

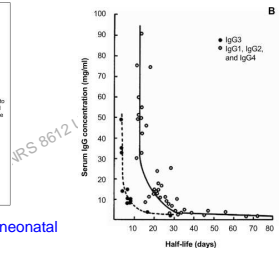
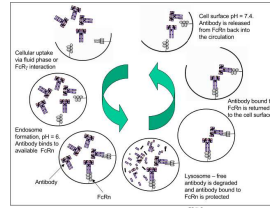
Formulation strategies for improving delivery of peptides and proteins by mucosal routes

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Comparative PK for peptides and proteins e.g. PK of daclizumab (autoimmune diseases)

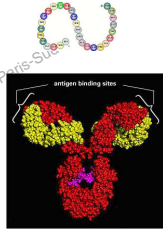


Mabs are recycled by recognizing the neonatal fragment Fc receptor (FcRn)

Parameter (unit)	Indication		
	Treatment of GvHD	Prevention of GvHD	Renal transplant
Clearance (l/h)	0.042	0.0314	0.015
Vd _{ss} (l)	5.81	6.91	5.9 ^a
Half-life (h)	79 to 94	165.4	480

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 ternary structure
 - Pharmacokinetics (ADME)
 - Elimination half-lives ranging from minutes (peptides) to days or weeks (e.g. albumin, Mabs,...)
 - Multiple degradation/denaturation mechanisms



The parable of the Good Samaritan

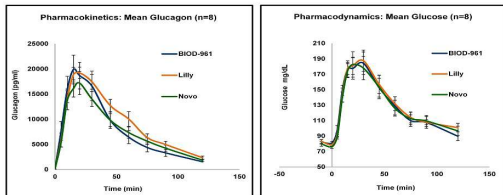


Vincent Van Gogh, 1890, Rijksmuseum, Pays-Bas

Comparative PK for peptides and proteins

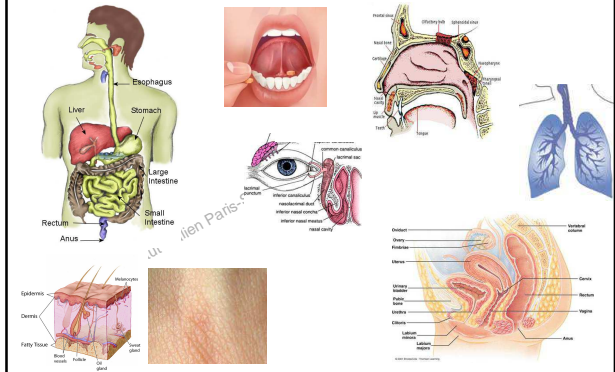
e.g. glucagon (mw 3485 Da)

Pharmacokinetic and Pharmacodynamic Profiles in Dogs of BIOD-961* Vs. Lilly and Novo Glucagon Rescue Products

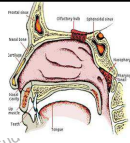


- short elimination half-lives (minutes)
- strong need for sustained-release formulations!

Peptides and proteins, parenteral for ever? Alternative routes of delivery by crossing epithelial barriers

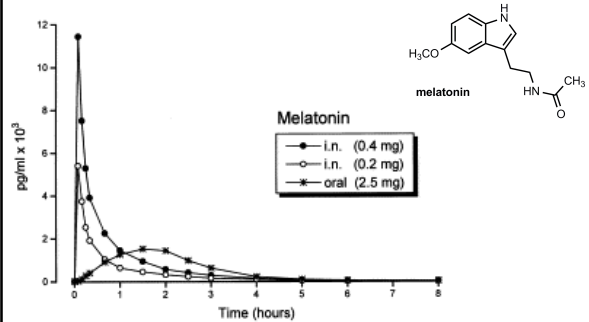


The nasal route of delivery



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Typical PK profile after nasal delivery of small molecules



(Merkus et al., ADDR, 1999)

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



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

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-1 2 3 4 5 6 7 8 9
 Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-10 11 12 13 14 15 16 17 18 19
 Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-20 21 22 23 24 25 26 27 28 29
 Gly-Thr-Pro-NH₂ 30 31 32
 Salmon calcitonin (3,400 Da)



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

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

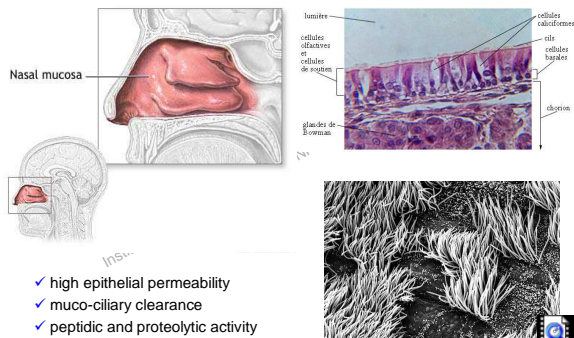
T_{max}: 13 minutes

Terminal half-life: 18 minutes

No accumulation was observed with multiple dosing.

