GLG Webcast

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DRUG DELIVERY SYSTEMS FOR PEPTIDES AND PROTEINS

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GLG Council Member

Ralph Tarantino, PhD

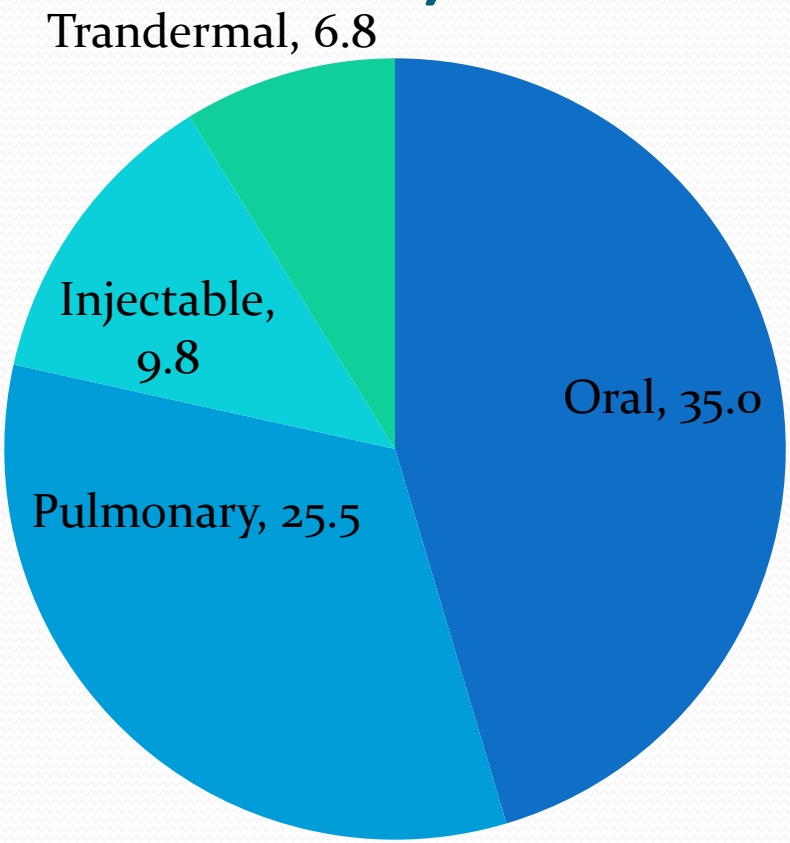
Ralph Tarantino, PhD, specializes in pharmaceutical formulations and drug delivery systems as a Senior Consultant and Principal at Steritech Solutions, LLC. He is a Subject Matter Expert in sterile product formulations and has served as an expert witness in patent litigation cases for formulation infringement cases. Dr. Tarantino started at Hoffmann-La Roche (US subsidiary of Roche Holdings Inc. in 1989) and was promoted to Research Director, Pharmaceutical and Analytical R&D in 1995, heading up the Sterile Formulation Development Group. During his tenure at Roche, he served as Head Sterile Formulations, Package Research and Clinical Manufacturing. His primary areas of research have been drug delivery systems (device and formulation approaches) formulation of peptides, solubilization and formulation of insoluble oncology small molecules. During this time period, Dr. Tarantino served also as a CMC Leader and Formulations Expert for four successfully launched pharmaceuticals. He has published in the area of drug delivery and formulation research and was the primary inventor for a patented subcutaneous sustained release formulation. Dr. Tarantino played a key role in the global harmonization of pharmaceutical formulations and processes at Roche over the last 20 years. He was a member of Roche's Global Formulation Research Management Team, and the Chair of the International Technology Working Group as well as the Global Peptide Delivery Champion.

Outline - Drug Delivery Systems for Peptides and Proteins

- Drug Delivery System – General Concepts
- Polypeptides- Definitions and Properties
- Factors to Consider when Developing a Polypeptide Drug Delivery System
- Polypeptide Drug Delivery Systems
  - Oral
  - Transdermal
  - Pulmonary
  - Nasal
  - Injectable
- Summary

Drug Delivery System – General Concepts

Worldwide Drug Delivery Market (2012 ,in $Billions)



Drug Product

“a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients. “(CFR Sec. 314.3)

Drug Products…

- Provide safe and effective means for administering drug substances
- In general, are passive systems
- Provide adequate and safe concentrations of drug substances at
  - at sites of absorption,
  - for intravenous administration
  - for local administration

Drug Delivery Systems are Drug Products “Plus”!

Drug Delivery Systems

All the attributes of Drug Products, plus do one or more of the following:

- Control release rate of the drug
  - Sustained
  - Prolonged
  - Delayed
- Enhance absorption
- Allow alternative routes of administration (transdermal, inhalation)
- Overcome barriers to administration
  - Needle free
  - Auto injectors
- Targeting

The last 25 years…

Factors affecting Technical Drug Product Development in last 25 Years

- Biotechnology
- Low Drug Substance Solubility
- Removal of Chlorofluorocarbons
- Nucleic Acid Therapeutics

Factors affecting Business Development Development for Drug Delivery Systems in last 25 Years

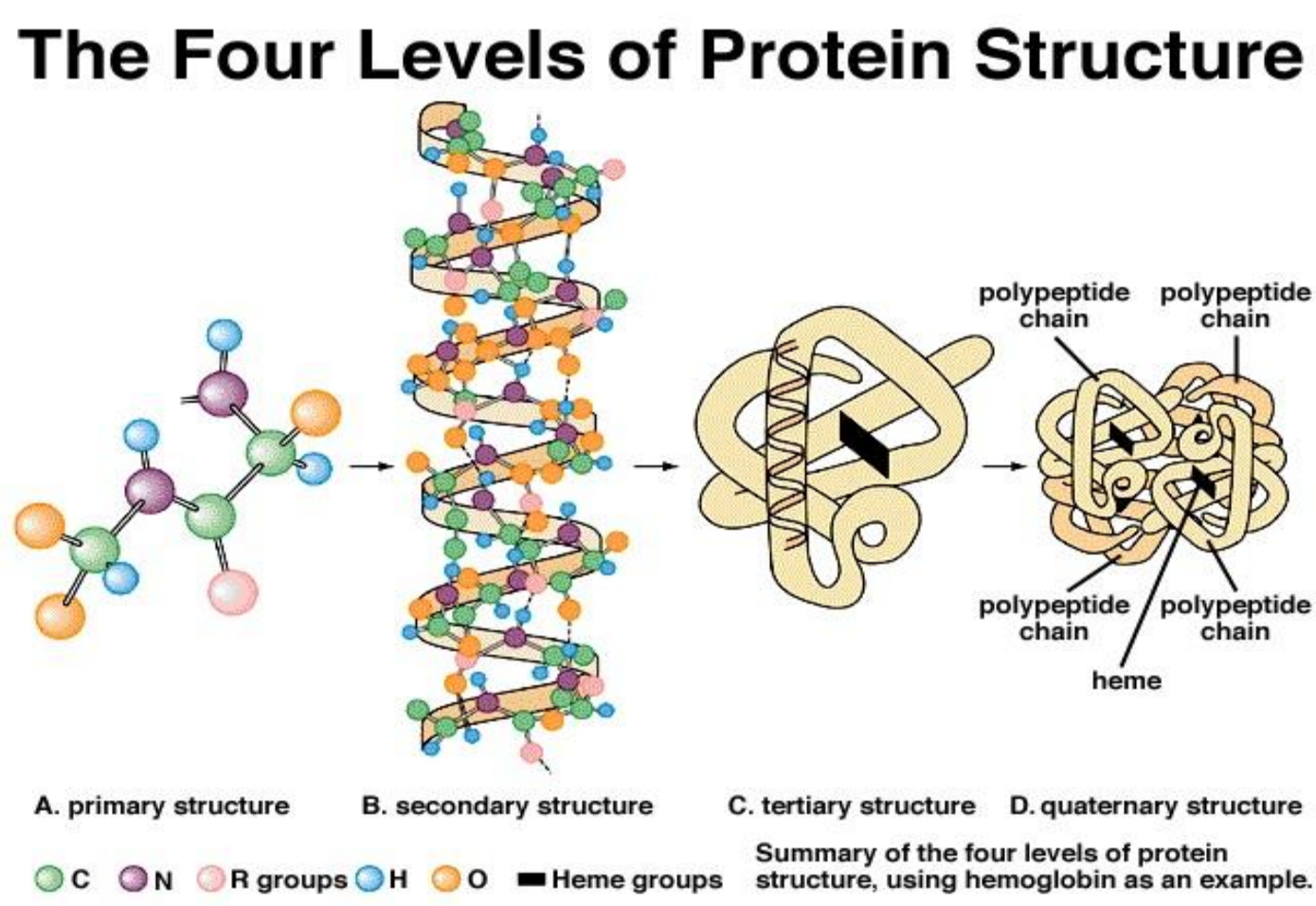
- Healthcare Cost/Reimbursement Issues
- First to Market Principle
- Compliance vs. Convenience
- Section 505(b)(2) of FDC Act

