A Novel QSAR Model of Pulmonary Absorption

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Presentation Overview

1. Physicochemical properties of inhaled marketed drugs

2. Physicochemical drivers of pulmonary absorption / retention

3. IPRLu model and data

4. A novel QSAR model of pulmonary absorption in the IPRLu

5. Summary
Physicochemical properties of inhaled drugs

• Unlike oral drugs there is relatively little information in the literature on the optimal physicochemical properties of inhaled drugs.

• Much of the information in the literature concerning the inhaled route of administration focuses on particulates, macromolecules or very water soluble molecules.

• Consequently, characterization and optimization of molecules for inhaled delivery rely largely on empirical testing in ex vivo and/or in vivo pre-clinical models.

• To aid design of small molecule inhaled drugs, a similar set of guidelines to those described for oral drugs would be advantageous.

Physicochemical Properties of Inhaled Drugs

• Analysis of the calculated physicochemical properties of respiratory drugs: Can we design for inhaled drugs yet?

• 81 Respiratory drugs, 29 of which are administered via inhaled or intranasal route.

• Inhaled respiratory drugs have a higher Hydrogen bonding capacity, polar surface area, molecular weight, and lower lipophilicity compared to oral respiratory drugs
  
  – H-bond donor & acceptor count 8.3 vs 6.0 (6.6 for all oral drugs)
  – PSA 89 vs 60.
  – MWt 373 vs 307 (333 for all oral drugs). GR Ag drives, i.e. not significant if removed.
  – cLogP 1.7 vs 2.5 (trend which becomes significant if GR Ag excluded)

• Inhaled drugs with different pharmacological action occupy distinct property space
Marketed Compounds Permeability vs Solubility
AMP pH7.4 vs CLND

Physicochemical drivers of lung absorption and retention
Pulmonary absorption inversely correlates with MWt.
Enna & Schanker. 1972 *American Journal of Physiology*. 222 (2) 409-414

**Table 2: Absorption of compounds from rat lung**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mol Wt</th>
<th>Diffusion coeff (D, nm² x 10⁻⁶)</th>
<th>Rate of Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea¹⁴C</td>
<td>60</td>
<td>17.8</td>
<td>4.0, 10.4</td>
</tr>
<tr>
<td>Erythritol-¹⁴C</td>
<td>122</td>
<td>10.6</td>
<td>33.0, 1.26</td>
</tr>
<tr>
<td>Mannitol-¹⁴C</td>
<td>182</td>
<td>9.16</td>
<td>65.0, 0.64</td>
</tr>
<tr>
<td>Sucrose-¹⁴C</td>
<td>342</td>
<td>6.60</td>
<td>87.0, 0.479</td>
</tr>
<tr>
<td>Inulin-COOH-¹⁴C</td>
<td>5,250</td>
<td>2.98</td>
<td>225, 0.300</td>
</tr>
<tr>
<td>Dextran-COOH-¹⁴C</td>
<td>75,000</td>
<td>1.33</td>
<td>1,070, 0.0289</td>
</tr>
</tbody>
</table>

*Fig. 2. Relative rates of absorption of ¹⁴C-labeled compounds from rat lung. Krebs-Ringer phosphate solution, 0.1 ml containing a compound (0.1 m) was administered intratracheally. For urea and mannitol, each point is mean value obtained in 6-10 animals; for erythritol, 4-7 animals; and for sucrose, 12-31 animals. Vertical brackets indicate st, and absence of brackets indicates that st was too small to be shown.*

- Pulmonary absorption rate of a range of saccharides and urea following intratracheal instillation in the rat inversely correlates with MWt.

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Pulmonary absorption correlates with permeability and lipophilicity
Tronde et al. 2003 *Journal of pharm Sci*. 92 (6) 1216-1233

**A**

- In vivo pulmonary absorption rate following nebulised delivery to the rat correlates with:
  - A) the apparent permeability of Caco-2 cells (Papp)
  - B) Lipophilicity (inversely proportional with %PSA)
Physchem Drivers of Pulmonary Absorption / Retention

Summary

• Larger compounds (MWt, CMR, Vx) are less permeable.

