Delivering the Best Formulation to the Right Patient

George Kirk, 16th May 2012
Introduction
Introduction

• Dr George Kirk:

- Current role: Global Project Manager in Oncology;

- 15 years in AstraZeneca;

- 10 years in Pharmaceutical Development;

- 2 years as Pharmaceutical Development Project Manager;

- 2 years as a Lean Sigma Black Belt;

- PhD in Organometallic Synthetic Chemistry;

- Scottish (and proud!)
Introduction: Phases of Development

PreClinical  Clinical  Registration  Launch

PreClinical → Phase I in Volunteers or Patients

Clinical → Phase II in Patients

Registration → Phase III in large numbers of Patients

Launch → Post launch activities /maximise asset

Product Information
Introduction: Principles of Drug Development

**Efficacy**
- Will it work?
- How do I take it?
- What dose is required?
- Any dosage instructions?

**Safety**
- Will it make me feel worse?
- Are there any contraindications?
- Are there any warnings?

**Quality**
- Will it be the same next time?
- Does it need preparation?
- Any storage requirements?
Why is Formulation so Important?

- Personalised medicines are becoming more important, particularly in Oncology;
- Targeted therapies are becoming more commonplace and are of increased interest to Payers and Regulators;
- Understanding how a drug is delivered to a patient and how it gets to its target is critical;
- Choosing the right dose is still a challenge;
- Targeted formulations can increase the chances of success of hitting the right target
Routes of Administration
Routes of Administration

<table>
<thead>
<tr>
<th>Site of Administration</th>
<th>Region</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Tract</td>
<td>Stomach</td>
<td>solution, suspension, tablet, capsule</td>
</tr>
<tr>
<td></td>
<td>Intestine</td>
<td>suppository, enema</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td></td>
</tr>
<tr>
<td>Buccal Cavity</td>
<td>Mouth</td>
<td>lozenge, solution, powder, aerosol</td>
</tr>
<tr>
<td></td>
<td>Nose</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Most areas</td>
<td>solution, lotion, cream, ointment, transdermal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>devices.</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td>inhaler, aerosol</td>
</tr>
<tr>
<td>Vagina</td>
<td></td>
<td>pessary, cream</td>
</tr>
<tr>
<td>Eye and Ear</td>
<td></td>
<td>drops, cream, inserts</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Intravenous</td>
<td>solution, emulsion</td>
</tr>
<tr>
<td></td>
<td>Intramuscular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intraperitoneal</td>
<td>}</td>
</tr>
<tr>
<td></td>
<td>Intrathecal</td>
<td>} solution, suspension, } emulsion and biodegradable</td>
</tr>
<tr>
<td></td>
<td>Intraarticular</td>
<td>} emulsion and biodegradable</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous</td>
<td>} depots.</td>
</tr>
</tbody>
</table>
Example – Intra-Articular Delivery

Current intra-articular clinical practice

- Previously accurate delivery to the intra-articular space - 10-20% of injections are not correctly placed
- Improvements with ultrasonic guidance and outpatient techniques such as "back-flow" claim virtually 100% correct IA placement

(Jones et al., 1993, Bliddall 1999, Jackson, 2002, Luc et al., 2006)
Biopharmaceutical Risk
Biopharmaceutics versus drug in vivo performance

Efficacy and Safety
Concentration at target site

Bioavailability / Exposure
- Fraction absorbed
- Absorption rate
- First pass metabolism / distribution / elimination

Absorption (CMC)
- Dosage form / formulations
- Solubility / dissolution
- Permeability

Biopharmaceutics

Depends on….
First a slight aside – time for you to work!

• Let’s think about solubility and dissolution?

• What’s this building?
  • Taj Mahal is an integrated symmetric complex of structures that was completed around 1648
  • What’s it made of?
  • While the white domed marble and tile mausoleum is most familiar

• What is the solubility of marble (calcium carbonate)?
  • 47 mcg/mL (normalised 100 mcM) at normal atmospheric CO₂ partial pressure, pH 8.3.
  • At pH 5.3 >1 mg /mL
Why is Solubility so Important in Pharmaceutical Development?