Polypeptides- Definitions and Properties

Protein, peptide, polypeptide, biologic…

- Biologic – sourced from a living organism
- Peptide – polypeptide with less than 50 amino acid units (or about MW 5000)
- Protein – polypeptide with more than 50 amino acid units (or about MW 5000)
- Peptides and proteins are polypeptides – a good general term

Polypeptide Structure



Factors to Consider when Developing a Polypeptide Drug Delivery System for Systemic Administration

Conventional Dosage Form or Drug Delivery System?

- Pre-NDA vs. NDA?
- Time to market?
- Physicochemical characteristics of peptide/protein
  - Stability
  - Degradation pathway
  - Tendency to aggregate
  - Solubility
- Dose
- Immunogenicity Potential
- COGS/Licensing costs?

Decisions

- When to initiate development
- Internal or external technology
- Appropriateness for Therapeutic Area/Patient
- Preferred Route of Administration
- Administration Method
  - Self-administration
  - Health provider administration

Preference of Dosage Forms

1. Oral
   - Transdermal
2. Pulmonary
   - Nasal
3. Injectable

Development of a Peptide/Protein Drug Delivery System

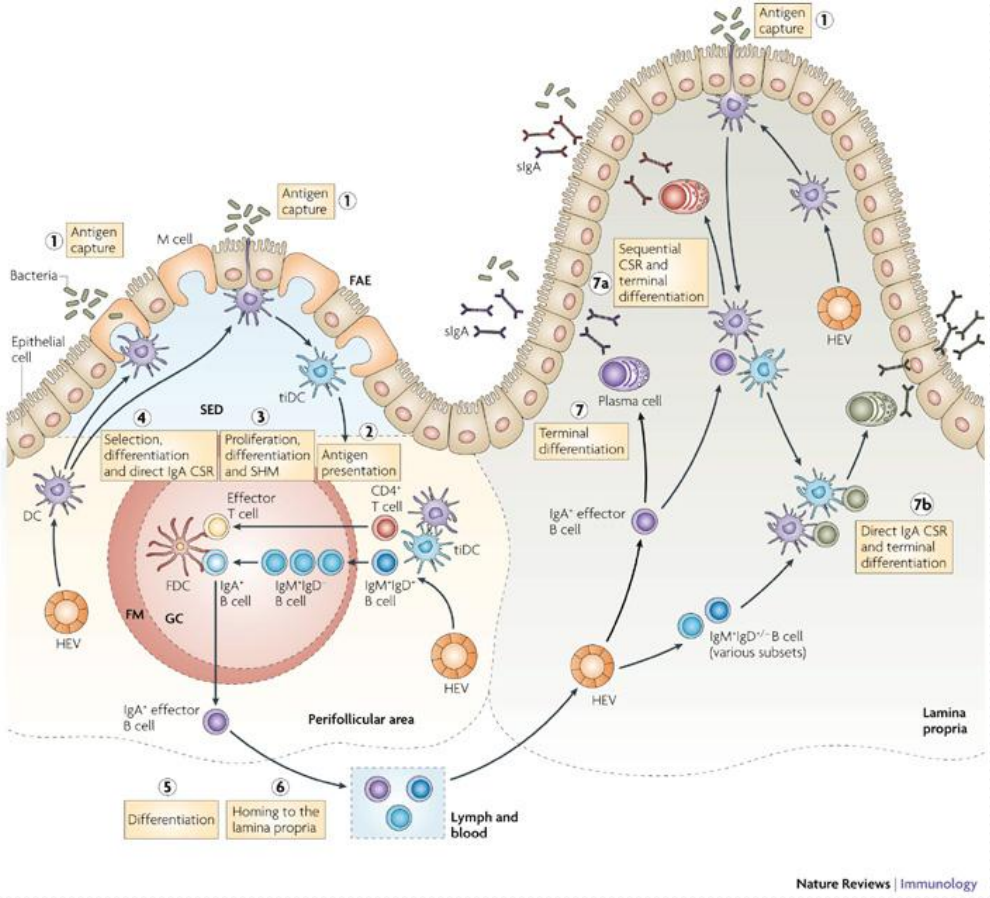
Preference of Dosage Forms

1. **Oral**
   - Transdermal
2. Pulmonary
   - Nasal
3. Injectable

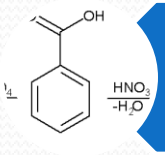
Barriers to Oral Delivery of Polypeptides

- pH
- Molecular weight
- Enzymatic degradation
- Hydrophilicity

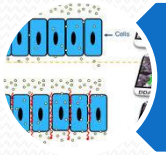
Peyer's Patches and absorption of polypeptides