• Lipophilic compounds (↑ LogP, ↑ LogD, ↓ PSA, ↓ HBD, ↓ HBA) are more permeable which drives absorption

• But as lipophilicity increases:
  – Compounds are more likely to have affinity for and bind non-specifically to lung tissue
  – Compounds may partition into membranes, indicated by a large volume of distribution.
  – Compounds become less soluble and if administered as a suspension may not dissolve in the aqueous mucus layer, the first barrier within the lung.

• Pulmonary absorption increases with solubility

• Overall
  – Permeability and solubility drive pulmonary absorption
  – Size and protein binding reduce pulmonary absorption
  – Lipophilicity has a bell shaped relationship with pulmonary absorption.
  – Ionisation increases solubility but reduces permeability and therefore requires optimisation.

IPRLu model & data
**IPRLu Model overview**

- Male CD rats, lungs remaining in situ, single pass perfusion via pulmonary artery & vein
  - Krebs-Ringer buffer pH 7.4 containing 3% BSA at 37°C.
- Compounds (7-40μg) administered (n=2) by intratracheal instillation of 100μL aq vehicle.
  - Solution & suspensions ranging from <1% to 100% compound in solution.
- Parent compound analysed in perfusate samples (1min intervals) & lungs.
  - 108 compounds
    - 91 discovery compounds
    - 17 marketed drugs
- Cumulative parent compound in perfusate over 20mins
  - %TDiP
  - %SDiP
- Initial rate of absorption
  - Half-life

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All animal studies were ethically reviewed and carried out in accordance with the Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.

**Distribution of IPRLu model data**

- Endpoint distribution across 98 IPRLu compounds:
  - 7 zwitterions
  - 8 acids
  - 31 bases
  - 52 neutral

- Mean lung absorption half-life = 212 mins (range 3.3 – 5210)
  - Mean %TDiP = 32 (range 0.1 – 100)
  - Mean %SDiP = 164 (range 0.1 – 2400)
Physchem distribution across 98 IPRLu compounds
7 zwitterions, 8 acids, 31 bases, 52 neutral.

Mean cLogP = 3.2 (range -3.7 - 9.1)
Mean cLogDpH 7.4 = 2.1 (range -4.4 – 6.5)
Mean MWt = 507 (range 177 - 842)
Mean PSA = 105 (range 24 - 198)

IPRLu data on marketed drugs
Diversity reflected across marketed drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>%TDiP</th>
<th>%SDiP</th>
<th>% Dose in solution</th>
<th>Lung T1/2 (mins)</th>
<th>Recovery of total dose (%)</th>
<th>Calculated LogP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indacaterol</td>
<td>11</td>
<td>12</td>
<td>88</td>
<td>273 (255-291)</td>
<td>91 (77-104)</td>
<td>3.03</td>
</tr>
<tr>
<td>Ambroxol</td>
<td>38</td>
<td>41</td>
<td>95</td>
<td>39 (14-64)</td>
<td>70 (66-74)</td>
<td>2.65</td>
</tr>
<tr>
<td>Formoterol Fumarate</td>
<td>47</td>
<td>47</td>
<td>100</td>
<td>24 (22-26)</td>
<td>73 (70-76)</td>
<td>0.83</td>
</tr>
<tr>
<td>Ipratropium Bromide</td>
<td>49</td>
<td>50</td>
<td>100</td>
<td>23 (14-32)</td>
<td>-1.82</td>
<td></td>
</tr>
<tr>
<td>Teicoplanin Bromide</td>
<td>61</td>
<td>59</td>
<td>16 (15,16)</td>
<td></td>
<td></td>
<td>-1.76</td>
</tr>
<tr>
<td>Amiloride</td>
<td>62</td>
<td>62</td>
<td>100</td>
<td>8 (7-10)</td>
<td>81 (76-85)</td>
<td>-0.5</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>75</td>
<td>75</td>
<td>100</td>
<td>4 (4.5)</td>
<td></td>
<td>1.54</td>
</tr>
<tr>
<td>Zanaridene</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>7 (5-8)</td>
<td>104 (100-107)</td>
<td>-6.54</td>
</tr>
<tr>
<td>Fluorodexide</td>
<td>41</td>
<td>46</td>
<td>42</td>
<td>15 (7-22)</td>
<td>139 (135-149)</td>
<td>1.56</td>
</tr>
<tr>
<td>Montelukast</td>
<td>67</td>
<td>78</td>
<td>73</td>
<td>42 (23-60)</td>
<td>77 (70-85)</td>
<td>8.49</td>
</tr>
<tr>
<td>Fluocinone Propionate</td>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td>1.15 (98-131)</td>
<td></td>
<td>3.72</td>
</tr>
<tr>
<td>Fluocinone Furoate</td>
<td>10</td>
<td>10</td>
<td>3.2</td>
<td>1.53 (112-194)</td>
<td></td>
<td>4.13</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>32</td>
<td>83</td>
<td>24</td>
<td>32 (24-40)</td>
<td>85 (79-90)</td>
<td>2.5</td>
</tr>
<tr>
<td>Tacrolimus (prograf)</td>
<td>38</td>
<td>176</td>
<td>21</td>
<td>28 (27-28)</td>
<td></td>
<td>5.59</td>
</tr>
<tr>
<td>Budesonide</td>
<td>77</td>
<td>540</td>
<td>14</td>
<td>3.3 (3.4)</td>
<td>84 (82-87)</td>
<td>2.73</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>15</td>
<td>16-66</td>
<td>36</td>
<td>1.46 (59-213)</td>
<td>69 (61-76)</td>
<td>3.59</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>42</td>
<td>60-93</td>
<td>55</td>
<td>21 (13-28)</td>
<td>78 (75-81)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

