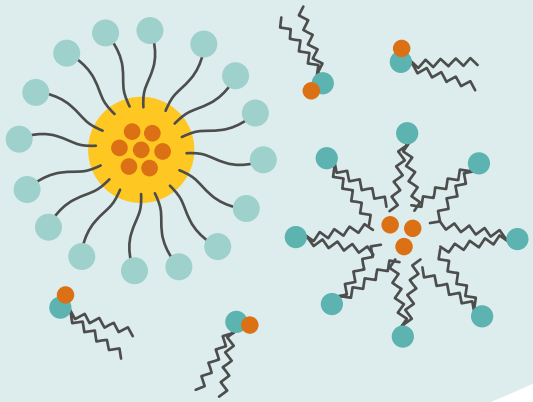
Experiment Overview

The shake-flask (quantification by HPLC) protocol is used to determine the solubility of a compound in the presence of various pure solvents typically used in the pharmaceutical industry. Typical assay conditions will involve an incubation period of 24 hours in the pure solvent medium, followed by a further 24 hours sedimentation period prior to vacuum filtration and quantitation by HPLC.

These experiments will determine the equilibrium solubility in the presence of selected pure solvents. Please contact Pion for more details on the types of solvents that can be used.

Sample Submission Details

20 – 50 mg dry compound required for Gold Standard solubility analysis based on a sample with a formula weight approximately 400 g/mol.



Supersaturation-Precipitation Screening – Excipient Effects

Introduction

Supersaturation-precipitation studies are used to understand the supersaturation propensity of APIs (Active Pharmaceutical Ingredients) and the impact of common pharmaceutical excipients on precipitation and crystallisation behaviour under aqueous conditions. Supersaturation and precipitation is an important consideration for poorly soluble drugs, especially for poorly soluble weak bases that might be soluble in the gastric environment and precipitate in the intestine. The presence of excipients can have a significant impact on enhancing solubility and prolonging supersaturation – the so-called "spring and parachute effect". Higher drug concentrations for solubility limited BCS Class II drugs will lead to increased flux across biological membranes and increase overall drug absorption. Supersaturation-precipitation-excipient screening can be used to rank order the influence of various excipients, helping to guide early development efforts and improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided showing the impact of the chosen excipients and highlighting the best options for further investigation during development.

Reports include: sample and customer details, the amorphous solubility for each compound, the study of the supersaturation-precipitation behaviour in the presence of various pharmaceutical excipients, and statement of methodology.

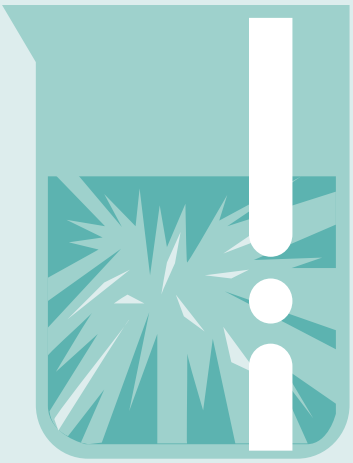
Experiment Overview

A supersaturation-precipitation study will first determine the amorphous or kinetic solubility level of API in aqueous medium at intestinal pH. This is performed by injecting aliquots of stock solution of an API dissolved in organic solvent (e.g. DMSO, methanol) into the intestinal dissolution buffer until the drug exceeds its maximum supersaturation level (i.e., the amorphous solubility, sometimes referred to as the kinetic solubility) and the drug precipitates as determined by light scattering. The next stages are to measure the concentration versus time curves at 80% of the maximum supersaturation level using *in situ* UV fibre-optic spectroscopy in the presence and absence of various pharmaceutical excipients. These experiments will determine the induction time (to first precipitation) and the precipitation rate and allow a comparison of the ability of different excipients to maintain and sustain supersaturation and to prevent crystallisation. Excipients that can be studied include (but are not restricted to) cyclodextrins, cellulose polymers, polyvinylpyrrolidone polymers, poloxamers, etc. Please contact Pion for a full list of excipient options.

Sample Submission Details

200 mg dry compound required for Gold Standard solubility analysis based on a sample with a formula weight approximately 400 g/mol.

Pre-formulation



Supersaturation-Precipitation – Impact of Biorelevant Media

Introduction

Supersaturation and precipitation studies are used to understand the supersaturation propensity of APIs (Active Pharmaceutical Ingredients). Supersaturation and precipitation is an important consideration for poorly soluble drugs, especially for poorly soluble weak bases that might be soluble in the gastric environment and precipitate in the intestine. The composition of intestinal fluids (e.g. bile acids and phospholipids) can have a significant impact on enhancing solubility and prolonging supersaturation – the so-called "spring and parachute effect". Higher drug concentrations for solubility limited BCS Class II drugs can lead to increased flux across biological membranes and increase overall drug absorption. Supersaturation-precipitation-SIF (simulated intestinal fluids) screening can be used to explore the effects of biorelevant fluids, helping to guide early development efforts and assess a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided showing the impact of SIF on the supersaturation- precipitation behaviour of the drug.

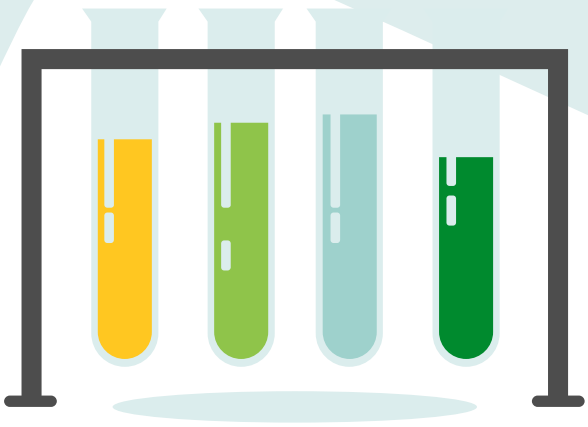
Reports include: sample and customer details, the amorphous solubility for each compound, the study of the supersaturation-precipitation behaviour in the presence of SIF (e.g. FaSSIF) or various SIF (bile acid and lecithin) compositions, and statement of methodology.

Experiment Overview

A supersaturation-precipitation study will first determine the amorphous or kinetic solubility level of API in aqueous medium at intestinal pH. This is performed by injecting aliquots of stock solution of an API dissolved in organic solvent (e.g. DMSO, methanol) into the intestinal dissolution buffer until the drug exceeds its maximum supersaturation level (i.e., the amorphous solubility, sometimes referred to as the kinetic solubility) and the drug precipitates as determined by light scattering. The next stage is to measure the concentration versus time curves at 80% of the maximum supersaturation level using *in situ* UV fibre-optic spectroscopy in the presence and absence of SIF, (e.g. FaSSIF). These experiments will determine the induction time (to first precipitation) and the precipitation rate and allow a comparison of the ability of SIF to maintain and sustain supersaturation and to prevent crystallisation. Different compositions of SIF (containing various ratios of bile acid to lecithin) can also be studied for a fuller understanding of the impact of these ingredients on solubility behaviour. Please contact Pion for more details on SIF recipes.