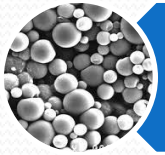
Oral Drug Delivery for Polypeptides



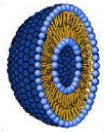
Chemical Modification



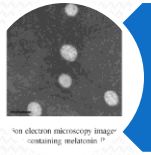
Absorption enhancers



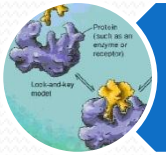
Microcapsules



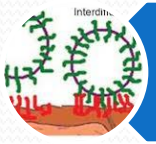
Liposomes



Nanocapsules

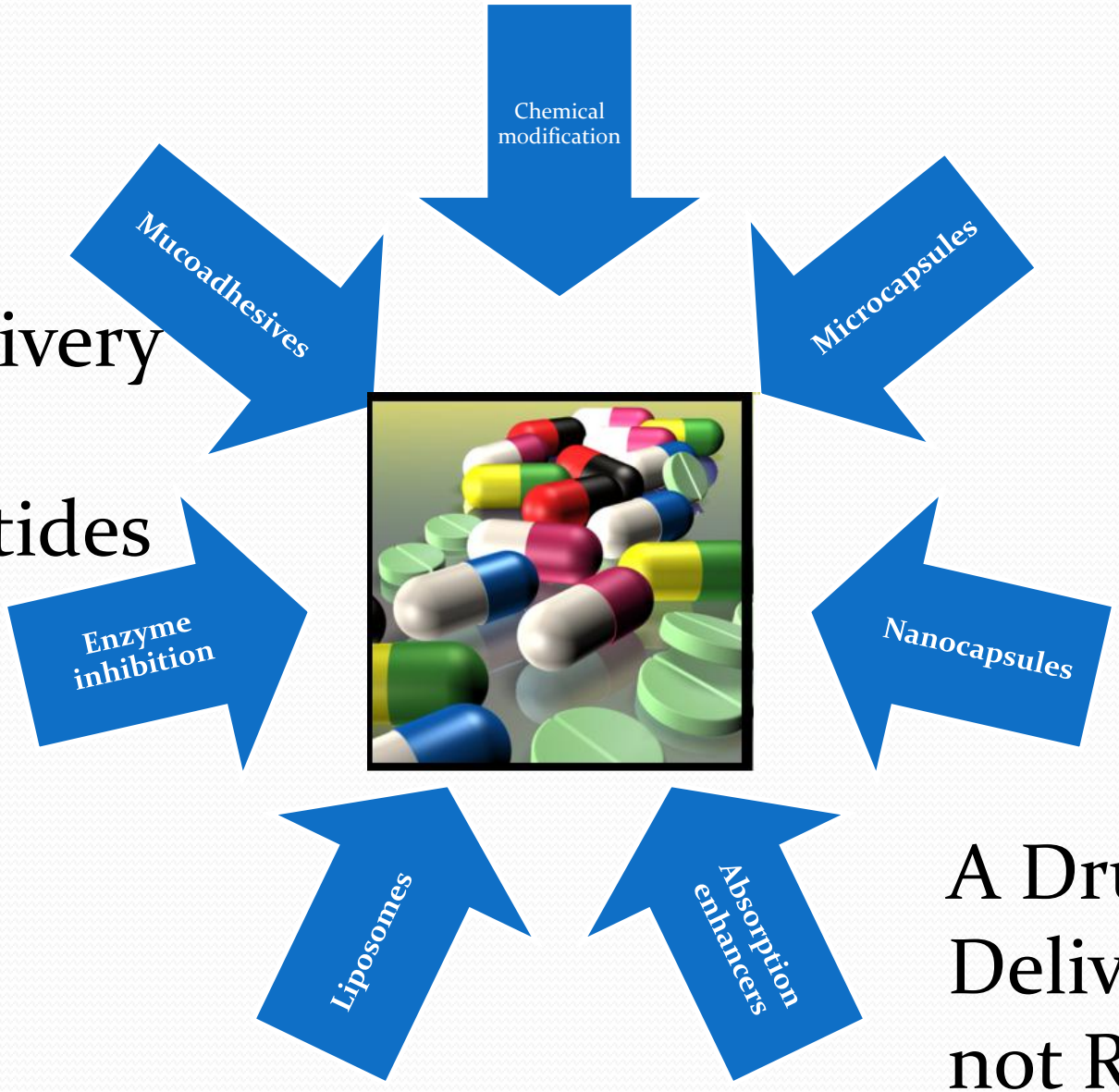


Enzyme Inhibition



Mucoadhesives

Oral Delivery of Polypeptides



A Drug Delivery Goal not Realized

Summary: Oral Delivery of Polypeptides

- Not efficient for Polypeptides > 1500 MW
- Oral products exist for low MW polypeptides
  - Desmopressin,
  - Cyclosporine
  - ACE Inhibitors
- Bioavailability of 1 – 2 % for larger polypeptides has been demonstrated however:
  - Feasibility is questionable
  - COGs prohibitive
- Still “Holy Grail ” of Drug Delivery

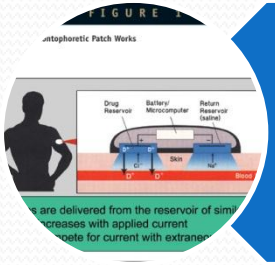
Preference of Dosage Forms

1. Oral
   - **Transdermal**
2. Pulmonary
   - Nasal
3. Injectable

Barriers to Transdermal Delivery of Polypeptides

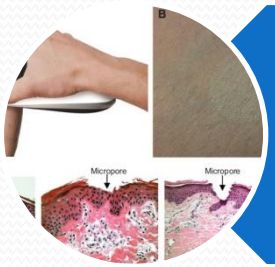
- Physicochemical issues
- MW greater than 500 is prohibitive
- Must be lipophilic in nature
- Generally high loss of Drug Substance

Transdermal Delivery of Polypeptides



Iontophoresis

Application of current to increase diffusion rate – limited success with polypeptides



RF Ablation

Application of radio waves to produce microchannels – shows promise for low dose polypeptides

Preference of Dosage Forms

1. Oral
   - Transdermal
2. **Pulmonary**
   - Nasal
3. Injectable

Advantages of Pulmonary Delivery of Peptides/Proteins

- The surface area of the lung is approximately 50 sq. meters - a large area for absorption
- Abundant blood supply
- Little enzymatic activity
- 30-50% bioavailability possible with polypeptides

Barriers to Pulmonary Delivery of Polypeptides

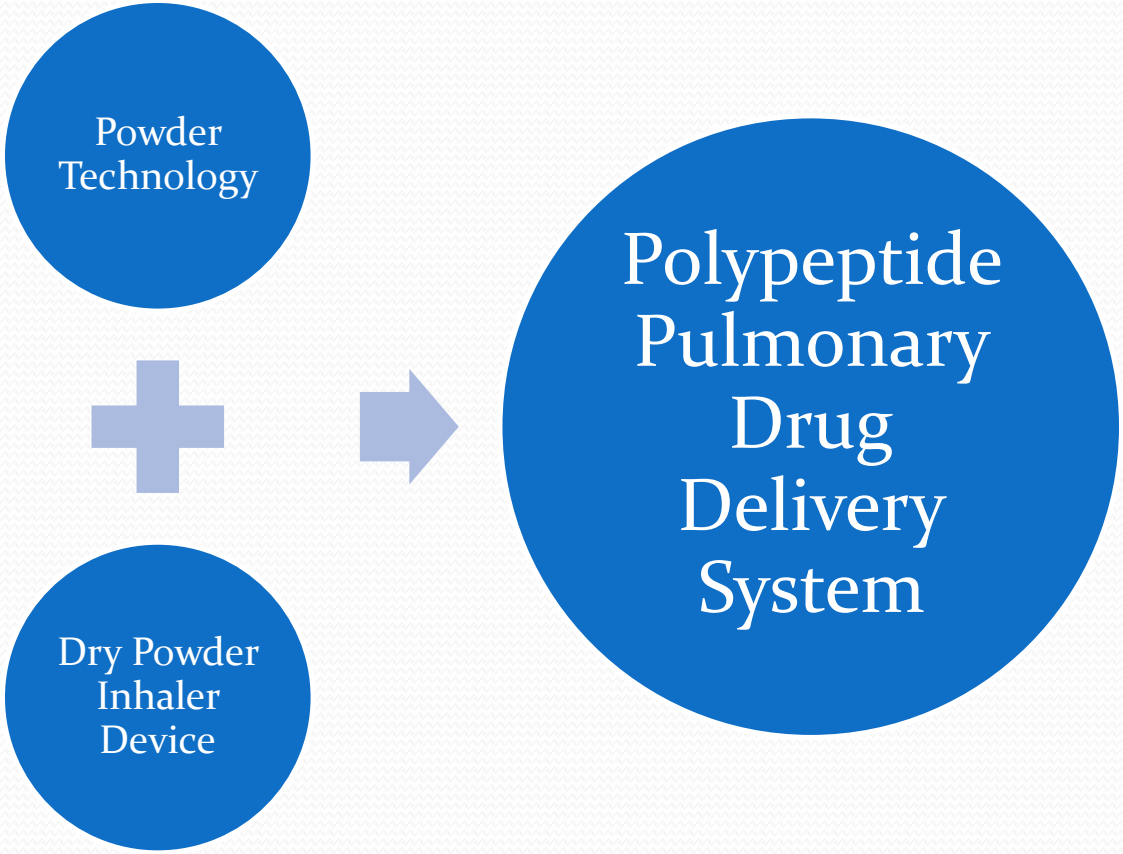
- Irritation
- Dose received depends on patient technique
- Patient health status
- Complex device /formulation necessary
- Disease state can alter performance

