Formulation strategies for improving delivery of peptides and proteins by mucosal routes

Gilles Ponchel

**Therapeutic peptides and proteins**

- Highly specific, highly potent drugs
- Narrow therapeutic index
- Similarities and differences:
  - Physico-chemical properties
    - Molecular weight (1000 Da to >150 000 Da)
    - Polarity
    - Electrically charged
    - Tendency to aggregation, adsorption
    - Loss of tertiary structure
  - Pharmacokinetics (ADME)
    - Elimination half-lives ranging from minutes (peptides) to days or weeks (e.g. albumin, Mabs, ...)
    - Multiple degradation/denaturation mechanisms

**Comparative PK for peptides and proteins**

e.g. glucagon (mw 3485 Da)

- short elimination half-lives (minutes)
- strong need for sustained-release formulations!

**Comparative PK for peptides and proteins**

e.g. PK of daclizumab (autoimmune diseases)

Mabs are recycled by recognizing the neonatal fragment Fc receptor (FcRn)

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Treatment of GHD</th>
<th>Prevention of GHD</th>
<th>Renal transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (L/h)</td>
<td>0.542</td>
<td>0.614</td>
<td>0.371</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>5.81</td>
<td>5.91</td>
<td>5.37</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>79</td>
<td>165</td>
<td>490</td>
</tr>
</tbody>
</table>

**The parable of the Good Samaritan**

Vincent Van Gogh, 1890, Rijksmuseum, Pays-Bas

**Peptides and proteins, parenteral for ever?**

Alternative routes of delivery by crossing epithelial barriers
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The nasal route of delivery

The nasal cavity is an interesting site for systemic absorption...

The nasal route

Typical PK profile after nasal delivery of small molecules

(Merkus et al., ADDR, 1999)

Formulations for nasal delivery of small/medium peptides can reach the market

Bioavailability of Miacalcin Nasal Spray relative to intramuscular administration in healthy volunteers is between 3% and 5%.

Tmax: 13 minutes

Terminal half-life: 18 minutes

No accumulation was observed with multiple dosing.

Formulation:
sCT in solution (water, NaCl, benzalkonium chloride

Salmon calcitonin (3,400 Da)

2012 : Risks of cancer associated to calcitonin use in osteoporosis management

Calcitonin PK is improved after monopegylation

Mono pegylation (PEG 5,000 kDa) improves calcitonin resistance to enzymatic cleavage

BS Shin et al. Chem Pharm Bull, 2004

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**Pro and cons of formulation strategies aiming to improve nasal absorption**

- **Absorption enhancers**
  - Efficient increase in apparent permeability but mucociliary toxicity concerns
- **Enzyme inhibitors**
  - Poor efficiency alone
- **Co-delivery with vasodilators**
  - Increase in the absorption gradient but safety concerns
- **Mucoadhesive formulations**
  - Decreased clearance from the nasal cavity, prolonged absorption, possibility to combine to other strategies

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**Mucociliary clearance of swelling microspheres is reduced by a «roll and adhere» mucoadhesion mechanism**

R.J. Soane et al., IJP, 2001

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**The pulmonary route of delivery**

**The oral route of delivery ....or the holy grail!**

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**Absorption of insulin following nasal delivery of cross-linked starch microspheres**

- cercles pleins: 1.7 IU/kg
- cercles creux: 0.75 IU/kg
- croix: microspheres non-chargées

(Morath et al., ADDR, 1998)

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**Mucoadhesive dosage forms for improving the transport of active molecules through epithelia**

\[ \text{Flux} = \text{Papp} \times C \times S \]

- Peristalsis and transit in GI tract
- Mucociliary transport
- Intestinal epithelial cells
- Basolateral side (B)
- Tight junctions opening and paracellular passage
- Mucoadhesive formulations should act on each determinant of the flux and very close to the epithelium.
Mucoadhesive polymers

\[ W_t = W_0 \cdot \Psi(R, T) \]