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**Gastrointestinal Physiology**

![Diagram of Gastrointestinal Physiology](image)

*Fig. 1. Diagrammatic sketch of the gastrointestinal tract (and subdivisions of the small and large intestines) along with associated organs. (Modified from Ref. 2.)*
Formulations for PO administration

- Solution
- Suspension
- IR solid dosage forms

- Fine particles dispersed in GI fluids
- Drug in solution in GI fluids
- Blood

Precipitation → dissolution
Disintegration

Best if compound dependent inherent dissolution properties not the limiting factor
Physiological aspects on solubility - pH

*pH affects solubility of compounds with ionizing groups.*

<table>
<thead>
<tr>
<th>Site</th>
<th>Fasted pH</th>
<th>Fed pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>1.4 – 2.1</td>
<td>4.3 – 5.4</td>
</tr>
<tr>
<td>Small intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>duodenum</td>
<td>4.9 – 6.4</td>
<td>4.2 – 6.1</td>
</tr>
<tr>
<td>jejunum</td>
<td>4.4 – 6.6</td>
<td>5.2 – 6.2</td>
</tr>
<tr>
<td>ileum</td>
<td>6.5 – 7.4</td>
<td>6.8 – 7.5</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>caecum</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>colon (upper)</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>colon (lower)</td>
<td>7.5</td>
<td></td>
</tr>
</tbody>
</table>

So insufficient solubility may mean:

- Insufficient exposure in preclinical species to support safety margins;
- Insufficient exposure in FTiM to confirm good margin in controlled environment;
- Conventional technology not appropriate for commercial product
Effect of permeability

- No fix for permeability: affects exposure/bioavailability and linearity at high dose

Exposure = 20,000
Exposure = 1,250
So insufficient permeability may mean:

• Insufficient exposure;
• High cost of goods (due to low fraction absorbed);
• No formulation fix available;
• Controlled release not an option
By understanding biopharm can understand what formulation approach is appropriate for FTiM, preclinical and commercial

Improving Solubility
Improving Solubility - Salts

• High biopharmaceutical Risk:
  - Salt Selection applied to compounds with high biopharmaceutical risk from a dissolution rate limited exposure perspective;

• Salt selection methodology:
  - 2 pKa rule:
    • pKa of acid must be two units or greater below that of the pKa for the base
    • pKa of base must be two units or greater above that of the pKa for the acid

• Intrinsic solubility ($S_0$):
  - has a bearing on what salts can form in an aqueous system;
  - The lower the intrinsic solubility, the lower the pHmax, the stronger the acid required to form stable salts;

• Aim of salts:
  - To predict or show improved exposure from salt form dosed at a relevant clinical dose in in vitro and/or in vivo models
Predicted and Measured pH Solubility Profile of a Weakly Basic Drug

- **Intrinsic Solubility:**
  - Defined as the solubility of the unionised or neutral form;
  - Can be useful to measure accurately in order to give good predictions of pH solubility profile;
  - Is not independent of crystalline form;
  - For a weak base with ionisation constants $k_1$ and $k_2$ solubility ($S$) at a given pH is given by the following equation:

\[
\frac{S}{S_0} = 10^{\log k_1 + \log k_2 - 2 \cdot pH} + 10^{\log k_1 - pH} + 1
\]

- Measured data (48h)

$S_0 = 0.6 \text{ug/ml}$

pKa’s 6.66, 4.97
Salt Selection - Haloperidol Example

Fig. 2. pH-solubility profile for haloperidol free base (■) and its HCl salt (○).

\[
\frac{S}{S_0} = 10^{\log k_{1-pH}} + 1
\]

\[
pH_{\text{max}} = pK_a + \log \frac{S_0}{\sqrt{K_{sp}}}
\]

Fig. 3. pH-solubility profile for haloperidol mesylate (●).

L Shoufen et al, Pharm Res, Vol 22, No. 4, April 2005, 628-635
Formulation Development
Overview

• Increasing numbers of poorly soluble compounds in industry
• Growing need for enabling technologies
• Need to move rapidly to get into clinic at earliest opportunity
  - Know if drug has potential to be a product
• Challenge is to integrate development of these potentially complex technologies, without delaying the overall drug development program
Early Formulation - which studies and when?