Pulmonary Delivery of Polypeptides

Nebulizers

Dry Powder Inhalers

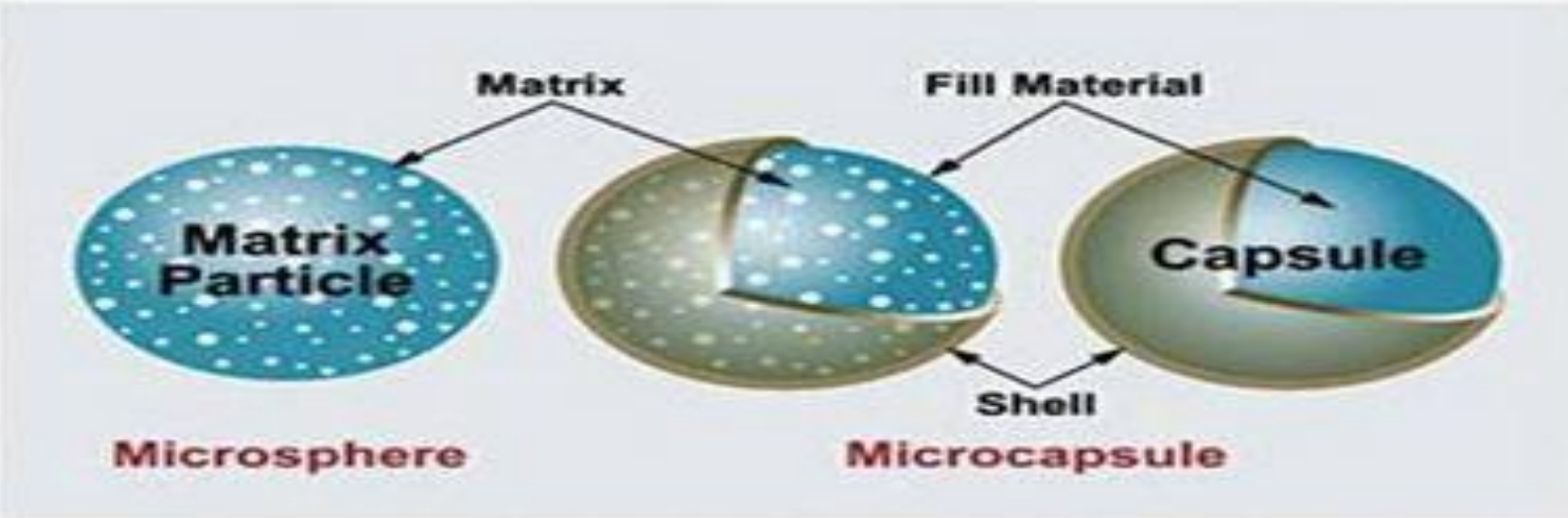
Dry Powder Inhalers



Description of Particles used in Drug Delivery Systems

- Microparticle – generally 1 -50 µM
- Nanoparticle – less than 1 µM
- Liposomes – micro or nanoparticles made of alternating lipid/aqueous layers
- Microspheres – homogeneous matrix
- Microcapsules – encapsulated cores
- Nanospheres – homogenous matrix
- Nanocapsules – encapsulated cores

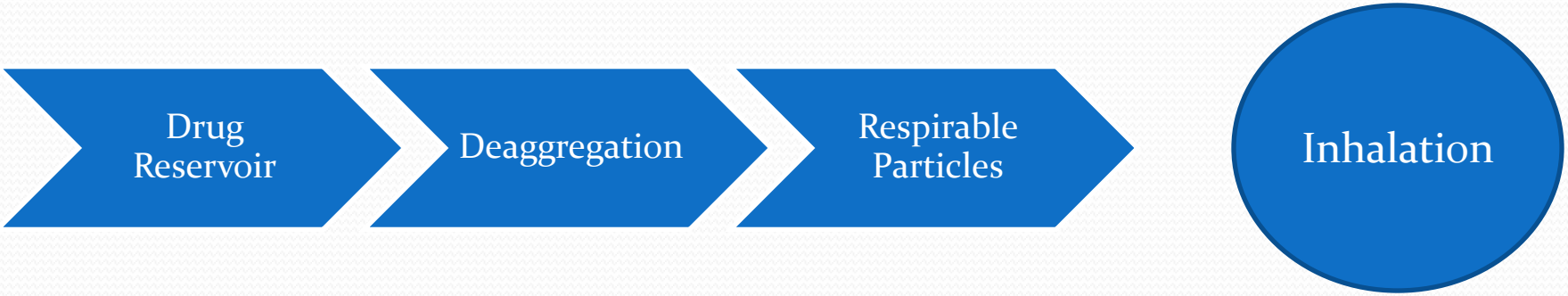
Microparticle Structure



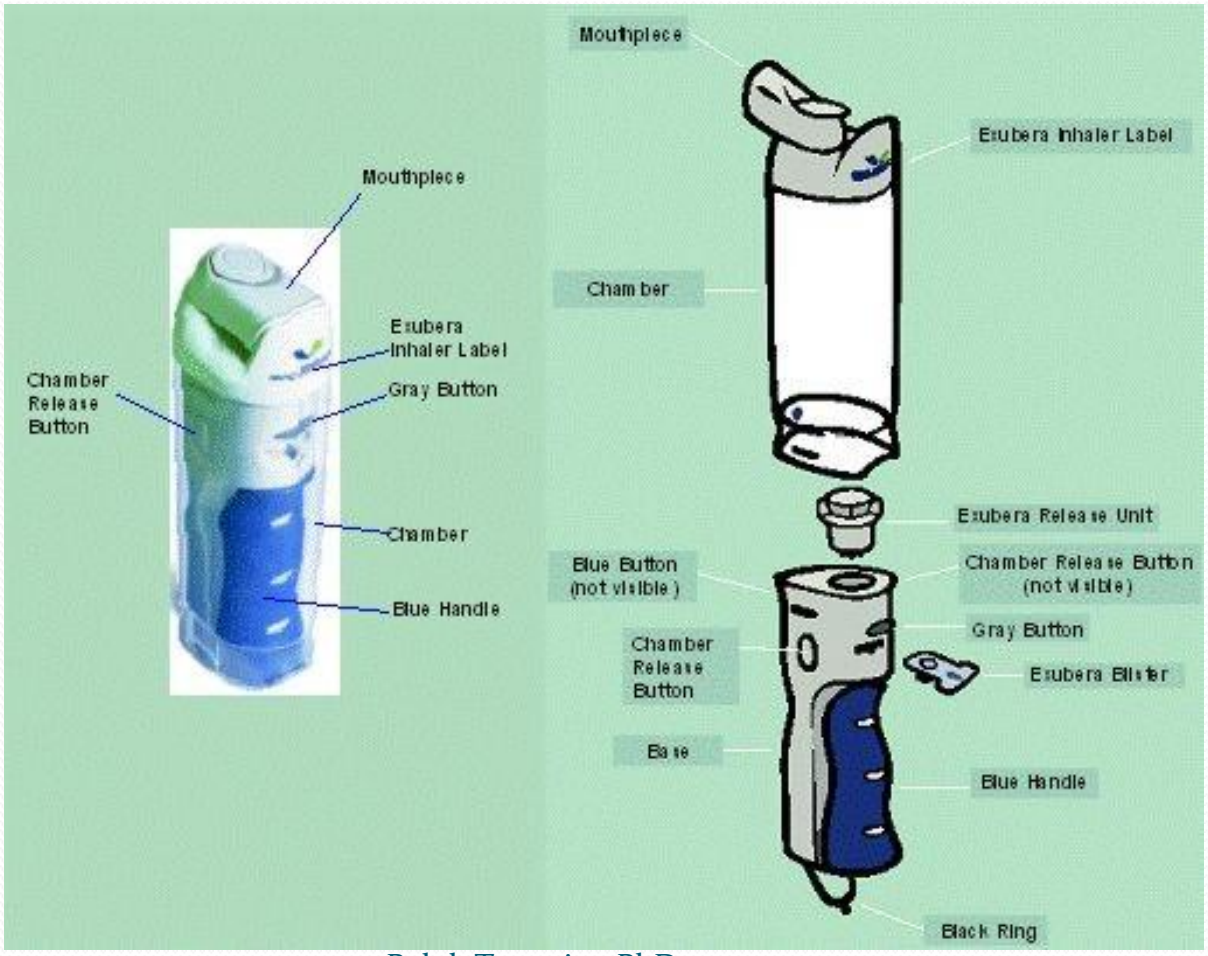
Dry Powder Inhalers

- Device of choice for polypeptides
  - No solvents
  - No propellants
- Components
  - Drug reservoir
  - Deaggregation mechanism
  - Expansion chamber
  - Mouthpiece
- Inhalation usually provides power for deaggregation
- Respirable particles in 5µM range required

