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Commercial challenges and emerging trends in oral delivery of peptide and protein drugs: A review

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ABSTRACT

The discovery of insulin in 1922 marked the beginning of research and development to improve the means of delivering protein therapeutics to patients. From that period forward, investigators have contemplated every possible route of delivery. Their research efforts have followed two basic pathways: one path has focused on non-invasive means of delivering proteins to the body; and the second path has been primarily aimed at increasing the biological half-life of the therapeutic molecules. Thus far, the commercial successes of protein delivery by the nasal, oral and pulmonary routes have been more opportunistic rather than the application of platform technologies applicable to every protein or peptide. In spite of significant efforts in academic and commercial laboratories, major breakthroughs in oral peptide and protein formulation have not been achieved. The major barriers to developing oral formulations for peptides and proteins include poor intrinsic permeability, luminal and cellular enzymatic degradation, rapid clearance, and chemical and conformational stability. The success achieved by Sandoz with cyclosporine formulations remains one clear example of what can be achieved, although it is likely that effective oral formulations for peptides and proteins will remain highly compound specific. However, recently novel oral delivery systems for 5-CNAC, formulated with the peptide salmon calcitonin, is in phase III clinical trials for the treatment of osteoporosis or osteoarthritis and could become the first marketed oral peptide. Thus present reviews focus on key findings and implications from studies undertaken till today for oral formulation of protein and peptides.

Keywords: Protein& peptides, oral delivery.

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INTRODUCTION

Better medical treatments do not always require a stronger medicine. The effectiveness of chemical agents depends on the method of administration, so treatments can often be improved by finding optimal drug formulations or delivery systems [1]. The tremendous growth in biotechnology and the completion of human genome sequencing have made large-scale production of therapeutic proteins a reality [2]. These macromolecules perform the function of their natural blueprints in soliciting desired responses from the body [3]. Unfortunately, proteins possess unique physical and chemical properties which create difficulties in formulation and delivery [4].

Peptides and proteins have become the drugs of choice for the treatment of numerous diseases as a result of their incredible selectivity and their ability to provide effective and potent action [5]. In general, they cause fewer side effects and have great potential to cure diseases, rather than merely treat their symptoms. A wide variety of peptide and protein drugs is now produced on a commercial scale as a result of advances in the biotechnology field [5–7]. The past decade saw an increased interest in formulating and delivering biological drugs for a range of diseases with significant unmet medical need. Unlike conventional small molecular drugs, clinical development of these types of drug will not be possible without some sort of sophisticated pharmaceutical technology. Administering drugs orally is by far the most widely used route of administration, although it is generally not feasible for peptide and protein drugs. The main reasons for the low oral bioavailability of biologicals are presystemic enzymatic degradation and poor penetration of the intestinal membrane [8,9]. Much has been learned in the past few decades about macromolecular drug absorption from the gastrointestinal (GI) tract, including the barriers that restrict GI absorption. Various strategies have been pursued to overcome such barriers and to develop safe and effective oral delivery systems for proteins [7–9]. The oral route for peptide and protein administration continues to present a significant challenge and represents a focus for many pharmaceutical researchers. However, we believe that only further research into delivery systems can make it possible for the oral route to represent a viable route of administration for peptide and protein drugs, improving convenience for, and compliance from patients who would benefit from these drugs.

Intestinal transport and issues in the oral delivery system of protein and peptides

Most therapeutic peptides and proteins are hydrophilic, with LogP values <0. Thus, they would not be expected to follow the transcellular route of absorption through passive diffusion [10]. The dimensions of the paracellular space lie between 10 and 30–50A° , and the paracellular route is not an option for macromolecular absorption because it is restricted to relatively small hydrophilic molecules that can fit in these spaces [11]. In the case of one of the most widely prescribed protein drugs, insulin, evidence of a paracellular route of absorption was not shown by either morphocytochemical or biochemical analyses [12]. It was demonstrated that insulin adsorbed to the apical membrane and was internalized by certain types of endocytosis [13]. Some proteins have been shown to be actively transported across the

