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Stabilization Challenges and Formulation Strategies Associated with Oral Biologic Drug Delivery Systems☆

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ABSTRACT

Delivery of proteins to mucosal tissues of GI tract typically utilize formulations which protect against proteolysis and target the mucosal tissues. Using case studies from literature and the authors' own work, the in-process stability and solid state storage stability of biopharmaceuticals formulated in delivery systems designed for oral delivery to the GI tract will be reviewed. Among the range of delivery systems, biodegradable polymer systems for protection and controlled release of proteins have been the most studied; hence these systems will be covered in greater depth. These delivery systems include polymeric biodegradable microspheres or nanospheres that contain proteins or vaccines, which are designed to reduce the number of administrations/inoculations and the total protein dose required to achieve the desired biological effect. Specifically, this review will include a landscape survey of the systems that have been studied, the manufacturing processes involved, stability through the manufacturing process, key pharmaceutical formulation parameters that impact stability of the encased proteins, and storage stability of the encapsulated proteins in these delivery systems.

Contents

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1. Introduction and challenges with oral delivery route

Due to the rapid progress in biotechnology, the industry has produced a large number of therapeutic peptides and proteins on commercial scale. Over 130 biotechnologically derived drug products are approved by the US Food and Drug Administration (FDA) [1]. Most biopharmaceutical drug products (proteins, peptides, and vaccines) are administered parenterally because of their poor bioavailability from different alternate routes of administration, including the oral route. Poor intestinal absorption of these drugs, for example, is due to their susceptibility to acid and enzymatic hydrolysis, unfavorable physico-chemical properties including size, charge, and hydrophilicity. In addition to hydrolysis in the stomach and gastrointestinal (GI) tract, peptide and protein drugs targeting a local therapeutic effect in the colon [16] must also survive degradation via bacterial fermentation. Despite these challenges a number of alternate routes of administration for biologic drugs have been pursued with varying degrees of success. Some examples of these alternative routes that have advanced to human use are provided in Table 1. Alternate delivery routes can offer convenience/non-invasiveness, enhanced targeting to diseased tissues, controlled release rate, improved compliance, and can provide a game-changing commercial opportunity.

Table 1
Routes of administration and dosage forms developed for non-parenteral administration of biopharmaceuticals [77].

Administration route	Examples of Dosage forms/Drug delivery vehicles	Examples of biopharmaceuticals tested (C – clinical trials, A – approved product)
Oral	Pills Capsules Microspheres Hydrogels Nanoparticles Enteric coated tablets Enteric coated dry emulsions Liquid dropper	Calcitonin (C) Insulin (C) Exenatide (C) Octreotide (C) Rotavirus vaccine (A) Typhoid vaccine (A) Adenovirus vaccine (A) Anthrax vaccine Cholera vaccine (C) H5N1 Avian flu vaccine (C) Polio vaccine (A) Smallpox vaccine
Buccal	Mucoadhesive patches/films Liquid spray	Insulin (C) Interferon (C) Oxytocin
Sublingual	Tablets	Desmopressin (A)
Ocular	Eye drops Injections	VEGF-targeted Fab and IgG1 mAb (A)
Vaginal	Gels	LHRH (luteinizing hormone releasing hormone) analogue (C)
Rectal	Suppositories	
Cutaneous/Topical	Micro-needles Transdermal patches, creams, sprays, gels	Influenza virus (A) Parathyroid hormone (PTH) (C) Insulin (C) Testosterone (A)
Nasal	Aerosol sprays	Influenza vaccine (A) Salmon calcitonin (A)
Inhalable	Aerosol and dry powder sprays	Insulin (A,C) Dornase alfa (A)

Development of an effective oral delivery system for biologics requires a detailed understanding of the several barriers along the digestive tract (See Fig. 1), as well as the mechanisms involved in their absorption across targeted tissues. It is generally believed that the challenges to oral delivery of biopharmaceuticals are significant, and substantial opportunities remain to optimize delivery approaches, formulation components and processing conditions for each peptide and protein drug.

Obviously the most convenient route for the systemic delivery of pharmaceuticals is oral; however, attempts to deliver large molecular weight proteins and peptides orally have seen limited successes. Bioavailability via this route is poor for molecules of molecular mass greater than a couple hundred Daltons. In addition, proteins are susceptible to hydrolysis and modification at gastric pH levels and can be degraded by proteolytic enzymes in the small intestine. Various approaches currently under investigation include amino acid backbone modifications [2], conjugation of bacterial and viral transcytosis peptide sequences [3,4], formulation design, chemical modification, use of proteolytic inhibitors, and passive absorption enhancers; all have shown variable successes.

Parenteral delivery of proteins and peptides has been the method of choice for systemic delivery mainly for avoidance of biological barriers through which it is difficult for proteins to pass, and the ability to achieve pharmacologic levels of circulating protein over a relatively short period of time. In addition to parenteral administration, interest has increased in the area of local delivery of proteins through mucosal tissues of the buccal area [15], gut, sinus and lungs by both oral and inhalation delivery systems.[1] In these applications, proteins typically must be administered in formulations which protect against unwanted proteolysis and target the mucosal tissues. In recent years, there has been a rise in quick dissolving oral thin films in commercial application ranging from Listerine® breath freshener strips to analgesics, thus warrants some review coverage. There are already a number of excellent reviews on the biological barriers to oral delivery related to absorption mechanisms, molecular approaches to absorption enhancement, including comprehensive reviews of different oral delivery systems [5]. Using case studies from literature and from our own work on oral thin films, we will continue this special edition's theme on protein stability and focus on the manufacturing processes, the in-process stability and storage stability of biopharmaceuticals formulated in delivery systems designed for oral delivery to the gastro-intestinal (GI) tract. Among the range of delivery systems, biodegradable polymer systems for protection and controlled release of proteins have been the most studied; hence, we will review these systems in greater depth. These include polymeric biodegradable microspheres or nanospheres that contain proteins or vaccines, which are designed to minimize both administration frequency and biologically effective protein dosage. Specifically, this review will include a landscape survey of the systems that have been studied, the manufacturing processes involved, stability through the manufacturing process, key pharmaceutical formulation

[1] Examples of products in this area include Generex Biotechnology's insulin buccal spray Oral-lyn™ (in Phase III clinical trials) and the oral thin film products of MonoSol Rx®, which include both the marketed small molecule products Zuplenz® and Suboxone® as well as several complex-molecule-containing oral films in development, such as insulin that is in clinical trials.