Sample Submission Details

200 mg dry compound required for Gold Standard solubility analysis based on a sample with a formula weight approximately 400 g/mol.



Small-scale Powder Dissolution and Solubility Assay

Introduction

The dissolution rate and apparent solubility of a pure active pharmaceutical ingredient (API) can be obtained from small quantities of powdered drug. In addition, the effective particle size of the powder suspended in the dissolution medium can be calculated. Knowledge of the dissolution rate and apparent solubility determined from these assays is important during the development of new drug molecules as it is possible to predict potential problems using only small quantities of material. It has applications in evaluating drug behaviour in accordance with the biopharmaceutics classification system (BCS), comparison of the dissolution rate during salt selection or polymorph screening to choose the best candidate, and setting specifications for particle size in order to achieve complete dissolution of the required dose within the typical gastrointestinal transfer time. Small scale dissolution testing can be applied to promising drug candidates to guide early development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the powder IDR (mass/time/area) for each sample for the chosen buffer system, apparent solubility, effective particle size are determined, and statement of methodology.

Experiment Overview

Powdered samples are added into 20 mL vials containing aqueous dissolution media in the heating block of the MicroDISS Profiler™ with magnetic stirring available in each dissolution vessel. The Rainbow™ detection instrument is used in real time, monitoring the concentration by employing up to eight photodiode array (PDA) spectrophotometers, each with its own dedicated fibre-optic dip-probe. Probes are positioned in the dissolution vessels and measurements commenced on the addition of samples. Concentration is determined using the *in situ* UV probes to capture UV spectra with predefined time intervals over the duration of the assay.

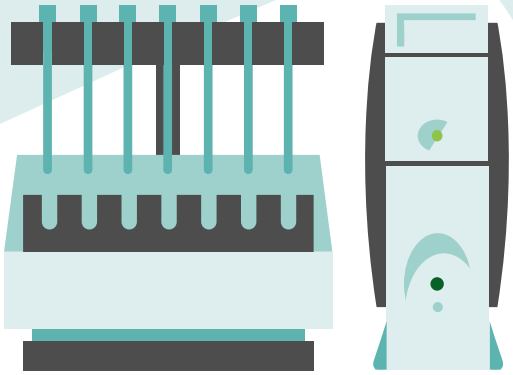
Some of the challenges of traditional testing methods which use external sampling of the test solutions are avoided by the use of the *in situ* fibre-optic UV dip-probe apparatus, since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time.

Typical dissolution media that can be chosen include aqueous 0.1 N HCl, diluted HCl (pH 1.2, pH 1.6 or pH 2), acetate buffer (pH 4.5), phosphate buffers (pH 6.5, 6.8 or pH 7.4) and TRIS buffer (pH 8). *See also pages 16-17*.

Sample Submission Details

100 mg dry compound required for Gold Standard MicroDISS™ assays and 50 mg dry compound required for MicroDISS™ screening assays based on a sample with a formula weight approximately 400 g/mol.

Pre-formulation



Small-scale Powder Dissolution and Solubility Assay in Biorelevant Media

Introduction

The impact of biorelevant media on the dissolution rate and apparent solubility of a pure active pharmaceutical ingredient (API) can be obtained from small quantities of powdered drug. In addition, the effective particle size of the powder suspended in a biorelevant medium can be calculated. Solubility studies in the presence of biorelevant media are used to understand the sensitivity of APIs to be influenced by components found in the gastrointestinal tract and is an especially important consideration for poorly soluble drugs. The composition of intestinal fluids (e.g. bile acids and phospholipids) can have a significant impact on enhancing solubility and dissolution rate. Higher drug concentrations for solubility limited drugs can lead to increased flux across biological membranes and increase overall drug absorption. Small-scale Powder Dissolution and Solubility in SIF studies can be used to understand the impact of biorelevant media on compound dissolution/solubility behaviour and guide early development efforts to assess a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the powder IDR (mass/time/area) for each sample for the chosen biorelevant buffer system, apparent solubility, effective particle size, and statement of methodology.

Experiment Overview

Powdered samples are added into 20 mL vials containing biorelevant dissolution media in the heating block of the MicroDISS Profiler™ with magnetic stirring available in each dissolution vessel. The Rainbow™ detection instrument is used in real time, monitoring the concentration by employing up to eight photodiode array (PDA) spectrophotometers, each with its own dedicated fibre-optic dip-probe. Probes are positioned in the dissolution vessels and measurements commenced on the addition of samples. Concentration is determined using the *in situ* UV probes to capture UV spectra with predefined time intervals over the duration of the assay.

Some of the challenges of traditional testing methods which use external sampling of the test solutions are avoided by the use of the *in situ* fibre-optic UV dip-probe apparatus, since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time.

Typical dissolution media that can be chosen include Fasted State Simulated Intestinal Fluid; FaSSIF-v1 (pH 6.5) and FaSSIF-v2 (pH 6.5), Dog FaSSIF (pH 7.5), Fed State Simulated Intestinal Fluid; FeSSIF-v1 (pH 5.0) and FeSSIF-v2 (pH 5.8), and fasted and fed state simulated colonic fluids; FaSSCoF (pH 7.8) and FeSSCoF (pH 6.0). Other compositions of bile acids, lecithin, oleate can also be studied. Please contact Pion for the full range of available media options. *See page 17*.

Sample Submission Details

100 mg dry compound required for Gold Standard MicroDISS™ assays and 50 mg dry compound required for MicroDISS™ screening assays based on a sample with a formula weight approximately 400 g/mol.

Small-scale Gastric to Intestinal Transfer Assay

Introduction

The dissolution rate and apparent solubility behaviour of a pure active pharmaceutical ingredient (API) can be obtained from small quantities of powdered drug using a protocol that simulates transition from a gastric pH environment to intestinal (FaSSIF) conditions. Knowledge on how the compound behaves in these assays is important during the development of new drug molecules as it is possible to predict potential problems using only small quantities of material. It has applications in biopharmaceutics risk assessment and understanding the solubility and precipitation risks inherent in transitioning from gastric conditions to those representing the intestinal environment. The gastric to intestinal transfer Assay can be applied to promising drug candidates to guide early development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the dissolution and/or precipitation behaviour for each sample for the chosen gastric to intestinal buffer system, and statement of methodology.

Sample Submission Details

100 mg dry compound required for Gold Standard MicroDISS™ assays and 50 mg dry compound required for MicroDISS™ screening assays based on a sample with a formula weight approximately 400 g/mol.