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

The nasal route



Calcitonin PK is improved after monopegylation

Cys¹-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys¹¹-Leu-Ser-Gln-Glu-Leu-His-Lys¹⁸-Leu-Gln-Thr-Tyr-Pro-Arg²⁴-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH₂

Fig. 1. Primary structure of salmon calcitonin. Possible PEGylation sites are Cys¹, Lys¹¹, and Lys¹⁸ and trypsin cleaves sCT at three points, i.e. Lys¹¹, Lys¹⁸, and Arg²⁴.

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

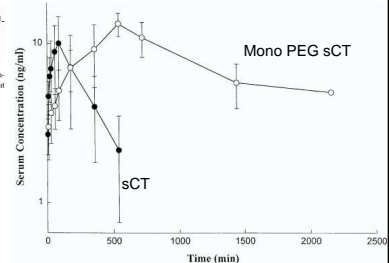
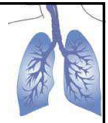


Fig. 3. Average Serum Concentration of Intact sCT vs. Time Curves Following Nasal Administration of Unmodified sCT (●) and Mono-PEG_{5k}-sCT (○) in Rats (n=9 Each)

BS Shin et al. Chem Pharm Bull, 2004

Pro and cons of formulation strategies aiming to improve nasal absorption

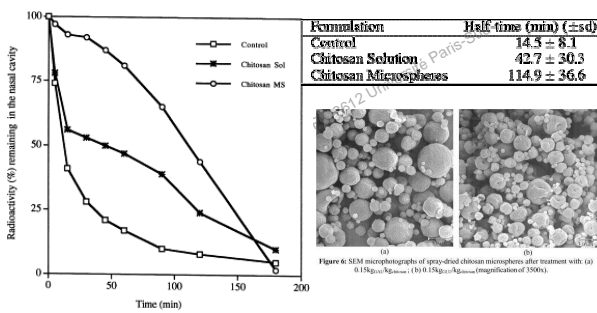
- Absorption enhancers
 - Efficient increase in apparent permeability but muco-ciliary toxicity concerns
- Enzyme inhibitors
 - Poor efficiency alone
- Co-delivery with vasodilators
 - Increase in the absorption gradient but safety concerns
- Mucoadhesive formulations
 - Decreased clearance from the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



The pulmonary route of delivery

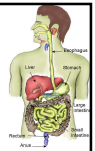
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Mucociliary clearance of swelling microspheres is reduced by a «roll and adhere» mucoadhesion mechanism



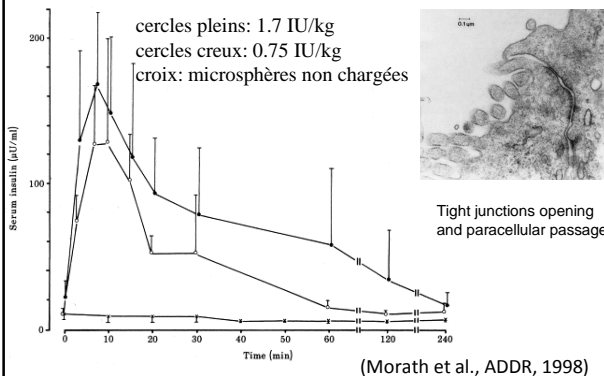
R.J. Soane et al., IJP, 2001

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

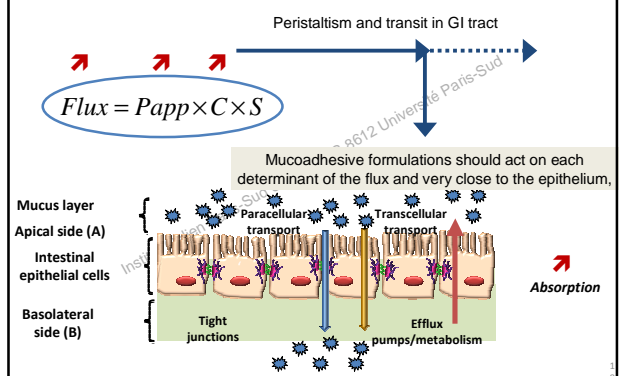


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Absorption of insulin following nasal delivery of cross-linked starch microspheres



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



Mucoadhesive polymers

Polymères hydrophiles

Gonflent en présence d'eau

N. Peppas et al. JCR 1987

$Wt = W_0 \cdot \Psi(R, T)$ F. Lejoux et al., 1989

Force vs Elongation graph showing F_{max} and Wt .