>80% in solution: %TDiP=<%SDiP, mean cLogP 0.3. Permeability/binding limited %TDiP.

<80% in solution: %TDiP>%SDiP, mean cLogP 3.6. Solubility/dissolution limited %TDiP.

>100% SDiP indicates some dissolution of particulate drug during IPRLu experiment.
<100% SDiP indicates that permeability/binding may contribute to limiting %SDiP.
Effect of Solubility on IPRLu-profiles

- Three different versions of the same discovery compound administered to IPRLu as 15μg in saline.
  - Hydrochloride salt (HCl) 73% in solution
  - Free base (FB) 47% in solution
  - Hydroxynaphthoate (HNA) 18% in solution
- Solubility in keeping with dissolution profiles
- IPRLu profiles: % total dose in perfusate:
  - HCl > FB > HNA
- Differentiated based on solubility / dissolution rate:
  - HCl > FB > HNA
- Similar profiles when plot % solubilised dose in perfusate

A novel QSAR model of pulmonary absorption in the IPRLu
Multivariate OPLS model generated within SIMCA P+

- Built on %SDiP endpoint
  - predicts inherent ability of parent compound to cross the lungs and appear in the perfusate once it is in solution.
  - removes variability associated with solubility of different batches, salt forms and dose vehicles.

- Increasing size & increasing intensity of the spots equates with the size of the response (Log%SDiP)
  - OPLS: Greatest differentiation is along PC1

**IPRLu OPLS model coefficient plot**
Contribution of each of the 20 descriptors & 6 ADME model outputs of the x variable block.
Development of a QSAR model to predict pulmonary absorption

- Associated statistics $R^2 = 0.621$, $Q^2 = 0.491$ suitable for ranking and classification
- $<10\%$ SDiP = Low
- $10\%-100\%$ SDiP = moderate
- $>100\%$ SDiP = high

IPR Lu QSAR Model Validation

- Observed vs predicted %SDiP for the "Test set" compounds displays an $R^2$ of 0.85.
- "Test set" data successfully validated the QSAR model for prospective use.
Summary

• Many of the physical properties governing the lung disposition of small molecule inhaled drugs have not been clearly defined.

• Here we present a novel in silico model constructed using the largest, diverse & relevant pulmonary absorption data set available to date, combining both marketed inhaled drugs and novel inhaled compounds.

• We successfully validated the QSAR model for prospective use, the “Test set” data confirming its applicability in ranking compounds according to their lung disposition.

• As this model is built with in silico inputs it can be applied at the drug design stage to rank, classify and prioritise compounds prior to synthesis.

• It will also provide scientists working in the field of inhaled drug discovery with a deeper understanding of the physicochemical drivers of pulmonary absorption based on a relevant respiratory compound dataset.