Pre-Clinical R&D

Clinical R&D

Phase 1

Phase 2

Phase 3

PK, efficacy studies etc

Toxicological studies

Short-term

Long-term

30day safety review

NDA submitted

Adapted from FDA CDER Handbook – New Drug Development and Review
Surfactants

- May change ADME properties
- Tolerability may limit dose
- Low solubilising capacity
- Less susceptible to precipitation on dilution

Cyclodextrins

- May change absorption kinetics if binding constant high
- Less susceptible to precipitation on dilution
- GI motility
- Simple, easy to prepare
- Size and polarity of API molecule determines stability of complex

Co-solvents

- Tolerability may limit dose
- High risk of drug precipitation on dilution in GI tract
- Simple to prepare
- High solvent levels often required to solubilise drug

pH adjustment

- Tolerance rarely sufficient on own
Drug Delivery technologies

- Solid dispersions
- Lipid-based drug delivery systems (LB-DDS) – Lipidics
- Crystalline nanosuspensions/nanoparticles
- Amorphous nanosuspensions
Lipid-based drug delivery systems (LB-DDS)

- Liquid or semi-solid lipidic formulations
- Dosed as a liquid, pre-dispersed in aqueous media or as a capsule/tablet
- Lipid Formulation Classification System proposed by Colin Pouton

<table>
<thead>
<tr>
<th>Formulation type</th>
<th>Materials</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Oils without surfactants (e.g. tri-, di- and monoglycerides)</td>
<td>Non-dispersing, requires digestion</td>
</tr>
<tr>
<td>Type II</td>
<td>Oils and water-insoluble surfactants</td>
<td>SEDDS formed without water-soluble components</td>
</tr>
<tr>
<td>Type III a/b</td>
<td>Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)</td>
<td>SEDDS/SMEDDS formed with water-soluble components</td>
</tr>
<tr>
<td>Type IV</td>
<td>Water-soluble surfactants and cosolvents (no oils)</td>
<td>Formulation disperses typically to form a micellar solution</td>
</tr>
</tbody>
</table>

- SEDDS = Self emulsifying drug delivery systems, SMEDDS = Self microemulsifying drug delivery systems. Both disperse under gentle agitation in gut
Formulation Feasibility Case Study

Phase I formulation – (PEG/Cremophor/water RTU Solution)

Target – to develop an alternative formulation suitable for clinical study with similar or higher exposure to current Phase I formulation

Key issues: Tolerability of excipients; Palatability; Stability

Formulation technology approaches

Semi-Solids
- Gelucire based formulations

Liquid Lipidics
- Gattefosse based vehicles
- Other lipidic vehicles

Amorphous Solid Dispersions
- Modelling to confirm feasibility based on current data

Nanotechnology
- IOTA Technology and in-house on amorphous only

Alternative Salts
- Not considered to add any value at this time

In Vitro testing

In Vivo testing

Recommendation
Summary

- Multiple formulation options exist for early formulation development of poorly solubles
  - Clinically and preclinically

- Decision of which technology to apply based on many factors
  - Theoretical assessments combined with screening
  - Provide recommendation on way forward and associated risks/opportunities

- No one technology suitable for all API’s
Summary
Summary

“Novel observations in Research constitute Discoveries, novel observations in late Development constitute Disasters, Pharmaceutical Development includes those elements of research that may limit Development Disasters”
Back ups
Biopharmaceutics Classification System

- Defines drugs based on solubility (dose in <250mL pH 1 to 7.5) and permeability (fa >90%).
- Class 1: high solubility and high permeability.
- Class 2: low solubility and high permeability.
- Class 3: high solubility and low permeability.
- Class 4: low solubility and low permeability.

A regulatory guidance that allows us to avoid some clinical studies
Dissolution and Solubility

Modified Noyes-Whitney Equation:

\[
\frac{dX_d}{dt} = A \cdot \frac{D}{h} \cdot \left( C_s - \frac{X_d}{V} \right)
\]