Functionalized PIBCA/thiolated chitosan NPs

Thiolated chitosan
Hydrophilic drug
Poly(isobutylcyanoacrylate)

Thiolated chitosan:

- Mucoadhesive properties
- Opening the tight junctions
- Divalent ions chélation
- Antipeptidase activity

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

BIOADHESION

(100.000 g/mol Papp = $7,3 \pm 0,6 \times 10^{-6}$ cm/s)

I. Bravo et al. Biomaterials 2007
 Mazzaferro S et al. J Drug Del Sci Tech. 2011, 21(5), 385-393.

Carboxypeptidase A
 hyppuryl-L-phe → phe

Improvement of intestinal transport of active drugs

Intestinal micropatches

Teutonico D & Ponchel., Drug Discov Today, 2011
 Teutonico D et al., Int J Pharm, 2011
 Teutonico D et al., Expert Opin Drug Delivery, 2012

Polymethacrylic acid-polyethylene glycol-chitosan based microgels

Sajeesh S, Sree Chitra Tirunal Institute for Medical Sciences & Technology, India
 Sajeesh S et al., J Control Release, 2010
 Sajeesh S et al., Eur J Pharm Biopharm, 2010

Polyanhydride/CDs NPs (Gantrez)

Gantrez® AN, ISP

Collaboration Université de Navarre, Espagne. Pr. Juan-Manuel Irache
 Agüeros M et al., Eur J Pharm Biopharm, 2009
 Zabaleta V et al., Eur J Pharm Biopharm, 2012

Functionalized PIBCA/chitosan NPs

Petit B et al., Pharm Res, 2012
 Mazzaferro S et al., Int J Pharm, 2011
 Mazzaferro S et al., Drug Discov Today, 2012

Typical hypoglycemic effect after oral delivery of mucoadhesive insulin loaded nanoparticles

Whatever the systems, bioavailabilities are low

Pan Y et al. Acta Pharm Sin. 2001

Nanoparticles for oral delivery

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

Genetic structure of a mucus monomer: oligosaccharide, cysteine residues, repeat structure, COOH

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

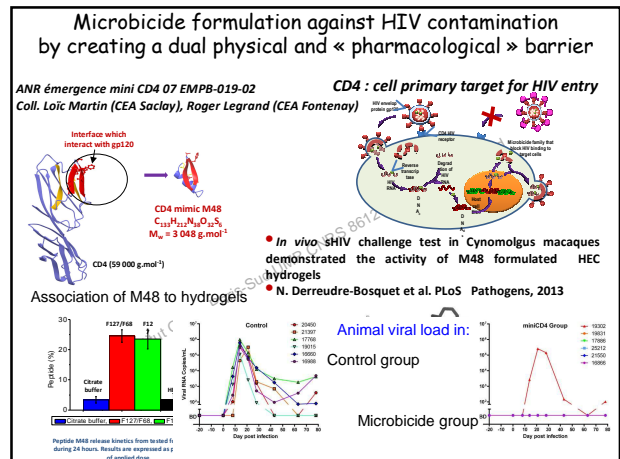
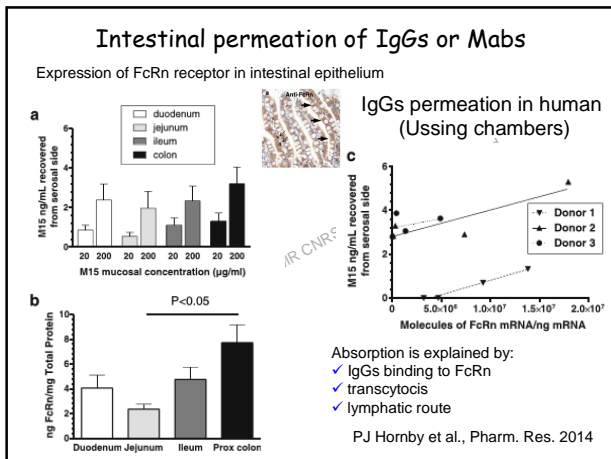
C. Dürrer et al.

Ongoing projects aiming to oral delivery of peptides

Company	Details	Technology	Reports/Claims	Phase
Access	Oral, receptor-mediated uptake	CoBio®	Insulin, GH	Pre
Argis	Buccal, oral	Intraall®	AlfPep, Octreotide	Pre
ArcoGen	Buccal, oral	Arscrown	Exendin, HPTH/Insulin	Pre
Biodel	Sublingual film tablet	Vitab	Insulin	PI
Proxima Concepts	Oral, enteric-coated capsule	Accos™	Calcitonin, hPTH	PII
Chiasma	Oral, oily suspension of enhancers	TPE Technology	Octreotide	PIII
Emisphere	Oral, passive transcellular uptake	Eligen®	Calcitonin, Insulin, GLP-1, PYY	PI-PIII
Merion	Oral, enteric coated tablet	GIPET®	Insulin, GLP-1, GlRH Analog	PI
Midatech/Monosol	Buccal film, nanoparticles	PharmFilm	Insulin	PI
NanoMega Medical	Oral, nanoparticles		Insulin	Pre
NDD Pharmaceuticals	Oral, nanoparticles	NDD	Insulin	PI
Oramed	Oral, enteric coated tablet		Insulin, Exenatide	PI
Urigene	Oral, enteric coated tablet	Peptelligence®	Calcitonin, hPTH, CR845	PI-PIII

Final dosage form is a capsule, a tablet, etc

R. Lax et al. Innov. Pharm. Tech,



Local delivery to vaginal epithelium

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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!