• Presented data recently published:
  – DOI: 10.1007/s11095-016-1983-4

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• Edith Hessel – Refractory Respiratory Inflammation (RRI) DPU head, GSK.

• All animal studies were ethically reviewed and carried out in accordance with the Animals (Scientific Procedures) Act 1986 and the GSK Policy on the Care, Welfare and Treatment of Animals.
Thank you

Supporting Data
Pulmonary absorption: Lipophilicity & MWt relationship
Henderson et al. 1998 Toxicol. Appl. Pharmacol. 95 515-521

IT administration of organic compounds suspended in saline + 0.2% gelatin to rats

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Molecular weight</th>
<th>Log P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl bromide</td>
<td>93</td>
<td>1.10</td>
</tr>
<tr>
<td>1,3-Dichloropropane</td>
<td>111</td>
<td>1.60</td>
</tr>
<tr>
<td>Anthrazone</td>
<td>178</td>
<td>4.54</td>
</tr>
<tr>
<td>2-Aminonaphthalene</td>
<td>193</td>
<td>4.13</td>
</tr>
<tr>
<td>Phenanthridine</td>
<td>194</td>
<td>3.30</td>
</tr>
<tr>
<td>Pyrene</td>
<td>202</td>
<td>4.88</td>
</tr>
<tr>
<td>Benz[a]anthracene</td>
<td>230</td>
<td>5.89</td>
</tr>
<tr>
<td>1-Chloropyrene</td>
<td>247</td>
<td>4.82</td>
</tr>
<tr>
<td>Benz[a]pyrene</td>
<td>213</td>
<td>6.00</td>
</tr>
<tr>
<td>Pyrene, o-chlorobenzene</td>
<td>267</td>
<td>6.05</td>
</tr>
<tr>
<td>3,2-Quinoly(l), 3-nitroaniline</td>
<td>273</td>
<td>3.90</td>
</tr>
<tr>
<td>6-Nitrobenz(a)pyrene</td>
<td>297</td>
<td>5.72</td>
</tr>
</tbody>
</table>

* P is the octanol/water partition coefficient.

- Organic soluble compounds with a LogP <6 clear the lung rapidly (t1/2 <12hrs)
- Anthraquinone dyes with LogP >6 have an increasing percentage of compound remaining in the lungs 24hrs
  - Taken together with Tronde data, suggests a bell shaped relationship with lipophilicity:
    • insoluble fraction / membrane interactions?
- Suggests MWt cut off of ~300 daltons above which a significant percentage of compound is retained in the lungs at 24hrs.

**Marketed drugs: Statistical difference in cLogP**
between groups <80% / >80% solubilised compound in dose vehicle
% Solubilised dose in perfusate vs permeability data

IPRLu vs In Vivo PK

<table>
<thead>
<tr>
<th>IPRLu Model (n=2 rats + spare)</th>
<th>In Vivo IT PK (n=2/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td></td>
</tr>
<tr>
<td>• Allows more timepoints to be taken from a single rat.</td>
<td>• Non-surgical.</td>
</tr>
<tr>
<td>• Better definition of initial absorption phase.</td>
<td>• In Vivo Model (physiological, perfusion rate etc.)</td>
</tr>
<tr>
<td>• No influence of extra-pulmonary factors eg. hepatic clearance on perfusate profile.</td>
<td>• Directly comparable to any IT dosed PD study therefore relevant for PD comparison.</td>
</tr>
<tr>
<td>• Indirect generation of lung profile</td>
<td>• More scope for scaling data to human</td>
</tr>
<tr>
<td>Disadvantages</td>
<td></td>
</tr>
<tr>
<td>• Some compounds can display large variability between profiles</td>
<td>• Not clear how to predict data in humans (dry powder formulations etc.)</td>
</tr>
<tr>
<td>• Perfusate flow rate &lt; pulmonary blood flow.</td>
<td>• Requires IV data to calculate absorption rate and half-life and via deconvolution a lung profile.</td>
</tr>
<tr>
<td>• Not clear how to predict actual lung levels in rodents and humans.</td>
<td></td>
</tr>
<tr>
<td>• Data only presently collected out to 20mins focusing very much on initial rate</td>
<td></td>
</tr>
</tbody>
</table>