Transmucosal Delivery Using Mucoadhesive Polymers

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Outline

- Mucoadhesion and mucoadhesives
- Mucoadhesive drug delivery
- Mucoadhesive vaccine delivery
- Chitosan for vaccine delivery
- Conclusion
Mucosal delivery

- Oral (buccal, sublingual, gingival)
- Nasal
- Rectal
- Vaginal
- Pulmonary
- Ophthalmic
- Intestine, stomach
Mucosal Delivery

- Drugs
- Vaccine antigen / allergen
Transmucosal delivery

- Provides direct entry into the systemic circulation, avoiding:
  - hepatic first-pass effect
  - degradation (enzymatic and hydrolytic) in the GI tract
- Ease of application
- Readily accessible area (nasal and oral mucosae)
- Ease of removal (oral mucosa)
- Non-sterile delivery systems
- Good patient compliance
Factors affecting the bioavailability of drugs across the mucosa

- physicochemical properties of the drug
- structure and physiology of the mucosa
- the formulation of the delivery system
To improve availability of drugs across mucosa

- chemical modification of drug
- permeation enhancement
- physical means
  - (sonophoresis, iontophoresis and electroporation)
- mucoadhesion
Bioadhesion (mucoadhesion)

- the attachment of synthetic or biological macromolecules to a biological tissue when applied to a mucosal epithelium, bioadhesion occurs primarily with the mucus layer → mucoadhesion
General theories of adhesion

- electronic theory
- wetting theory
- adsorption theory
- diffusion theory
- mechanical theory
- fracture theory

• **Single layered epithelia** (e.g. stomach, small and large intestine, bronchi) contain goblet cells which secrete mucus directly onto the epithelial surfaces

• **Multilayered/stratified** (e.g. oesophagus, buccal, sublingual, vagina, cornea) are adjacent to specialised glands such as salivary glands that secrete mucus onto the epithelial surface
Mucus

- mucin glycoproteins
- non-mucin components (secretory IgA, lysozyme, lactoferrin, lipids, polysaccharides, and various other ionic species)
- water (95%)
## Potential bioadhesive forces

<table>
<thead>
<tr>
<th>Type of force</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent</td>
<td>Cyanoacrylate</td>
</tr>
<tr>
<td>Hydrogen bond and Van der Waals</td>
<td>Carbopol, polycarbophil, acrylates</td>
</tr>
<tr>
<td>Electrostatic interaction</td>
<td>Chitosan</td>
</tr>
</tbody>
</table>
Why mucoadhesion?

- increase contact time with the absorbing membrane
- prolong the residence time
- allow targeting and localization of the drug at a specific site
Why mucoadhesion?

- enhance permeation
- inhibit luminal proteolytic enzymes in the gastrointestinal tract (e.g. polyacrylates)
Why mucoadhesion?

• coat and protect damaged tissues (gastric ulcers or lesions of the oral mucosa)

• act as lubricating agents (in the oral cavity, eye and vagina)
First generation mucoadhesive polymers

- Anionic polymers (polyacrylic acids-carbomers, sodium alginate)
- Cationic polymers (chitosan)
- Non-ionic polymers (cellulose derivatives)

hydroxyl, carboxyl or amine groups on the molecules favours adhesion

Formulation challenges due to hydrophilicity and limited solubility in other solvents
New generation mucoadhesive polymers

Allow specificity, or prolong and strengthen the mucoadhesion process

- existing mucoadhesive polymers have been modified
- new materials are developed
New generation mucoadhesive polymers

- thiol groups placed into a range of mucoadhesive polymers such as polyacrylic acids, chitosans and alginates
- polyethylene glycol (PEG) grafted onto polyacrylic acid polymers
- chemical combination of Pluronics with polyacrylic acids
- target-specific, lectin-mediated bioadhesive polymers (*cytoadhesion*)
Factors affecting mucoadhesion

- **Polymer properties**
  - functional group contribution
  - degree of hydration
  - molecular weight, chain length, conformation, and degree of cross-linking
  - pH and charge

- **Physiological factors**
  - pH, ionic strength
  - the amount of fluid at the applied site
  - turnover rate and viscosity of mucus
Methods to Study Mucoadhesion

- Tensile (Detachment) Method
- Rotating Disc Method
- Flow-Through Method
- Rheological Method ...