Dry Powder Inhaler Function



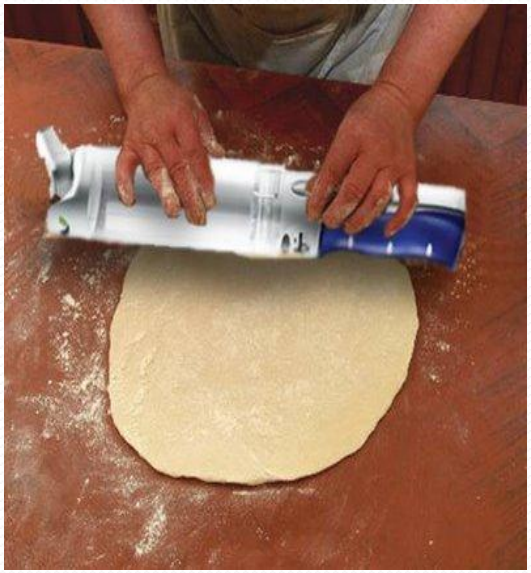
EXUBERA® – insulin dry powder inhaler

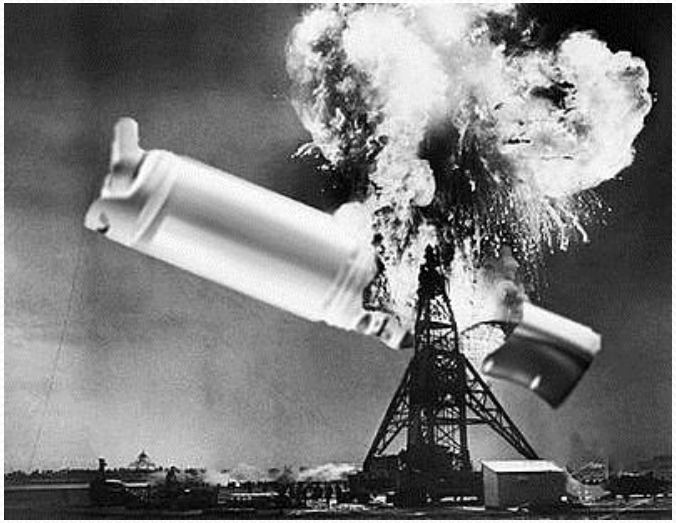


EXUBERA…in practice

Large expansion chamber

Led to…some bad press

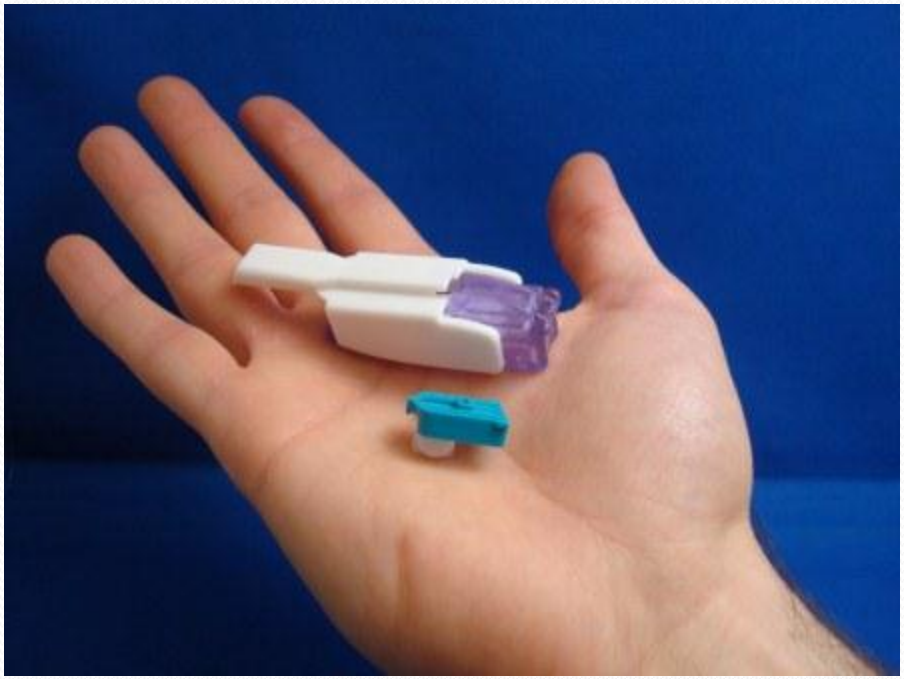




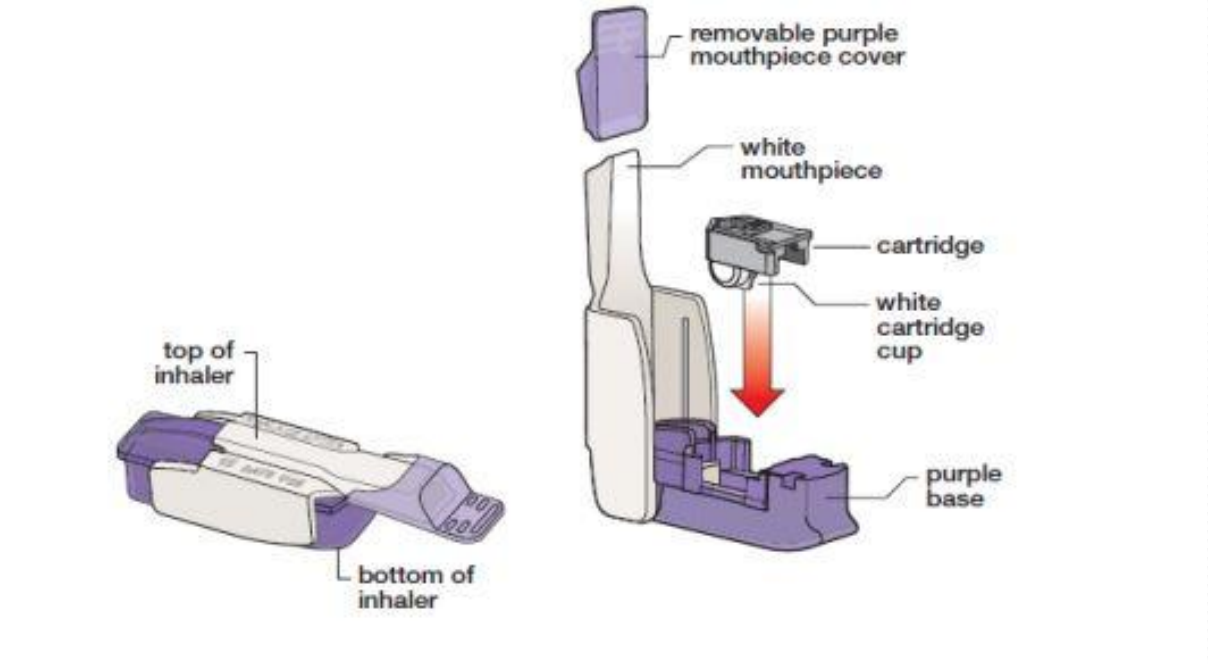
EXUBER failed

- 11 years of development – I year of sales
- 1 – 4 billion in sales predicted – 12 million realized
- What went wrong?
  - Physician cautiousness?
  - Poor marketing?
  - Lung cancer scare?
  - Unwieldy device ?
- From a technical standpoint – a significant achievement