Experiment Overview

Powdered samples are added into 20 mL vials initially containing gastric dissolution media in the heating block of the MicroDISS Profiler™ with magnetic stirring available in each dissolution vessel. After a specified time, concentrated Simulated Intestinal Fluid is used to adjust the dissolution vessel conditions to represent intestinal medium (e.g. FaSSIF-v2 at pH 6.5). The Rainbow™ detection instrument is used to monitor the concentrations by employing up to eight photodiode array (PDA) spectrophotometers, each with its own dedicated fibre-optic dip-probe. Probes are positioned in the dissolution vessels and measurements commenced on the addition of samples. Concentration is determined using the *in situ* UV probes to capture UV spectra with predefined time intervals over the duration of the assay. Experiments typically run for 1 hour in gastric conditions followed by a further 6 hours at intestinal pH. Dissolution and precipitation risk will be assessed from both pH conditions.

Some of the challenges of traditional testing methods which use external sampling of the test solutions are avoided by the use of the *in situ* fibre-optic UV dip-probe apparatus, since concentration measurements are performed directly in the dissolution media, with processed results plotted in real time.

Typical dissolution media that can be chosen for the gastric conditions includes aqueous 0.1 N HCl or diluted HCl (pH 1.2, pH 1.6 or pH 2), whilst pH 6.5 FaSSIF (fasted state simulated intestinal fluid) v1 or v2, or pH 5.0 FeSSIF can be used for the intestinal conditions. The impact of excipients can also be studied. Please contact Pion for the full range of available media and excipient options.

Pre-formulation

Parallel Artificial Membrane Permeability Assay (PAMPA) Oral Pre-formulation

Introduction

The Parallel Artificial Membrane Permeability Assay (PAMPA) is used to determine passive diffusion across an artificial lipid membrane impregnated onto a porous filter support. Passive diffusion is an important factor in determining absorption of orally administered compounds in the gastrointestinal tract (GIT). PAMPA can also be used to assess the impact of solubility enhancing ingredients on the overall flux behaviour of poorly soluble drugs. PAMPA-GIT-Excipient screening can be applied to promising drug candidates to rank order excipient effect and guide early development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the apparent permeability coefficient for each candidate compound (P_{app}) in the presence and absence of various excipients at different concentration levels, permeability map showing the impact of the chosen excipients and highlighting the best options for further investigation during development, and statement of methodology.

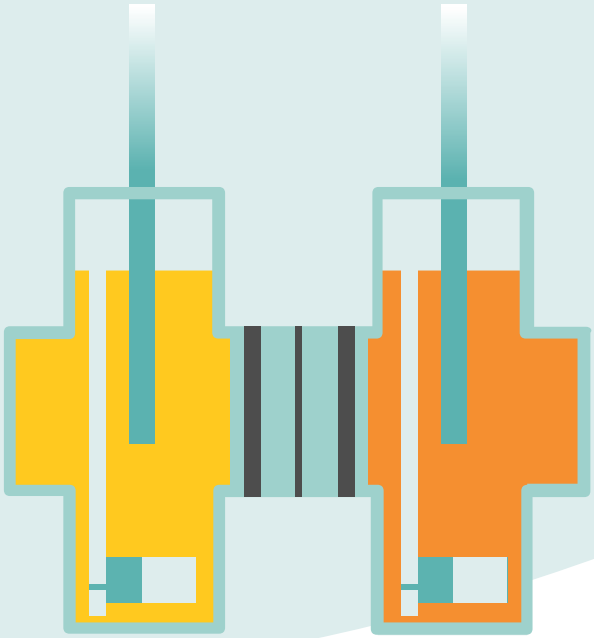
Sample Submission Details

1000 µL 10mM stock solution required for GIT excipient screenings.

Experiment Overview

PAMPA uses two 96-well plates that are assembled into a "PAMPA sandwich". The top plate (acceptor plate) contains a porous filter at the bottom of each well which is placed on top of a second plate (donor plate). The filter is coated with a solution of lipid material to prepare the artificial membrane layer. The test compound solutions and various excipients are added to pH-adjusted buffer in the wells of the donor plate and acceptor buffer solution is added to each well of the acceptor plate. The acceptor plate is placed on top of the donor plate allowing the donor excipient solution to come into contact with the filter support. The plates are then incubated at room temperature, in a humid environment, for up to 4 hours depending on the assay conditions. Each donor well can be individually stirred using magnetic stir discs. Standard solutions are prepared for each test compound in order to calculate the permeability. The donor and acceptor samples for the test are quantified by UV plate reader. The experimental analyte recovery is calculated using both donor and acceptor compartment concentrations and can also be used to determine membrane retention percentage.

Excipients that can be studied include (but are not restricted to) cyclodextrins, PEG solvents, cellulose polymers, polyvinylpyrrolidone polymers, bile acids, etc. Please contact Pion for a full list of excipients options.



MicroFLUX™ Assay

Introduction

The MicroFLUX™ apparatus works to assess the *in vitro* absorption potential (transmembrane flux) of prototype formulations using small-scale experiments. It is frequently used during the early stages of development for optimising prototype formulations and to determine which excipients will improve the expected bio-performance of poorly soluble candidate API molecules. The impact of excipients on drug behaviour when conducting these simultaneous dissolution-absorption studies provides an understanding of the complex interplay between solubility, permeability and dissolution rate *in vitro* and establishes the MicroFLUX™ as a valuable tool for ranking *in vivo* outcomes.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, acceptor drug concentrations and flux values across the membrane, the percent release (%mass/time) of drug for each donor vessel showing release profiles and dissolution performance, and statement of methodology.

Sample Submission Details

200 mg dry compound required based on a sample with a formula weight approximately 400 g/mol.

Experiment Overview

The MicroFLUX™ device consists of a low-volume absorption (receiver) chamber separated from a low-volume donor chamber with a biomimetic gastrointestinal tract permeation membrane. The receiver chamber contains pH 7.4 Acceptor Sink Buffer and the donor dissolution compartment holds an aqueous or biorelevant dissolution buffer. The MicroFLUX™ chambers are used with the MicroDISS™ platform to provide temperature control and magnetic stirring. Fibre-optic UV probes are positioned in both the donor and receiver compartments allowing real time dissolution and absorption concentration monitoring in both chambers. Concentration monitoring is enabled by connecting the fibre-optic UV probes to the Rainbow™ detector.