excised tissue, mucin discs ...
Oral Mucosal Drug Delivery

Aftach®
Triamcinolone Acetonide
Adhesive-type therapeutic preparation for Aphthous Stomatitis

T. Nagai,
Japan National Invention Prize (1984)
Challenges

- various regions which differ in
  - Flexibility
  - Permeability
  - Thickness

- saliva, chewing and swallowing
  - continuously produced throughout the day (0.5-2 litres per day)
  - removal from oral cavity

- Pather SI, Rathbone MJ, Şenel S, Expert Opin. Drug Deliv. 5(5), 1-12, 2008-
Oral Mucosal Drug Delivery Systems

- aqueous solutions
- tablets (immediate and slow release)
- lozenges, gums
- adhesive tablets, gels, films and patches, wafers
- devices mechanically attached into the oral cavity
- sprays
Insulin PharmFilm Buccal

Midatech Group Ltd/ MonoSol Rx

binding a peptide hormone to a gold nanoparticle (GNP) enables the needle-free delivery of insulin across buccal mucosa

• Phase II clinical study planned to start in 2014

PharmFilm® technology (MonoSol Rx)

Fast dissolving film (polyethylene oxide, HPMC, maltitol)

http://midatechgroup.com/project-pipeline
Oral-lyn™ Buccal Insulin Spray

(Generex Biotechnology)

An oral insulin spray for the treatment of diabetes

a liquid formulation of regular human insulin
delivered to the buccal mucosa by RapidMist™ device

This technology uses the formation of microfine, thin membrane, mixed micelles made from the combination of insulin and specific absorption enhancers that encapsulate and protect the insulin molecules

Phase III clinical trials continuing in USA and Canada

Oral-lyn™

- Preliminary results of clinical trials in patients with type 1 diabetes and patients with impaired glucose tolerance was completed with promising results (July, 2011)

- Phase III trial in type 2 diabetes patients was completed in India showing rapid reductions of HbA1 (July, 2013)

received approval for commercial sale in Ecuadoror

Mucosal (non-invasive) Vaccine Delivery
Mucosal Immunisation

- protect mucosal surfaces against colonization and invasion by pathogens
- provide both local and systemic immune responses

Application of non-invasive delivery improves accessibility, safety, and cost-effectiveness
Mucosal vaccine delivery

- Oral
- Nasal
- Sublingual

- Vaginal and Rectal
  - poor patient compliance
  - induce immune responses mainly at the site of immunization
Mucosal Immunisation

_major challenge to mucosal immunisation_
- most antigens are poorly immunogenic

_to enhance the immune response_
- adjuvants
- appropriate delivery systems
Mucosal vaccine formulation

- thermostable
- protect the vaccine from physical elimination and enzymatic digestion
- target mucosal inductive sites including membrane or M cells
- enhance immune response
- increases contact to mucosal tissue
- extends the residence time
Mucoadhesives for vaccine delivery

- Starch
- Alginate
- Carbomer
- Lectin
- Hyaluronic acid
- Chitosan and derivatives
GelSite®
(patented by DelSite, Inc., Nov 2008)

• high molecular weight anionic polysaccharide (sodium polygalacturonate) extracted from Aloe vera L.

• exerts mucoadhesive properties

• exists in liquid form or a dry powder formulation called GelVac™

• capable of in situ gelation at the site of administration
GelVac™

• Nasal powder H5N1 (bird flu) influenza vaccine (Nanotherapeutics Inc)
  Phase I study completed (October 03, 2011)
  no safety issues, no serious adverse events occurred during the trial

• Dry powder nasal vaccine
  Norwalk virus-like particles (NV VLP)
  mice studies

Lissette S. Velasquez et al, Vaccine 29 (2011) 5221–5231
http://www.prweb.com/releases/2011/10/prweb8844555.htm
Antigen adjuvant/delivery systems

- Insoluble aluminum compounds
- Calcium phosphate
- Liposomes
- Virosomes
- ISCOMs
- Emulsions (e.g., MF59, Montanides, AS01, AS02, AS04)
- Virus-like particles and viral vectors
- Micro/nano particles (e.g., PLG, chitosan)
Mucosal vaccines