AFREZZA® - inhaled insulin – approved June 2014

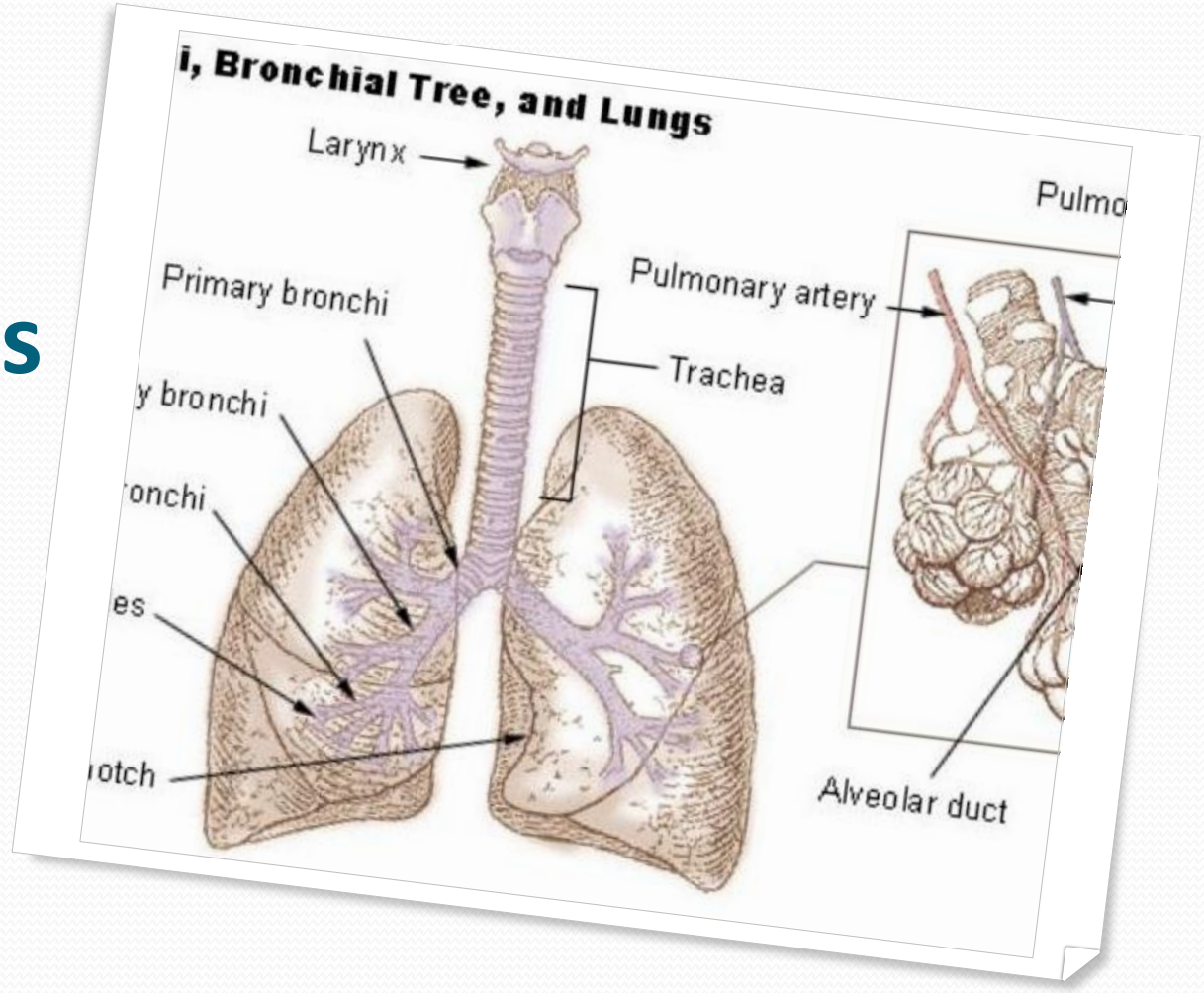


AFREZZA® - inhaled insulin



Pulmonary Delivery of Polypeptides

Still promising due to high bioavailability, and generally high patient acceptance



Preference of Dosage Forms

1. Oral
   - Transdermal
2. Pulmonary
   - **Nasal**
3. Injectable

Advantages Nasal Delivery for Polypeptides

- Convenient route
- Adequate blood supply
- Reasonable surface area for absorption

Barriers to Nasal Delivery of Polypeptides

- Peptide bioavailability about 1%
- Mucociliary clearance
- Disease states
- Irritation
- Mostly lipophilic molecules
- Limited volumes
- Stability

Some peptide intranasal products

Drugs	Molecular weight (Da)	Formulation	Commercial name	Company	FDA approval date
Desmopressin acetate	1183	Solution, Spray	Minirin®	Sanofi-Aventis	1978
Salmon calcitonin	3432	Solution, Spray	Miacalcin®	Novartis	1995
Buserelin acetate*	1239	Solution, Spray	Suprefact®	Sanofi-Aventis	-
Nafarelin acetate	1321	Solution, Spray	Synarel®	Pfizer	1990
Oxytocin	1007	Solution, Spray	Syntocinon®	Novartis	1995
Cyanocobalamine	1355	Gel	Nascobal®	Par Pharm Co.	1996
Cyanocobalamine	1355	Solution, Spray	Nascobal®	Par Pharm Co.	2005

* Approved in Canada.

Summary Intranasal Delivery of Polypeptides

- Still limited by molecular weight and bioavailability
- Numerous approved products – probably second to injections
- Promising for carefully selected drug substance

Preference of Dosage Forms

1. Oral
   - Transdermal
2. Pulmonary
   - Nasal
3. **Injectable**

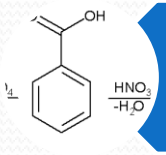
Injectable Drug Delivery of Polypeptides

- The simplest route with respect to polypeptides
- No absorption step needed for IV
- Usually 50% to 80% absorption from subcutaneous and intramuscular routes
- Stability addressed by processing methods such as lyophilization

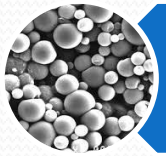
Barriers to Injectable Drug Delivery of Polypeptides