N. Pappas et al. JCR 1987
F. Lejayoux et al., 1989

Thiolated chitosan
- Hydrophilic drug
- Poly(isobutylcyanoacrylate)

Mannitol flux (paracellular) is increased x2 or x3 by chitosan-TBA-coated (PIBCA) NP

(100,000 g/mol Papp = 7.3 x 0.6 x 10^-6 cm/s)

I. Bravo et al. Biomaterials 2007

Elongation

Uphypyl-L-phe

Typical hypoglycemic effect after oral delivery of mucoadhesive insulin loaded nanoparticles

Whatever the systems, bioavailabilities are low


Improvement of intestinal transport of active drugs

Intestinal micropatches
Teutonico D & Ponzelli, Drug Discov Today, 2011
Teutonico D et al., Int. J.Pham. 2011
Teutonico D et al., Expert Opin Drug Delivery, 2012

Polyanhydride/CDs NPs (Gantrez)
Collaboration Université de Navarre, Espagne, Pr. Juan-Manuel Incha
Aguiaros M et al., Eur J Pharm Biopharm. 2010

Polymethacrylic acid-polyethylene glycol-chitosan based microgels
Sajeev S, Sree Chitra Thirunal Institute for Medical Sciences & Technology, India
Sajeev S et al., J Control Release. 2010
Sajeev S et al., Eur J Pharm Biopharm. 2010

Polyanhydride/CDs NPs (Gantrez)
Collaboration Université de Navarre, Espagne, Pr. Juan-Manuel Incha
Aguiaros M et al., Eur J Pharm Biopharm. 2010

Divalent ions chelation

i-glycol-chitosan based microgels

1,4-N-

N

S

-e

u

S

Ongoing projects aiming to oral delivery of peptides

1. Nanoparticles have an ideal size for diffusion and retention into the mucus layer

< 1 μm

C. Dörner et al.

2. Nanoparticles properties can be modulated, e.g.
- Mucoadhesion (NPs surface/corona)
- Preventing local drug recrystallization
- Opening tight junctions
- Localizing the activity of efflux pumps/metabolism inhibitors, antipeptidase activity, etc

> 1 μm

Final dosage form is a capsule, a tablet, etc

**Intestinal permeation of IgGs or Mabs**

Expression of FcRn receptor in intestinal epithelium

- **a**
  - Intestinal permeation of IgGs or Mabs
  - Expression of FcRn receptor in intestinal epithelium

- **b**
  - IgGs permeation in human (Ussing chambers)

- **c**
  - Absorption is explained by:
    - IgGs binding to FcRn
    - Transcytosis
    - Lymphatic route

P.J. Hornby et al., Pharm. Res. 2014

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**Microbicide formulation against HIV contamination by creating a dual physical and pharmacological barrier**

AMR emergence mini CD4-07 EMF8-013-02

CD4: cell primary target for HIV entry

Cell: CD4+ T cells (CEA Saclay), Roger Legrand (CEA Fontenay)

- In vivo HIV challenge test in Cynomolgus macaques demonstrated the activity of MAb formulated HEC hydrogels
- N. Derenou-Bouquet et al. PLGS Pathogens, 2013

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**Local delivery to vaginal epithelium**

- Expression of FcRn receptor in intestinal epithelium
- Mucus

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**Microbicide formulation by creating a physical barrier against viral particles**

- Thermosensitive Pluronic hydrogels

- Rheological, Physico-chemical, Mucoadhesive properties

Bouchet al., J Collid Interface Sci (2009) 330, 163-176
Bouchet al., J Mol Recognit (2009) 22, 212-241

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**Therapeutic peptides and proteins: parenteral for ever?**

1. Certainly not!
2. Non parenteral delivery of peptides and proteins was long believed impossible...
3. ...better understanding of the epithelial barriers properties and development of improved delivery platforms have made it feasible.
4. … further improvements in delivery platforms can be expected!