The use of *in situ* fibre-optic dip-probe UV analysis overcomes many of the challenges of traditional testing methods which use external sampling of the test solutions, since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time. *See also pages 25-26.*

Pre-formulation

Biphasic Dissolution Assay

Introduction

Biphasic dissolution experiments involve many steps, and can be difficult to perform using conventional dissolution apparatus. The inForm platform's biphasic dissolution assay was developed to mimic dissolution and absorption within the human gastrointestinal tract (GIT). The pH and composition of the aqueous phase can be adjusted to simulate GI conditions. The passage of drug into the lipid phase simulates the absorption into the gut wall. Biphasic dissolution assays are useful for investigating the dissolution, solubilisation, supersaturation, precipitation and absorption behaviour of poorly soluble drugs under various conditions.

Key Deliverable

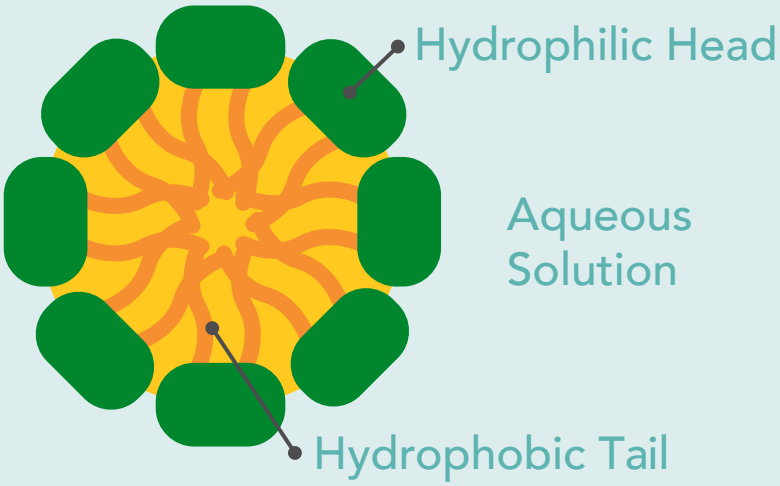
A full study report is provided. Reports include: sample and customer details, the partition rate (mass/time) for each sample in the biphasic dissolution system showing drug uptake and absorption rates into the lipid layer, other parameters such as aqueous concentration profiles are also reported where appropriate, and statement of methodology.

Experiment Overview

Experiments typically start with 40 mL of aqueous solution at gastric or intestinal pH. Probes and the sample are automatically lowered into the solution, the stirrer is activated and turned continuously at a constant rate, and measurement is commenced. A lipid layer (40 mL decanol) is introduced above the aqueous layer to represent the absorptive component of biological membranes. The concentration of drug is monitored by multi-wavelength UV-absorption spectroscopy using two in-situ fibre-optic UV probes. After the experiment, UV absorbance data is converted to sample concentration using previously determined pH-dependent molar extinction coefficients (MEC).

Sample Submission Details

200 mg dry compound required based on a sample with a formula weight approximately 400 g/mol.



Surface Tension Assays

Introduction

Many pharmacologically active compounds are amphiphilic (or hydrophobic) in nature and can therefore be surface active. This can have an impact on wettability, dissolution and solubilisation of drugs, selection of formulation delivery vehicles, and interactions with biological membranes.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, plate concentrations and details of serial dilutions, tables and graphs of surface tension values and CMC results, and statement of methodology.

Sample Submission Details

For CMC analysis, the amount of sample required will be determined upon enquiry.

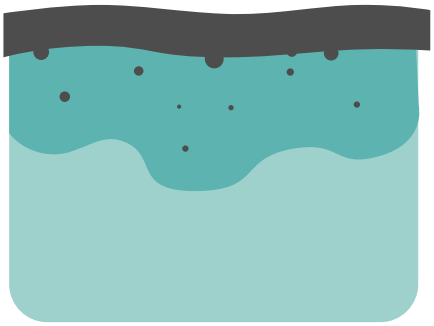
Experiment Overview

Surface tension is measured with a tensiometer with an 8-channel microbalance capable of measuring up to 8 samples simultaneously. Samples are prepared in standard footprint 96-well plates.

The technique measures the weight of the meniscus using a high performance micro balance. A thin rod is immersed into the sample and then pulled out and the maximum force is measured (also known as the *Du-Nouy-Padday method, J. Chem. Soc., Faraday Trans. 1, 1975, 71, 1919 - 1931, DOI: 10.1039/F19757101919)*. The weight of the meniscus depends only on surface tension, rod diameter, and the density of the liquid.

Surface active molecules absorb at the air/water interface, decreasing surface tension. As the interface becomes saturated, the molecules start to form aggregates or micelles in the bulk of the liquid with the surface tension then remaining constant. The critical micelle concentration (CMC) results in a sharp transition above which, the concentration of the free surfactant/amphiphile molecules at the surface interface remains constant. No further reduction in surface tension with increasing concentration occurs resulting in a plateau in the surface tension *versus* concentration curve.

Formulation



Surface Dissolution Imaging Assay (Whole Dose Flow Cell)

Introduction

Surface Dissolution Imaging (SDi2) is used to visualise and determine dissolution related phenomena in a USP IV-type flow-cell. The technique can be used to measure release rates of drug from various types of dosage form (e.g. tablets, capsules, immediate release, extended release, etc.) as well as recording information on physical changes such as tablet swelling, erosion, drug diffusion within the surface layers, and disintegration, in addition to drug dissolution. Surface Dissolution Imaging can be applied to formulation efforts, both to look at swelling and erosion in controlled release polymer systems, or in characterising the behaviour of coatings.

Key Deliverable

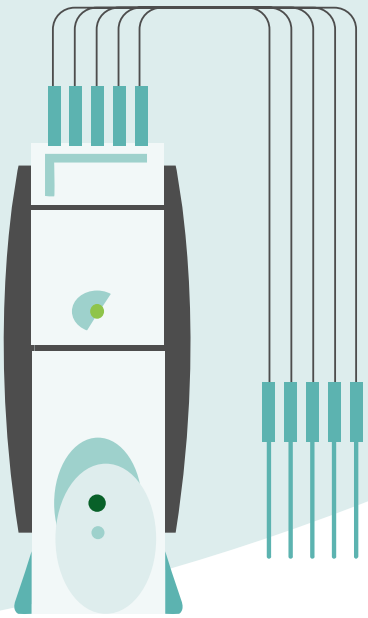
A full study report is provided. Reports include: sample and customer details, the release rate (mass/time) for each sample for the chosen buffer system, other parameters relating to physical changes (e.g. tablet dimensions of swelling polymer systems) are optional to be reported, high resolution dissolution videos at the selected wavelengths, and statement of methodology.

Sample Submission Details

For whole dose flow cell analysis, the amount of sample required will be determined upon enquiry.