<table>
<thead>
<tr>
<th>Factor</th>
<th>Physicochemical parameter</th>
<th>Physiological parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface area (A)</td>
<td>Particle size</td>
<td>Gastric surfactants</td>
</tr>
<tr>
<td>Diffusivity of drug (D)</td>
<td>Wettability</td>
<td>SI bile salts</td>
</tr>
<tr>
<td>Boundary layer thickness (h)</td>
<td>Molecular size,</td>
<td>Viscosity of luminal contents,</td>
</tr>
<tr>
<td>Solubility (Cs)</td>
<td>Hydrophilicity</td>
<td>'bile' micelle size</td>
</tr>
<tr>
<td>Amount of already dissolved drug (Xd)</td>
<td>Crystal structure</td>
<td>Motility pattern and flow rate</td>
</tr>
<tr>
<td>Volume of solvent available (V)</td>
<td></td>
<td>pH, buffer capacity, bile, food components</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Permeability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secretions,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Co-administered fluids</td>
</tr>
</tbody>
</table>
Permeability: Transport Pathways across intestinal epithelial cells

- **LUMEN**
  - **EFFLUX MECHANISM**
  - **CARRIER-MEDIATED TRANSPORT**
- **BLOOD**
  - **PARACELLULAR DIFFUSION**
  - **TRANSCELLULAR DIFFUSION**

Apical membrane (AP) (brush-border)
Basolateral (BL) membrane
Lipid-based drug delivery systems (LB-DDS)

Solid dosage form manufacturing methods include
• Liquid or semi-solid filled capsules
• Conversion to solid particles for filling into capsules, sachets, compression to tablets via
  - melt granulation, melt pelletisation or spray congealing of semi-solids
  - Adsorption onto inert matrices (liquid or semi-solid lipidics)
• Complex in vivo behaviour
• Bioavailability may be enhanced via *
  - Maintaining drug in solution/solubilising drug along GI tract
  - Alteration of composition of intestinal fluids
    • Activation of Lipid digestion
  - Inhibition of efflux/CYP enzymes
  - Protection from chemical/enzymatic degradation in GI tract
  - Alteration of gut permeability
  - Promotion of lymphatic uptake (compounds with logP>5, oil solubility >50mg.ml)

Lipid-based drug delivery systems (LB-DDS)

• API criteria
  - Log P>2, (log P >4 for oily vehicles)*
  - Log P >5 may be absorbed through lymphatic pathway
  - Increased drug bioavailability in fed state

• Key issues
  - Predicting in vivo performance from in vitro data
  - Regulatory and Safety status of lipidic excipients
    • High surfactant levels in type IIIa/b and IV lipidics
  - Characterisation of semi-solid lipidics
  - Batch to batch variability in excipients

Solid dispersions

• Dispersion of API in polymer matrix (Shanbhag et al *)
  - molecularly dispersed drug
  - multiparticulate dispersed drug
    • crystalline or amorphous drug as domains
• Commonly used polymers types include PVP, PEG & HPMC
• Bioavailability enhanced by
  - increasing dissolution rate
  - increasing solubility in GI tract (supersaturated)
  - prevention of subsequent drug precipitation
• Manufacturing methods include:
  - evaporation-based methods ie drug/polymer dissolved in organic solvent which is subsequently removed by spray drying, vacuum/heat driven methods
  - hot melt methods ie mixing of molten drug/polymer or drug dissolves in molten polymer eg melt extrusion, hot-melt encapsulation
• Solid dosage form or pre-disperse in aqueous media for early studies

Solid dispersions

• General API properties
  - Solvent solubility (spray drying)
  - High temperature stability (melt extrusion)

• Key issues
  - Physical and chemical instability of drug/formulation
  - Residual solvents
  - Hygroscopicity (excipients may be hygroscopic and water uptake may potentiate recrystallisation where drug is amorphous)
  - Analytically more challenging to characterise
Crystalline Nanosuspensions

- Crystalline drug nanoparticles stabilised with surfactants/polymers *
- Prepared by number of techniques eg wet milling, high pressure homogenisation, microfluidisation
- Bioavailability enhanced by increasing drug dissolution rate due to high surface area
- Potential for high drug:excipient ratio
  - less risk of excipient tolerability limiting dose
- Viscosity may limit concentration achievable and hence dose

Crystalline Nanosuspensions

- **API properties**
  - Dissolution-rate limited bioavailability
  - Free form and most stable form preferred
  - Low solubility reduces Ostwald ripening
  - More likely to succeed with low aqueous solubility and high melting point API’s than other technologies eg lipidics

- **Key issues**
  - Physical instability
    - Agglomeration – overcome by electrostatic repulsion or steric stabilisation
  - Potentially long processing times (milling)

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