- Needle phobia
- Cost
- Sterility requirement

Injectable Drug Delivery of Polypeptides: Formulation Approaches

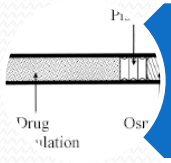


Chemical Modification



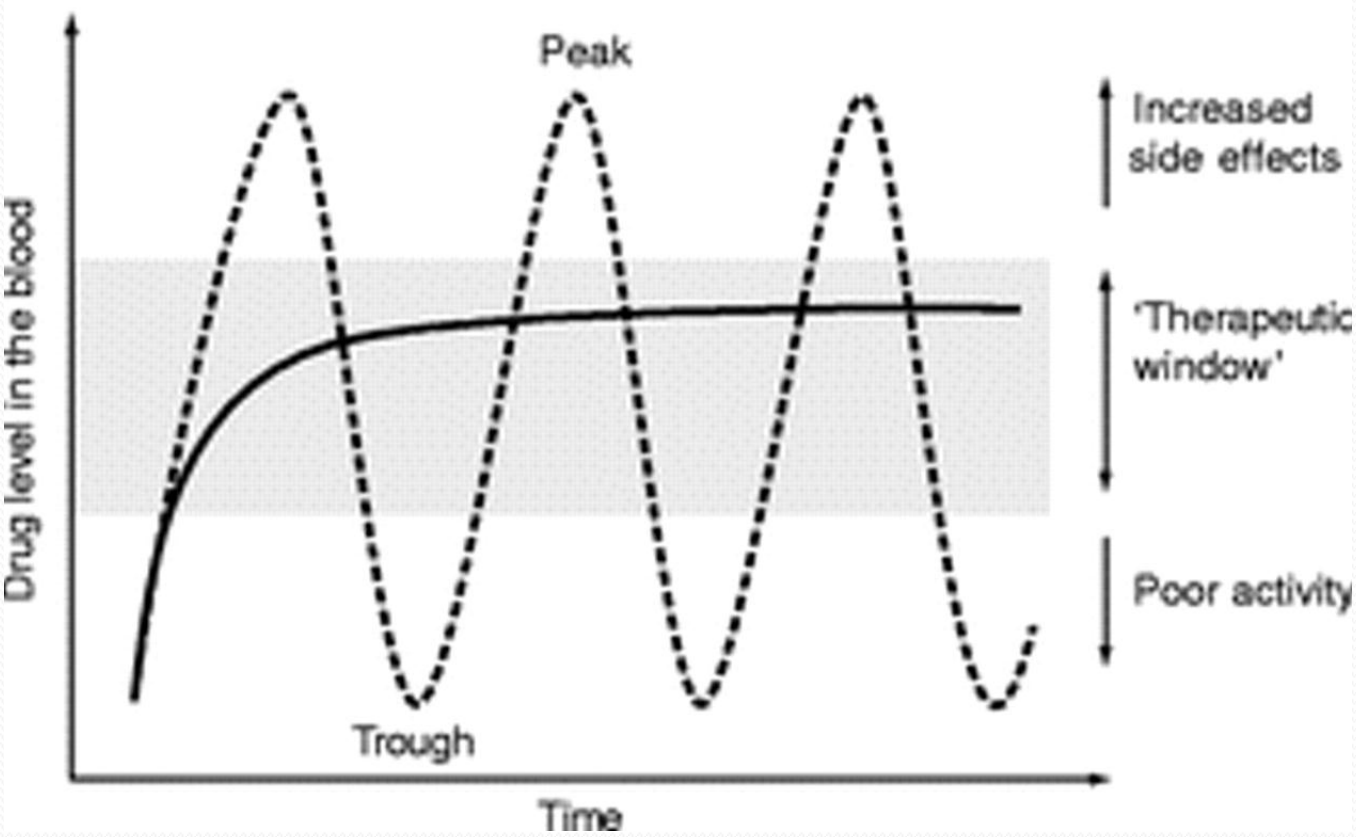
Biodegradable Microspheres

Biodegradable Implants



Non-Biodegradable Implants

Minimize Dosing Frequency/Reduce Adverse Effects



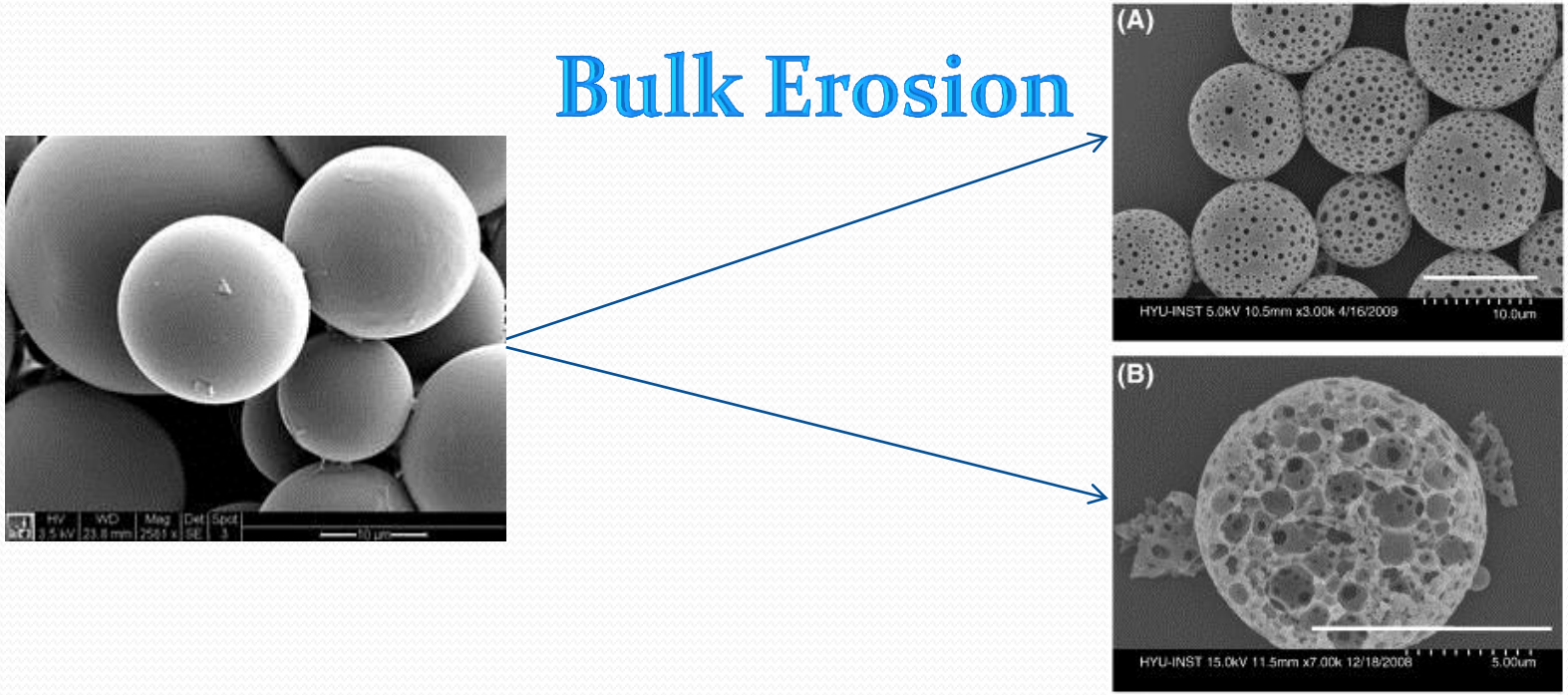
Chemical Modification

- Pegylation (interferon, erythropoietin
- Reduces immune response
- Reduces clearance rate
- 1 day to 1 week delivery
  - PEGAYSY®
  - MIRCERA®

Biodegradable Microspheres

- Poly(lactic-co-glycolic acid) – ester which degrades to lactic and glycolic acid
- Safe - used in resorbable sutures
- 1 – 6 months delivery possible
- Multiple products most notable LHRH analogs such as LUPRON® Depot

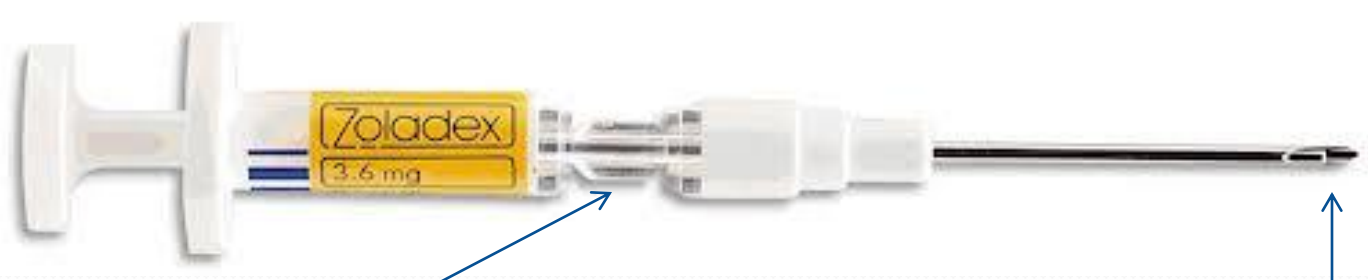
PLGA Microspheres



Biodegradable Implants

- Poly(lactic-co-glycolic acid) – ester which degrades to lactic and glycolic acid
- Longer durations 3 -6 month
- Minor surgery needed for implantation or trocar

ZOLADEX ®Implant



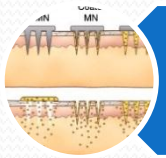
16 Gauge Trocar

Biodegradable Polymeric Rod Containing Drug Substance

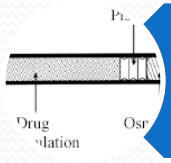
Injectable Drug Delivery of Polypeptides: Devices