Experiment Overview

The technique records the release of material directly from the surface of a dosage form (e.g. tablet) and from near downstream to calculate release rates. The instrument comprises a USP IV-type sample flow cell, sample holder, pump system, light source and detector. Light at two pre-selected single wavelengths (selected between 255 – 520 nm) and is used to illuminate the flow cell. A pump is used to flow buffer at a pre-set controlled temperature through the flow cell. The transmitted light in the presence of flowing medium is captured by the detector during the sample run. The light intensity at each pixel is converted into an absolute absorbance, and the images collected for the duration of the experiment are used to create a high resolution 2D movie of UV/visible absorbance data. This provides a detailed view of the dissolution process at the solid–liquid interface and downstream of the sample. Applying proprietary software tools then allows extraction of drug release rates as well as recording information on physical changes. *See also page 09.*



Compendial USP II Dissolution Assay

Introduction

A dissolution experiment evaluates the rate and extent that a compound forms a solution under carefully controlled conditions. Dissolution studies are used during formulation and product development to (i) evaluate whether certain formulation changes affect drug dissolution, and consequently, bio-performance of a certain drug product, (ii) to compare test to reference formulations, (iii) to ensure continuity of product quality (batch to batch consistency) and performance of the manufacturing process, and (iv) as a requirement for regulatory approval for product marketing.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the percent release (%mass/time) of drug for each vessel showing release profiles and dissolution performance, and statement of methodology.

Sample Submission Details

For compendial USP II dissolution analysis, the amount of sample required will be determined upon enquiry.

Experiment Overview

The Erweka dissolution tester is used in combination with the Rainbow™ detection system to conduct USP II dissolution studies.

The Erweka USP II dissolution tester uses the Paddle method with 6 test stations with 1000 mL vessels. Dissolution tests are conducted at 37 ± 0.5°C and with paddle rotational speed of 50 – 75 rpm. Dissolution profiles can be generated in various compendial dissolution media for example; pH 1.2, 4.5 and 6.8 buffers.

The Rainbow™ detector is used in the real time concentration monitoring of the drug product by employing six photodiode array (PDA) spectrophotometers, each with its own dedicated fibre-optic dip-probe. Probes are positioned in the dissolution vessels and used to record real time UV spectra.

Some of the challenges of traditional testing methods which use external sampling of the test solutions (e.g. sampling errors due to filter clogging, mechanical sipper malfunction, sample contamination, adsorption of compound to tubing) are avoided by the use of the *in situ* fibre-optic dip-probe UV apparatus, since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time. *See also page 24.*

Formulation

Compendial Two-Stage USP II Dissolution Assay

Introduction

The dissolution rate and solubility behaviour of a formulated drug product is studied in a USP II dissolution chamber using a protocol that simulates transition from a gastric pH environment to intestinal conditions. Knowledge on how the drug product behaves in these assays is important during the formulation stages of pharmaceutical development as it is possible to predict potential *in vivo* biopharmaceutical performance problems. The USP II gastric to intestinal transfer Assay can be used to understand the solubility and precipitation risks inherent in transitioning from gastric conditions to those representing the intestinal environment. This can guide product development efforts to improve a drug's *in vivo* characteristics.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, the percent release (%mass/time) of drug for each vessel showing release profiles and dissolution performance for the gastric to intestinal transfer experiment, and statement of methodology.

Experiment Overview

The Erweka dissolution tester is used in combination with the Rainbow™ detector system to conduct USP II gastric to intestinal transfer dissolution studies.

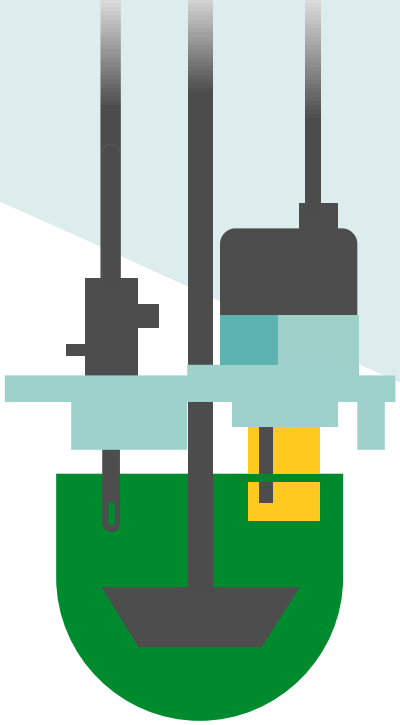
The Erweka USP II dissolution tester uses the Paddle method with 6 test stations with 1000 mL vessels. Dissolution tests are conducted at 37 ± 0.5°C and with paddle rotational speed of 50 – 75 rpm. Dissolution profiles are generated in compendial gastric dissolution media (SGF, pH 1.2) followed by transition to pH 6.5 FaSSIF (v1 or v2) medium.

The Rainbow™ detector is used in the real time concentration monitoring of the drug product by employing six photodiode array (PDA) spectrophotometers, each with its own dedicated fibre-optic dip-probe. Probes are positioned in the dissolution vessels and used to record real time UV spectra.

Some of the challenges of traditional testing methods which use external sampling of the test solutions are avoided by the use of the *in situ* fibre-optic dip-probe UV apparatus, since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time.

Sample Submission Details

For compendial two-stage USP II dissolution analysis, the amount of sample required will be determined upon enquiry.



BioFLUX™ Assay

Introduction

The BioFLUX™ apparatus can be used for conducting simultaneous dissolution-absorption studies. Such studies allow assessment of the complex interplay between solubility, permeability and dissolution rate *in vitro* and provide valuable tools for understanding *in vivo* outcomes.

BioFLUX™ accurately assesses the *in vitro* absorption potential (transmembrane flux) of finished dosage forms using biorelevant dissolution volumes of 200 – 250 mL. It is often used during formulation development for optimising product performance and to evaluate whether certain formulation changes will affect the bio-performance of a certain drug product. A more accurate *in vitro* representation of the oral absorption process could be performed whereby an initially gastric medium is converted to a biorelevant intestinal buffer such as FaSSIF.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, acceptor drug concentrations and flux values across the membrane, percent release (%mass/ time) of drug for each donor vessel showing release profiles and dissolution performance, and statement of methodology.

Sample Submission Details

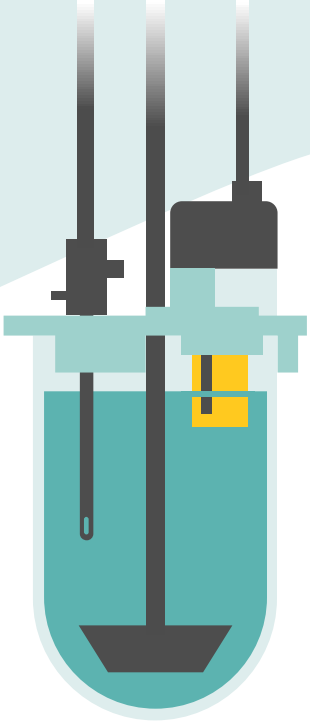
For BioFLUX analysis, the amount of sample required will be determined upon enquiry.