- Oral polio
- Enteric infections
  - *V. cholerae*, *S. typhi* and rotavirus
- Respiratory infections (e.g. influenza)
- Immunotherapy
- Autoimmune diseases
<table>
<thead>
<tr>
<th>Licensed mucosal vaccines</th>
<th>Rotarix</th>
<th>GlaxoSmithKline Biologicals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rotavirus Vaccine, Live, Oral</strong></td>
<td></td>
<td></td>
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<tr>
<td>FDA approval: April 2008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA approval: Feb 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rotavirus Vaccine, Live, Oral, Pentavalent</strong></td>
<td>RotaTeq</td>
<td>Merck &amp; Co., Inc.</td>
</tr>
<tr>
<td>FDA approval: Feb 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMA approval: 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Typhoid Vaccine Live Oral Ty21a</strong></td>
<td>Vivotif</td>
<td>Berna Biotech, Ltd</td>
</tr>
<tr>
<td>FDA approval: Oct 2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Licensed mucosal vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No Trade Name</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus Type 4 and Type 7 Vaccine, Live, Oral</td>
<td>No Trade Name</td>
<td>Barr Labs, Inc.</td>
</tr>
<tr>
<td><strong>FDA approval: March 2011</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated Travellers. Diarrhea and Cholera Vaccine, Oral</td>
<td>Dukoral</td>
<td>Sanofi Pasteur Limited</td>
</tr>
<tr>
<td><strong>No FDA approval</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Approved in Canada: Aug 2010</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Internationally licensed mucosal vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza Vaccine, Live, Intranasal spray suspension</td>
<td>MedImmune, LLC AstraZeneca</td>
</tr>
<tr>
<td>Flumist Fluenz</td>
<td></td>
</tr>
</tbody>
</table>

*FDA approval: June 2003*

*EMA approval: Feb 2011*
Risk of Bell’s palsy limited the nasal formulations containing enterotoxin-based adjuvants
Sublingual immunisation

United States Patent Application Publication

Czerkinsky et al.

Publication Classification

METHOD FOR INDUCING MUCOSAL HUMORAL AND CELL-MEDIATED IMMUNE RESPONSES BY SUBLINGUAL ADMINISTRATION OF ANTIGENS

Int. Cl.
A61K 39/12 (2006.01)
A61K 39/02 (2006.01)
A61K 48/00 (2006.01)

U.S. Cl. .................... 424/204.1; 424/234.1; 514/44

Inventors: Cecil Czerkinsky, Nice (FR); Jan R. Holmgren, Vastra Frolunda (SE)
Sublingual immunisation with HPV

- Characterisation of human disseminated cellular and humoral immune responses following sublingual or intramuscular deposition of antigens

St. George’s University of London
Prof. David J. M. Lewis (PI)

Dry vaccine formulations for sublingual administration

- Sublingual tablets based on HPMC or Carbopol 974
  ovalbumin, BALB/c mice
- Slow release reduced immune response

A. Borde et al, EJPS, 47 (2012) 695–700
# Licensed sublingual delivery

<table>
<thead>
<tr>
<th>Grass allergens</th>
<th>Oralair</th>
<th>Stallergenes SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sublingual immunotherapy tablet</td>
<td></td>
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</tr>
</tbody>
</table>

*Approved in Australia: May 2011*

*Mutual recognition in Europe*

*First approval in Germany: 2008*
Chitosan for mucosal vaccine delivery
Shells of crustaceans (crab, shrimp, etc)

Decoloration

Decalcification

Deproteination

Decoloration

Chitin

\( \text{N-acetyl-D-glucosamine} \)
Deacetylation in NaOH

Chitosan
Degree of deacetylation (DD)

The proportion of N-glucosamine units with respect to the total number of units

Degree of deacetylation of 65-70 % or above → Chitosan
Chitosan

- Natural cationic polymer
- Biodegradable
- Biocompatible
- Bioadhesive
- Penetration enhancing effect
- Enables to prepare different dosage forms (films, gels, sponges, particulate systems)
- Immunopotentiator
Applications of chitosan in human and veterinary medicine

- Biological properties
  - Antimicrobial
  - Hemostatic
  - Tissue regeneration
  - Wound healing

- Drug delivery systems

- Vaccine adjuvant/delivery systems
Mucosal immunisation and chitosan

- Adjuvant
- Delivery system
gel, sponge, micro/nanoparticulate systems
- Bioadhesive
- Penetration enhancer

Şenel S, Advances in Polymer Sci, 2011
Chitosan as adjuvant

Mode of mechanism

- induces both cellular and humoral responses when administered via parenteral, mucosal or dermal routes
Intranasal in human

- Formulation of the nasal diphtheria vaccine with chitosan significantly augmented Th2-type responses, which correlated with protective levels of toxin-neutralizing antibodies in intranasally boosted individuals

Neisseria meningitidis serogroup C polysaccharide (MCP)-CRM197 conjugate + chitosan

Nasal insufflation

- Increases in CRM197-specific IgG and diphtheria toxin-neutralizing activity were observed after nasal or intramuscular immunization, with balanced IgG1/IgG2 and higher IgG4.