Autoinjectors

Needle-Free



Microneedles



Non-Biodegradable Implants

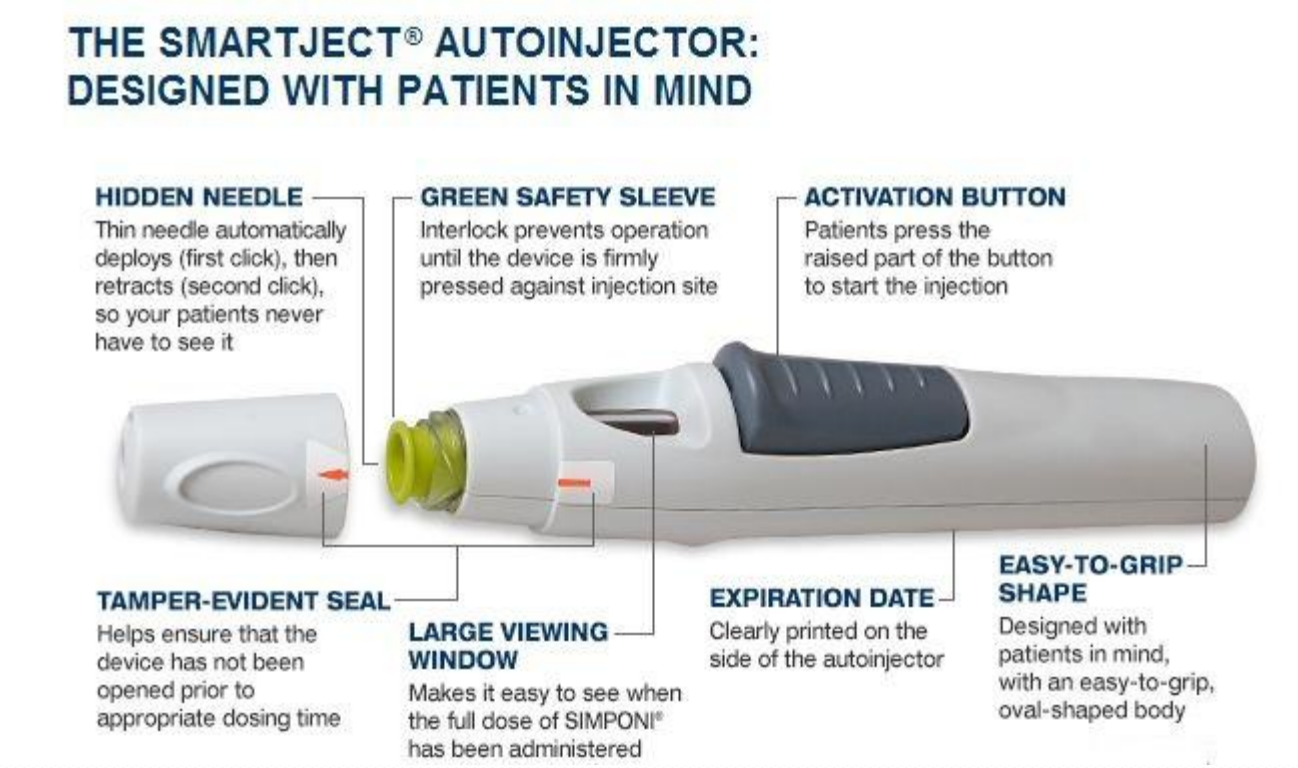
Autoinjectors

- Reduce needle phobia – maybe pain
- Some compatible with existing Prefilled Syringes Systems
- Single dose and multidose
- SIMPONI® SMARTJECT -

SMARTJECT

Single Dose

Disposable



Patient Never Sees Needle

Needle Free

- Pressurized nitrogen gas to force solution through skin
- Some bioavailability issues “wet spots” are common
- Needle free but not pain free
- Used for vaccines
- Sometimes bulky – portability would be a plus
  Concerns about sheer stress and protein stability

BIOJECTOR 2000®

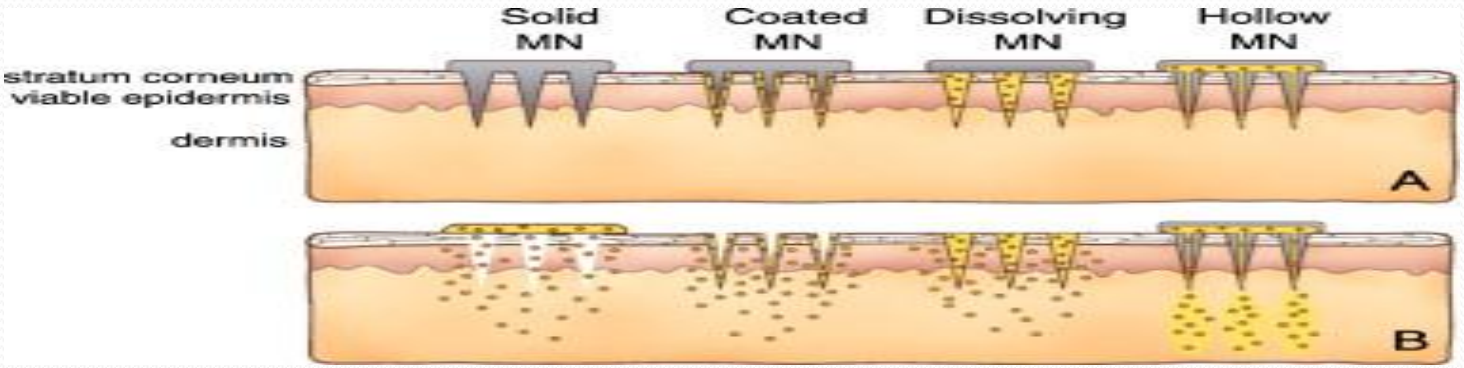
Needle-Free SC Delivery

Device

Nitrogen Cartridge

Drug Cartridge

Microneedles



- Injection into dermis for local and perhaps systemic delivery
- Vaccines polypeptides
- Little pain relative to injection
- Drug reservoir (volume)could be an issue
- Sterility
- Bioavailability of polypeptides could be an issue

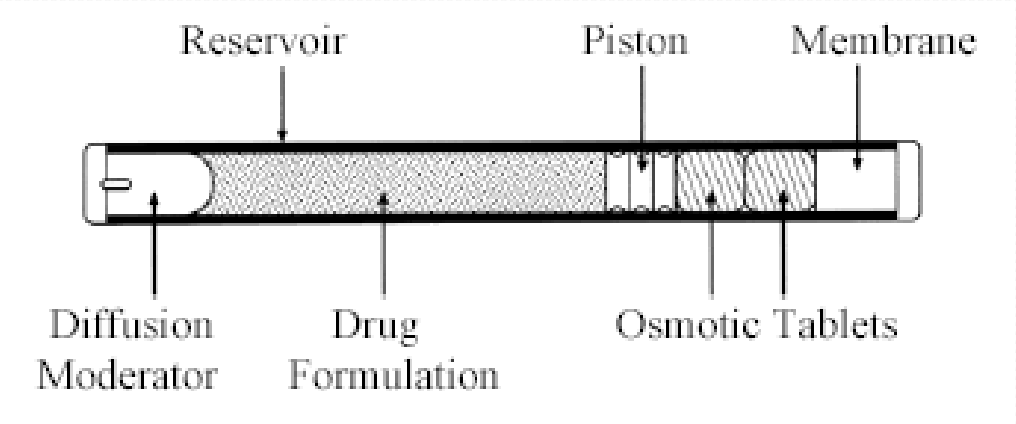
DEBIOJECT®

- Hollow
- 100 µL delivery
- 0.5 ml in less than 5 sec with 33 G needle
- Positives:
- Reduction of needle phobia and injection pain
- Portability

Non-Biodegradable Implants

- Implants which must be recovered
- 6 months to 5 years
- Ethylene vinyl acetate copolymer is common for matrix devices
- ALZET based on ALZA's OROS technology used for VIADUR®
- Inserted surgically or with trocar
- Manufacturing and stability issues reduce usefulness of non-biodegradable implants for polypeptides
- Although long duration, recovery procedure is not patient friendly

Viadur® Implant



Drug Release Driven by Osmotic Pump

Drug Delivery of Polypeptides – Some points to consider

Drug Delivery of Polypeptides – Points to consider

- Know you molecule and know your patient
- There is a multitude of biological barriers
- There has been little success with non-injectable Delivery systems for polypeptides greater than 5000 MW
- Meaningful oral absorption of peptides greater than 2000 MW may never happen
- Pulmonary and skin penetration technologies maybe something to watch
- Reduction of injection frequency and needles is always a good idea
- Survey field constantly and determine which technologies are market ready

GLG Q&A

Please submit your questions via the text box in the bottom-right corner of your window.

All questions will remain anonymous.

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