Experiment Overview

The BioFLUX™ device consists of an absorption (receiver) chamber integrated with a permeation membrane, overhead stirrer and fibre-optic UV probe that is inserted into a modified cover of a 500 mL dissolution vessel. The filter-supported artificial permeation membrane separates the dissolution (donor) compartment from the receiver compartment, containing pH 7.4 Acceptor Sink Buffer. The dissolution compartment typically holds 200 – 250 mL of compendial or biorelevant dissolution buffer. The modified vessel cover allows fibre-optic UV probes to be positioned in both the donor and receiver compartments allowing real time dissolution and absorption concentration monitoring in both chambers. Concentration monitoring is enabled by connecting the fibre-optic UV probes to the Rainbow™ detector.

The use of *in situ* fibre-optic dip-probe UV analysis, overcomes many of the challenges of traditional testing methods. Issues typically encountered with external sampling of the test solutions (e.g. sampling errors due to filter clogging, mechanical sipper malfunction, sample contamination, adsorption of compound to tubing), are minimized since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time. *See also page 26.*

Formulation



MacroFLUX™ Assay

Introduction

The MacroFLUX™ apparatus can be used for conducting simultaneous dissolution-absorption studies. Such studies allow assessment of the complex interplay between solubility, permeability and dissolution rate *in vitro* and provide valuable tools for understanding *in vivo* outcomes.

MacroFLUX™ can be used (i) during formulation development for optimising product performance and to evaluate whether certain formulation changes will affect the bio-performance of a certain drug product, (ii) during life-cycle management and product extensions to demonstrate bioequivalence, (iii) to compare brand and generic formulations to demonstrate bioequivalence, (iv) to compare test to reference formulations, (v) to ensure continuity of product quality (batch to batch consistency) and performance of the manufacturing process (in order to differentiate bioequivalent batches from non-bioequivalent batches within a range that guarantees comparable biopharmaceutical performance *in vivo*).

Key Deliverable

A full study report is provided. Reports include: sample and customer details, acceptor drug concentrations and flux values across the membrane, percent release (%mass/ time) of drug for each donor vessel showing release profiles and dissolution performance, and statement of methodology.

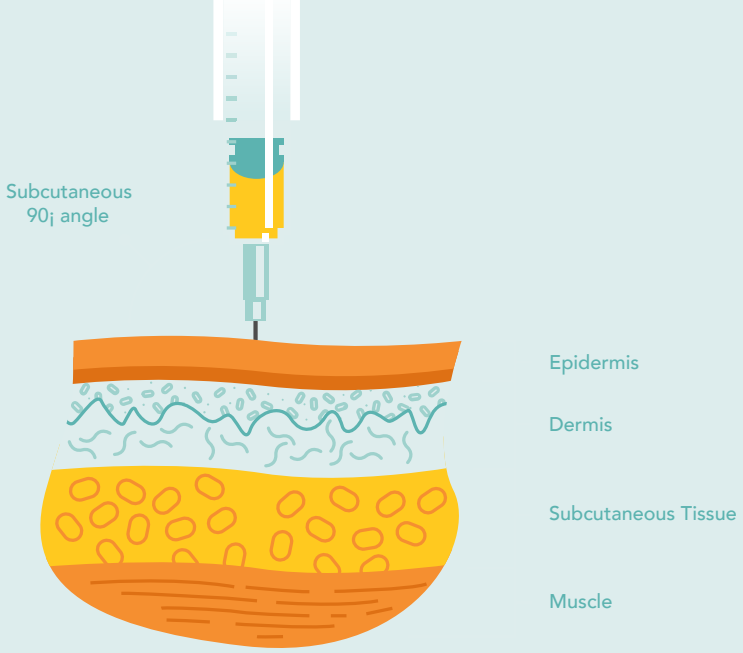
Experiment Overview

The MacroFLUX™ device consists of an absorption (receiver) chamber integrated with a permeation membrane, overhead stirrer and fibre-optic UV probe that is inserted in to a modified cover of a standard 900 mL USP II dissolution vessel. The filter supported artificial permeation membrane separates the dissolution (donor) compartment from the receiver compartment, containing pH 7.4 Acceptor Sink Buffer. The dissolution compartment typically holds 900 mL of compendial or biorelevant dissolution buffer. The modified vessel cover allows fibre-optic UV probes to be positioned in both the donor and receiver compartments allowing real time dissolution and absorption concentration monitoring in both chambers. Concentration monitoring is enabled by connecting the fibre-optic UV probes to the Rainbow™ detector.

The use of *in situ* fibre-optic dip-probe UV analysis, overcomes many of the challenges of traditional testing methods. Issues typically encountered with external sampling of test solutions (e.g. sampling errors due to filter clogging, mechanical sipper malfunction, sample contamination, adsorption of compound to tubing) are minimized since the concentration measurements are performed directly in the dissolution media, with processed results plotted in real time. *See also pages 19 and 25.*

Sample Submission Details

For MacroFLUX analysis, the amount of sample required will be determined upon enquiry.



Subcutaneous Injection Site Simulator (Scissor) Assay

Introduction

Scissor (Subcutaneous Injection Site Simulator) is an instrument developed by Pion that mimics the physiological properties of the subcutaneous tissue. It supports analytical techniques for monitoring post-injection stability and diffusional properties of subcutaneously administered biopharmaceuticals.

Scientists can evaluate early formulation performance of subcutaneously administered biopharmaceuticals, reducing the need for animal testing. The instrument has shown good applicability for the development of monoclonal antibody and insulin formulations.

Key Deliverable

A full study report is provided. Reports include: sample and customer details, release rate (mass/time) for each sample is determined, representing the sample uptake to the blood and lymphatic vessels, parameters recorded relating to pH and light transmission, monitor the physical stability of the drug upon injection as well as throughout the assay duration, and statement of methodology.

Experiment Overview

To simulate the injection site, a cartridge - which houses two customised dialysis membranes - is filled with materials that mimic the extracellular matrix (ECM) composition of the subcutaneous tissue. This is suspended within a chamber containing a bicarbonate based buffer bath which acts as a sink, representing the systemic circulation.

A subcutaneous formulation is injected into the simulated injection site and the optical density at the injection site is monitored to detect possible instabilities such as precipitation/aggregation upon injection. A pH probe is also placed in the simulated injection site to gain information on how the pH of the ECM is affected by the injection of formulation, and how long it takes the injection site to return to homeostasis following injection. This data can be used to infer whether the instabilities are related to a particular pH.

