PharmacoLearn

MPH102T Drug Delivery System, M.Pharm Semester 1

Unit 6: Protein and Peptide Delivery

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6.1 Why proteins are a special delivery problem

Proteins and peptides are large, fragile and active in tiny amounts. Insulin (51 amino acids), growth hormone, erythropoietin, interferons and monoclonal antibodies are all proteins or peptides, and nearly all of them are still given by injection. This unit explains exactly which barriers force that, and what formulation science is doing about it.

6.2 Barriers for protein delivery

Physicochemical and stability barriers:

- **Size and polarity:** molecular weights from about 1,000 (small peptides) to 150,000 (antibodies) daltons. They are too large and too hydrophilic to cross lipid membranes by passive diffusion in useful amounts.
- **Chemical instability:** hydrolysis of peptide bonds, deamidation of asparagine and glutamine, oxidation of methionine and cysteine, and racemisation proceed in solution, faster at extremes of pH and temperature.
- **Physical instability:** proteins unfold (denaturation) at interfaces, on shaking and on heating, and unfolded molecules aggregate into inactive, sometimes immunogenic clumps. Adsorption onto glass, plastic and tubing silently removes drug from solution.
- **Enzymatic barriers:** pepsin and pancreatic proteases (trypsin, chymotrypsin, carboxypeptidases) in the gut, peptidases in every mucosal surface, blood and tissue (including the brush border aminopeptidases) dismantle peptides within minutes. Insulin given orally is digested like food protein.
- **Absorption and distribution barriers:** poor membrane permeation means oral bioavailability of most proteins is under 1 to 2 percent; after injection, small peptides are cleared rapidly by the kidney (glomerular filtration under about 30 to 60 kDa effective range), and the liver and reticuloendothelial system remove carriers and aggregates.
- **Immunogenicity:** aggregates, impurities and non human sequences can provoke antibodies that neutralise the drug or, worst case, cross react with the body's own protein; formulation and purity are therefore safety issues, not only potency issues.

6.3 Formulation of delivery systems for proteins and macromolecules

Stabilisation inside the formulation comes first: buffer at the pH of maximum stability, stabilisers such as sugars and polyols (trehalose, sucrose, mannitol) that protect during drying and storage, surfactants in small amount (polysorbates) that stop adsorption and interface damage, antioxidants and chelators where oxidation is the risk, and presentation as a lyophilised (freeze dried) powder when solution stability is too short, reconstituted before use.

Delivery strategies by route:

- **Parenteral depots and carriers (the working present):** biodegradable PLGA microspheres and in situ forming gels turn daily or weekly injections into monthly ones (leuprolide depot for prostate cancer and endometriosis is the landmark example); liposomes and nanoparticles protect the protein and alter

distribution; PEGylation, attaching polyethylene glycol chains, shields the protein from enzymes and kidney filtration and extends half life (pegfilgrastim, peginterferons); implants and osmotic mini pumps give steady input for potent peptides.

- **Pulmonary delivery:** the lung offers a huge thin surface; inhaled insulin reached the market (Exubera, later withdrawn for commercial and device reasons, then Afrezza) and proves both feasibility and the difficulty of patient acceptance.
- **Nasal delivery:** a small but real route for peptides that act centrally or systemically in small doses (desmopressin, calcitonin), limited by mucociliary clearance, enzymes and dose size.
- **Oral delivery (the research frontier):** enzyme inhibitors co formulated, permeation enhancers that open tight junctions reversibly, mucoadhesive and nanoparticle carriers that protect the cargo to the intestinal wall, and device based approaches (microneedle capsules that inject the gut wall from inside). One oral peptide success exists in a related small molecule like class: oral semaglutide uses an absorption enhancer (SNAC) to carry a peptide analogue across the stomach wall, the teaching proof that enhancer assisted oral peptide delivery can work commercially.
- **Transdermal and buccal attempts:** iontophoresis and microneedles bypass the skin barrier physically (see Unit 5); buccal films place the peptide against a friendlier mucosa (see Unit 3), but enzyme activity and low flux keep doses tiny.
- **Gene and cell based production approaches** (recombinant expression in the body, encapsulated cell implants that secrete the protein) sit at the edge of this subject; one line of awareness is enough here.

6.4 Evaluation of protein delivery systems

- **Identity, purity and potency:** electrophoresis (SDS PAGE), chromatography (size exclusion for aggregates, reverse phase for related impurities), mass spectrometry for identity, and a biological potency assay, because chemical content alone does not prove an active folded protein.
- **Aggregation and particle checks:** size exclusion chromatography, light scattering and subvisible particle counting; aggregates are tracked as a critical quality attribute throughout.
- **Delivery performance:** in vitro release from depots and carriers (with the caution that release media must not denature the protein being measured), encapsulation efficiency and loading, residual solvent in microspheres, syringeability of suspensions, and dose uniformity of inhalation and nasal devices.
- **Stability programme:** real time and accelerated studies watching potency, aggregation, moisture of lyophilised cakes and reconstitution time; cold chain behaviour (2 to 8 degrees Celsius typically, freezing is damaging for many proteins) is part of the product design, not an afterthought.
- **In vivo evaluation:** pharmacokinetics with immunoassays or LC MS that distinguish intact active protein, duration of action for depots, and immunogenicity monitoring (anti drug antibodies) in animal and clinical studies.

Barrier	Core problem	Main formulation responses
Gut enzymes	Peptide bonds hydrolysed in minutes	Injection routes, enzyme inhibitors, protective carriers
Size and polarity	No passive membrane crossing	Carriers, enhancers, physical methods, depot injection
Physical instability	Unfolding and aggregation	Stabilisers, lyophilisation, cold chain, gentle processing
Rapid clearance	Kidney filtration and proteolysis in blood	PEGylation, depot systems, albumin and Fc fusion designs
Immunogenicity	Antibodies against drug or aggregates	High purity, low aggregation, humanised sequences