
This version is available at https://strathprints.strath.ac.uk/61265/

Strathprints is designed to allow users to access the research output of the University of Strathclyde. Unless otherwise explicitly stated on the manuscript, Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Please check the manuscript for details of any other licences that may have been applied. You may not engage in further distribution of the material for any profitmaking activities or any commercial gain. You may freely distribute both the url (https://strathprints.strath.ac.uk/) and the content of this paper for research or private study, educational, or not-for-profit purposes without prior permission or charge.

Any correspondence concerning this service should be sent to the Strathprints administrator: strathprints@strath.ac.uk

The Strathprints institutional repository (https://strathprints.strath.ac.uk) is a digital archive of University of Strathclyde research outputs. It has been developed to disseminate open access research outputs, expose data about those outputs, and enable the management and persistent access to Strathclyde's intellectual output.
The Pharmaceutical Challenge of Cancer Research

Gavin Halbert
Cancer Research UK Formulation Unit
Strathclyde Institute of Pharmacy and Biomedical Sciences
University of Strathclyde
Formulation Unit

• Remit
To develop novel anti-cancer drugs selected by Cancer Research UK New Agents Committee for Phase I and II Clinical Trial
Pharmaceutical Translation Research

• Established in 1983
Bench to Bedside – Powder to Product – Molecule to Medicine
Formulation

• Multiple factors
• One goal
• Limited
  Knowledge
  Resource
  Time

Drug
Distribution
Product
Biopharmacy
Excipients
Manufacture
Regulatory
Quality
• Early Projects
• Research Advances
• Recent Projects
• Currents Trends
• Potential Answers
Early Example - 1984

- 1, 2, 4-triglycidyl urazol - Limited solubility & stability
- Reconstitution Fluid
  Switch from dextrose to NaCl

The analysis and animal pharmacokinetics of 1,2,4-triglycidyl urazol using a high-pressure liquid chromatographic technique

J. Welsh¹, J. F. B. Stuart², A. Setanoians¹, R. G. G. Blackie¹, P. Billiaert¹,², G. Halbert¹, and K. C. Calman¹

¹ Department of Clinical Oncology, University of Glasgow, 1 Horselethill Road, Glasgow G12 9LY, Scotland
² Department of Pharmaceutics, University of Strathclyde, Glasgow, Scotland
Early Projects

• Many and varied
  
  Exact number unknown

• Small molecules

---

Trimelamol

RH1

Limonene

SRI 62 834

---

Chemical Stability Lyophilised RH1

Mannitol

Dextran

Cyclodextrin

PVP
Clinical Trials

- 1, 2, 4-triglycidyl urazol
- Starting Dose
  30mg/m² escalated to 900mg/m
- Toxicity
  - Myelosuppression, nausea, vomiting, phlebitis

- RH1
- Eligibility criteria
  Proven cancer, refractory to treatment, no conventional therapy, >18 yrs, life expectancy >3 months

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>8</td>
</tr>
<tr>
<td>Gastric</td>
<td>3</td>
</tr>
<tr>
<td>NSCLC</td>
<td>2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2</td>
</tr>
<tr>
<td>Merkel cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
</tr>
</tbody>
</table>
Common Issues

• Pharmacology
  Cytotoxic chemotherapy
  Limited administration
• Majority of formulations injections
• Drug solubility
  Range of formulation techniques applied
• Drug stability
  Hydrolytic – lyophilisation
  Non-hydrolytic – physicochemistry
• General trials
Research Advances

• Imatinib – 2001
  “Dawn of targeted treatments”
Very Different Drugs

- **imatinib**
  - Solubility: 200mg/ml
  - Oral Bioavailability: 98%

- **nilotinib**
  - Solubility: sparingly
  - Oral Bioavailability: 31%

- **sorafenib**
  - Solubility (1:2 DMSO:PBS): 0.3mg/ml
  - Oral Bioavailability: 50%
Intestinal Solubility Variation

- Impact of simulated gastrointestinal fluid composition

Impact on Dissolution

- Low solubility
  Slower dissolution
- Natural GIT variation
- Not applicable
  Amorphous
  Bioenhanced
  But does it stay in solution?
Biopharmaceutics Classification System

- **I**: Good Solubility & Permeability
- **II**: Poor Solubility & Good Permeability
- **IIa**: Dissolution Rate Limited
- **IIb**: Solubility Limited
- **III**: Good Solubility & Poor Permeability
- **IV**: Poor Solubility & Poor Permeability

Dose/Solubility ratio: 250, 500, 1,000, 5,000, 10,000, 100,000

Predicted/Measured Peff Permeability (cm/s x 10^-4)
- 0.1
- 1.0
- 10
- 100
Impact on pharmacokinetics

• Phase 1 Dose escalation studies – BCS I to BCS II

CRUK07/13

Impacts receptor exposure
Bioenhanced Formulations

- Improve dissolution
  Amorphous
  Solid solutions
- Spring and parachute effect
- Stability
  Chemical & Physical
- Solid solution
  Drug/Excipient
  Intimate contact
- Excipient Quality
Common Issues

- Pharmacology
  - Targeted chemotherapy
    - Single pathway
  - Continuous administration
- Majority of formulations oral
- Drug solubility – impacts on drug absorption
- Bioenhanced formulations
  - Stability problems
- Targeted trials
Current Trends I

- Smaller patient numbers
- Therapy cost increases
- Combination therapies
- Agile therapy

Rapid changes
Current Trends II

Pharmaceutical Hockey Stick
Regulation
Targeted Therapies
Patient Population
Trial Duration
Regulation
Treatment Costs
Personalised Therapy
Low Cost Mass Customisation
Mass Customisation

• This is not new!
Future Pharmaceutical Challenge

Solutions – scaleable, quick, agile, low cost, GMP compliant, patient friendly
Does one formulation and manufacturing technology fit all?
Are there other aspects that can change?
Basic and applied research required

3D Printing
Just in time manufacture
Small scale development
Individual patient trials
3D Printing & Injection Moulding

- **Hot topic – a la mode**
  - Multiple groups UK and world-wide - multiple approaches
- **Marketed product**
  - New field
- **Multiple areas of research**
  - Equipment, process, parameters, formulation, product
- **Future**
  - Wide open

---

**Dose/Solubility ratio**

<table>
<thead>
<tr>
<th>Dose/ Solubility ratio</th>
<th>250</th>
<th>500</th>
<th>1,000</th>
<th>5,000</th>
<th>10,000</th>
<th>100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Solubility &amp; Good Permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Solubility &amp; Poor Permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor Solubility &amp; Good Permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor Solubility &amp; Poor Permeability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Predicted/Measured Peff Permeability (cm/s x 10^-4)**

- 0.1
- 1.0
- 10

- Good Solubility & Good Permeability
- Good Solubility & Poor Permeability
- Poor Solubility & Good Permeability
- Poor Solubility & Poor Permeability
Acknowledgements

• You for listening

• Collaborators
  Many and varied
    Local, national and international

• Cancer Research UK Funding
  EPSRC, EU FP7, MRC
Thank you

Gavin Halbert