Aliquots are taken from the biorelevant bicarbonate based buffer to determine time-concentration profiles of biopharmaceutical and formulation components that have diffused out of the simulated injection site, through the dialysis membranes, into systemic circulation over time.

Sample Submission Details

For Scissor analysis, the amount of sample required will be determined upon enquiry.

Analytical Services Part Numbers

Gold Standard & Platinum			
Analysis	Part #	Comments	Amount
pK_a Analysis			
Gold Standard pK_a (with a chemical structure provided)	1801010	Price per sample	10mg
Gold Standard pK_a (without a chemical structure provided)	1811010	Price per sample	10mg
Platinum Standard pK_a	1801210	Price per sample	10mg – 15mg
Upgrade from Gold Standard to Platinum	1811011	Price per sample	Determined upon enquiry
MEC (molar extinction coefficient) with a Chemical structure provided	1801110	Price per sample	10mg
LogP/D Analysis			
Gold Standard pH-metric LogP (with a chemical structure)	1801012	Price per sample	5mg
Gold Standard pH-metric LogP (without a chemical structure)	1811012	Price per sample	5mg
Shake-Flask			
Gold Standard Shake-Flask (HPLC) logP/D	1801013	Price per sample per pH	20-50mg
Solubility Analysis			
Platinum Standard pH-metric solubility CheqSol (aqueous)	1802001	Price per sample	20-50mg
Platinum Standard pH-metric solubility CheqSol (co-solvent)	1802002	Price per sample	20-50mg
Platinum Standard pH-metric solubility CheqSol (biorelevant)	1802410	Price per sample	20-50mg
Platinum Standard pH-metric solubility CheqSol (in presence of excipients)	1802430	Price per sample	20-50mg
Shake-Flask			
Gold Standard shake-flask solubility (aqueous)	1802401	Price per sample per pH	20-50mg
Gold Standard shake-flask solubility (co-solvent)	1802403	Price per sample per pH	20-50mg
Gold Standard shake-flask solubility (biorelevant media)	1802402	Price per sample per pH	20-50mg
Gold Standard shake-flask solubility (in presence of excipients)	1802405	Price per sample per pH	20-50mg

**Terms and conditions apply. Note: Failure of the correct assay submission may prevent the ability of our scientists to obtain reliable data. In such cases the samples must be resubmitted for the correct assay with associated additional costs.*

Screening Analysis

Analysis	Part #	Comments	Amount
pK_a - High throughput pK_a measurement using the Fast UV pK_a assay (pH2.0 to pH12.0)			
10 samples			
Multi sample pK_a screening	1801201	Batch of 10 samples	200µL / 10mM stock
Additional multi sample pK_a screening	1801202	Per additional sample	200µL / 10mM stock
5 samples			
Multi sample pK_a screening	1801203	Batch of 5 samples	200µL / 10mM stock
Additional multi sample pK_a screening	1801204	Per additional sample	200µL / 10mM stock
LogD - High throughput logD measurements using shake-flask HPLC methodology, based octanol/water partitioning assay at fixed pH. For ionisable & non-ionisable compounds. Performed at pH7.4 or pH2.5.			
10 samples			
Multi sample LogD screening	1801301	Batch of 10 samples	200µL / 10mM stock
Additional multi sample LogD screening	1801302	Per additional sample	200µL / 10mM stock
5 samples			
Multi sample LogD screening	1801303	Batch of 5 samples	200µL / 10mM stock
Additional multi sample LogD screening	1801304	Per additional sample	200µL / 10mM stock
Solubility - High throughput solubility measurements using 96-well UV-plate reader methodology at fixed pH. For ionisable and non-ionisable compounds. Performed at requested pH values			
10 samples			
Multi sample solubility screening (DMSO stock)	1822101	Batch of 10 samples	250µL / 10mM stock
Multi sample solubility screening (DMSO free)	1822102	Batch of 10 samples	3mg per sample
Surface Tension & Critical Micelle Concentration (CMC) Determination of surface activity. Performed at pH7.4 or pH2.5			
Multi sample surface tension and CMC screening plate	1807001	Per plate (6 samples)	Determined upon enquiry
Additional plate surface tension and CMC screening	1807000	Price per sample	Determined upon enquiry

Analytical Services Part Numbers

SDi2

Analysis	Part #	Comments	Amount
SDi2 Compact Flow-cell Analysis			
Gold Standard SDi2 Aqueous	1811101	Price per sample, in duplicate	100mg
Gold Standard SDi2 Biorelevant	1811102	Price per sample, in duplicate	100mg
Gold Standard SDi2 Excipients	1811104	Price per sample, in duplicate	100mg
Platinum Standard SDi2 Aqueous	1811111	Price per sample, in duplicate	100mg
Platinum Standard SDi2 Biorelevant	1811112	Price per sample, in duplicate	100mg
Platinum Standard SDi2 Excipients	1811114	Price per sample, in duplicate	100mg
SDi2 Whole-dose Flow-cell Analysis			
Gold Standard SDi2 Aqueous	1811201	Price per sample, in duplicate	Determined upon enquiry
Gold Standard SDi2 Biorelevant	1811202	Price per sample, in duplicate	Determined upon enquiry
Gold Standard SDi2 Excipients	1811204	Price per sample, in duplicate	Determined upon enquiry
SDi2 Comparison Study – Batches/Coatings/Capsules	1811205	Price per 3 samples, in duplicate	Determined upon enquiry
Platinum Standard SDi2 Aqueous	1811211	Price per sample, in duplicate	Determined upon enquiry
Platinum Standard SDi2 Biorelevant	1811212	Price per sample, in duplicate	Determined upon enquiry
Platinum Standard SDi2 Excipients	1811214	Price per sample, in duplicate	Determined upon enquiry

PAMPA

Analysis	Part #	Comments	Amount
Multi sample GIT PAMPA screening Aqueous	1820101	Batch of 10 samples	400µL / 10mM stock
Multi sample GIT PAMPA screening Excipients	1820104	Batch of 10 samples	1000 µL / 10mM stock
Multi sample BBB PAMPA screening Aqueous	1820102	Batch of 10 samples	400µL / 10mM stock

Scissor

Analysis	Part #	Comments	Amount
Scissor Analysis			
Gold Standard Scissor	1810101	Price per sample	Determined upon enquiry
Platinum Standard Scissor	1810111	Price per sample	
Extended Assay Runtime	1801811	Price per sample	
with HPLC Analysis	1801802	Price per sample	