- Significant MCP-specific secretory IgA was detected in nasal wash only after nasal immunization and predominantly on the immunized side.

Huo et al, Infection and immunity, 73 (2005) 8256–8265
Influenza+chitosan intranasal in human

- two intranasal doses (four weeks apart) of chitosan glutamate-influenza vaccine
- single intramuscular dose of standard inactivated trivalent vaccine

Enhanced HI levels were obtained with both administration

R.C. Read, et al., Vaccine 23 (2005) 4367–4374
Norovirus + chitosan intranasal in human

- dry powder formulation based on virus-like particle (VLP) antigens including Monophosphoryl Lipid A (MPL) (GSK) and chitosan (ChiSys®, Archimedes Development Ltd.)

provided protection against “experimental illness and infection” after challenge with a homologous virus

A Norwalk virus-specific IgA seroresponsne (defined as an increase by a factor of 4 in serum antibody levels) was detected in 70% of vaccine recipients

Single oral dose of chitosan

- chitosan acts by enhancing the T helper cell type 2 (Th2)/Th3 microenvironment in the mucosa

Chitosan based particulate systems

- high loading efficiency
- no organic solvent
- no elevated temperature
- no shear stress
- easy to prepare
- positive surface charge
- biodegradable
- adjustable particle size
- combination with other polymers
- stable systems

Şenel S, Advances in Polymer Sci, 2011
Studies performed on vaccine delivery

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Delivery system</th>
<th>Administration route</th>
<th>Animal model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovalbumin</td>
<td>microparticle</td>
<td>in vitro</td>
<td></td>
</tr>
<tr>
<td>Ovalbumin</td>
<td>gel, sponge</td>
<td>nasal, rectal</td>
<td>sheep</td>
</tr>
<tr>
<td>Tetanose toxoid</td>
<td>aqueous dispersion nanoparticle</td>
<td>nasal</td>
<td>mice</td>
</tr>
<tr>
<td>Heliotrine antigen</td>
<td>gel, sponge</td>
<td>nasal, rectal</td>
<td>sheep</td>
</tr>
<tr>
<td>Fouth and mouth disease (FMD) virus</td>
<td>gel, sponge</td>
<td>nasal</td>
<td>guinea pig</td>
</tr>
<tr>
<td>Bovine herpes virus (BoHV-1)</td>
<td>gel, microparticle</td>
<td>in vitro</td>
<td></td>
</tr>
</tbody>
</table>
TT loaded nanoparticles

TT specific serum Ig G antibody titres

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Day 20</th>
<th>Day 42</th>
<th>Day 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free TT i.n.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCC np i.n.</td>
<td></td>
<td></td>
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<tr>
<td>TMC np i.n.</td>
<td></td>
<td></td>
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<tr>
<td>CS np i.n.</td>
<td></td>
<td></td>
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<tr>
<td>TMC-MCC np i.n.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Ig G Antibody Titer

**Formulations**

- Free TT s.c.
- TMC-MCC sol.s.c.
- Free TT i.n.
- TMC-MCC np-i.n.

**Day 20**

**Day 42**

**Day 56**
Viscogel - A chitosan based adjuvant for prophylactic and therapeutic vaccination (ViVac)

FP7 SME
VISCOGEL AB, Sweden

09-2010 / 12-2012

- pre-clinical and clinical proof-of-concept for prophylactic vaccination with a model vaccine against Hib (Haemophilus influenzae) type
- therapeutic vaccination with model allergen, Bet v 1, via sublingual mucosa
Conclusion remarks

- Mucoadhesives are promising for mucosal vaccine and allergen delivery

- Well-established safety records needed for the “new generation mucoadhesives”

- More clinical studies needed to show the safety and efficacy of the developed “mucoadhesive systems”
Thank you ...

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