IDR

Analysis	Part #	Comments	Amount
MicroDiss™ IDR Analysis			
Gold Standard IDR Aqueous	1816101	Price per 3 samples, in duplicate	200mg
Gold Standard IDR Biorelevant	1816102	Price per 3 samples, in duplicate	200mg
Gold Standard IDR Excipients	1816104	Price per 3 samples, in duplicate	200mg
Additional IDR GS Sample	1801813	Price per sample, in duplicate	200mg
Extended Assay Runtime	1801803	Price per sample	
with ZIM Analysis	1801806	Price per sample	

inForm

Analysis	Part #	Comments	Amount
inForm Dissolution Analysis			
Platinum Standard inForm Dissolution Aqueous	1813111	Price per sample, in duplicate	200mg
Platinum Standard inForm Dissolution Biorelevant	1813112	Price per sample, in duplicate	200mg
Platinum Standard inForm Dissolution GI-transfer	1813113	Price per sample, in duplicate	200mg
Platinum Standard inForm Dissolution Excipients	1813114	Price per sample, in duplicate	200mg
Additional Platinum Sample	1801805	Price per sample, in duplicate	200mg
Extended Assay Runtime	1801803	Price per sample	
with HPLC Analysis	1801802	Price per sample	
inForm Biphasic Dissolution Analysis			
Platinum Standard inForm Biphasic Dissolution Aqueous	1813121	Price per sample, in duplicate	200mg
Platinum Standard inForm Biphasic Dissolution Biorelevant	1813122	Price per sample, in duplicate	200mg
Platinum Standard inForm Biphasic Dissolution GI-transfer	1813123	Price per sample, in duplicate	200mg
Platinum Standard inForm Biphasic Dissolution Excipients	1813124	Price per sample, in duplicate	200mg
Additional Platinum Sample	1801805	Price per sample, in duplicate	200mg
Extended Assay Runtime	1801803	Price per sample	
with HPLC Analysis	1801802	Price per sample	
inForm Supersaturation/Precipitation Analysis			
Platinum Standard Supersaturation/Precipitation Aqueous	1812131	Price per sample, in duplicate	200mg
Platinum Standard Supersaturation/Precipitation Biorelevant	1812132	Price per sample, in duplicate	200mg
Platinum Standard Supersaturation/Precipitation Excipients	1812134	Price per sample, in duplicate	200mg
Additional Platinum Sample	1801805	Price per sample, in duplicate	200mg
Extended Assay Runtime	1801803	Price per sample	
with HPLC Analysis	1801802	Price per sample	

Compendial USP II Dissolution

Analysis	Part #	Comments	Amount
USP II Dissolution Aqueous	1818201	Price per sample, 6 replicates	Determined upon enquiry
USP II Dissolution Biorelevant	1818202	Price per sample, 6 replicates	Determined upon enquiry
USP II Dissolution GI-transfer	1818203	Price per sample, 5 replicates	Determined upon enquiry
Additional USP II Dissolution Sample	1801814	Price per sample	Determined upon enquiry
Extended Assay Runtime	1801803	Price per sample	Determined upon enquiry
with ZIM Analysis	1801806	Price per sample	Determined upon enquiry

**Terms and conditions apply. Note: Failure of the correct assay submission may prevent the ability of our scientists to obtain reliable data. In such cases the samples must be resubmitted for the correct assay with associated additional costs.*

Analytical Services Part Numbers

MicroDiss™			
Analysis	Part #	Comments	Amount
MicroDiss™ Dissolution Analysis			
Gold Standard MicroDiss™ Dissolution Aqueous	1815101	Price per 3 samples, in duplicate	100mg
Gold Standard MicroDiss™ Dissolution Biorelevant	1815102	Price per 3 samples, in duplicate	100mg
Gold Standard MicroDiss™ Dissolution GI-transfer	1815103	Price per 3 samples, in duplicate	100mg
Gold Standard MicroDiss™ Dissolution Excipients	1815104	Price per 3 samples, in duplicate	100mg
Additional MicroDiss™ GS sample	1801812	Price per sample, in duplicate	100mg
MicroDiss Dissolution Screening Analysis			
Screening MicroDiss™ Dissolution Aqueous	1815121	Price per eight samples	50mg
Screening MicroDiss™ Dissolution Biorelevant	1815122	Price per eight samples	50mg
Screening MicroDiss™ Dissolution Excipients	1815124	Price per eight samples	50mg

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MicroFLUX™

Analysis	Part #	Comments	Amount
MicroFLUX™ Analysis			
Gold Standard MicroFLUX™ Aqueous	1817101	Price per sample, in triplicate	200mg
Gold Standard MicroFLUX™ Biorelevant	1817102	Price per sample, in triplicate	200mg
Gold Standard MicroFLUX™ GI-transfer	1817103	Price per sample, in triplicate	200mg
Gold Standard MicroFLUX™ Excipients	1817104	Price per sample, in triplicate	200mg
Additional Gold Standard MicroFLUX™ Sample	1801810	Price per sample, in triplicate	200mg
Extended Assay Runtime	1801803	Price per sample	
with ZIM Analysis	1801806	Price per sample	

MacroFLUX™

Analysis	Part #	Comments	Amount
Platinum Standard MacroFLUX™ Aqueous	1818111	Price per sample, four replicates	Determined upon enquiry
Platinum Standard MacroFLUX™ Biorelevant	1818112	Price per sample, four replicates	Determined upon enquiry
Additional MacroFLUX™ Platinum Standard Sample	1801815	Price per sample	
Extended Assay Runtime	1801803	Price per sample	
with ZIM Analysis	1801806	Price per sample	

BioFLUX™

Analysis	Part #	Comments	Amount
BioFLUX™ Analysis			
Platinum Standard BioFLUX™ Aqueous	1819111	Price per sample, four replicates	Determined upon enquiry
Platinum Standard BioFLUX™ Biorelevant	1819112	Price per sample, four replicates	Determined upon enquiry
Platinum Standard BioFLUX™ GI-transfer	1819113	Price per sample, in triplicate	Determined upon enquiry
Additional BioFLUX™ Platinum Standard Sample	1801816	Price per sample	
Extended Assay Runtime	1801803	Price per sample	
with ZIM Analysis	1801806	Price per sample	

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Analytical Services Part Numbers

Additional Services	
Analysis	Part #
Rush Order	1801800
Controlled Drug	1801801
With HPLC Analysis	1801802
Extended Assay Runtime	1801803
Surcharge for reagents/solvents/excipients not listed	1801804
Additional inForm Platinum Sample	1801805
with ZIM Analysis	1801806
Raw data (per hour)	1801807
Editing Report (per hour)	1801808
Special handling (toxic samples)	1801809
Additional MicroFLUX™ GS sample	1801810
Extended Scissor Runtime	1801811
Additional MicroDISS™ GS sample	1801812
Additional IDR GS Sample	1801813
Additional USP II Dissolution Sample	1801814
Additional MacroFLUX™ Platinum Standard Sample	1801815
Additional BioFLUX™ Platinum Standard Sample	1801816

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