epithelial lining of the small intestine in membrane-bound vesicles after binding to cell-surface receptors or binding sites [14]. However, only a tiny fraction is released at the basolateral membrane and secreted into the interstitial space in an intact form. Although, interestingly, there is evidence that significant quantities of peptides and proteins (enough to demonstrate a pharmacologic effect) can be absorbed if they are protected from proteolytic enzymes in the GI tract [15,16]. To increase the oral bioavailability of biologicals, a strategy involving permeation enhancement or protease inhibitors as additives could be effective, and could provide higher reproducible bioavailability. Although such approaches can be very successful in the laboratory [7,17], they still represent a challenge for widespread acceptance by clinicians and regulatory bodies. The use of enzyme inhibitors in long-term therapy remains questionable because of possible absorption of unwanted proteins, disturbance of the digestion of nutritive proteins and stimulation of protease secretion as a result of feedback regulation [7]. A strategy for modulating tight-junction permeability to increase paracellular transport of drug molecules has been studied [18,19]. In fact, the Zonula Occludens toxin [19,20], chitosan [21], thiolated polymers [22] and Pz-peptide [23] all demonstrate a powerful capacity to increase macromolecular drug absorption. However, potentially, such a strategy is not without safety concerns. Once tight junctions have been opened, transport is enhanced not only for drugs, but also for potentially toxic or unwanted molecules present in the GI tract [17,18]. Because many biologicals are used for the treatment of chronic conditions, the long-term implications of unwanted protein absorption could represent a source of concern.

Strategies for delivery protein and peptides drugs

a. Modifying the physicochemical nature of macromolecule.eg prodrugs [24,25] and analogs [26] of biologicals might protect them from degradation by proteases and other enzymes present in the GI tract.

b. Adding novel functionality to macromolecules For example, by attaching a drug to a dipeptide that is recognized by a peptide-influx transporter, its oral absorption can be increased [27]. Efflux transporters such as P-gp might contribute significantly to the poor bioavailability of certain drugs, including peptides [28].

c. Using particulate delivery carrier systems So far, polymeric drug delivery systems based on hydrogels, nanoparticles, microspheres, and lipid-based drug delivery systems (e.g. microemulsions, liposomes, and solid lipid nanoparticles) have been developed and employed for oral macromolecular drug delivery[29]

Table.1 Various pharmaceutical approaches and their outcomes

Approaches	Outcomes
Chemical modification a. Amino acid modification b. Hydrophobization Use of enzyme inhibitor	Improve enzyme stability Improve membrane penetration Resistant to degradation by enzymes
Formulation vehicles	
Emulsions	Protect drug from acid and luminal proteases in GIT.
Microspheres	Restrict release in favorite area of stomach
Nanoparticles	Increases intestinal epithelial absorption
Liposomes	Achieve site specific delivery

PROTEINS & PEPTIDES: DEPENDENT ON ADVANCES IN DRUG DELIVERY

Efforts toward the development of oral formulations of protein peptide drugs have been exaggerated in the recent past, as a corollary of the increased number of potential therapeutic proteins and peptides that are being developed to combat human diseases. However, delivering therapeutically active protein and peptide by the oral route has been a challenge and has often been considered an unattainable goal due to their poor oral bioavailability. The problem associated with oral delivery of proteins and peptides can be overcome by incorporating novel technologies into the delivery systems. This results in the raised membrane permeability of macromolecules necessary to attain higher oral bioavailability, thus making this method acceptable in clinical applications. This chapter describes various transport mechanisms and anatomical and physicochemical barriers to absorption of proteins and peptides in the gastrointestinal track. Various approaches that can be adapted to improve oral delivery of proteins and peptides and techniques to study oral absorption are also described in this chapter

Macromolecular conjugation

Polypeptides can be conjugated to a macromolecular carrier, such as a polymer or a protein. The advantage of using conjugation technology for improving peptide GI absorption is that it will change only the molecular properties of the drug, not the function of epithelial cells, and might therefore avoid some of the side effects observed in using penetration enhancers. Amphiphilic polymers, such as alkylated polyethylene glycol derivatives, have been developed by NOBEX [30] their insulin oral delivery system, co-developed with GlaxoSmithKline [31], is in mid-Phase II clinical trials and preliminary reports are promising.

Encapsulation

Peptide encapsulation technology in particulate carriers has been developed extensively over the past few years. As a result of their stability in the GI tract, solid microparticles or nanoparticles appear more favorable than liposomes for oral delivery, and two types of particle, chitosan [32] and hydrogels [33], have recently drawn much attention. These particles appear to be effective for oral vaccine delivery where the particles are likely to be absorbed at the area of Peyer's patches in the GI tract, and subsequently targeted to the immune system [32]. However, in general drug absorption, more work needs to be done regarding the efficiency and mechanism of either transcellular or paracellular transport in the GI epithelium and regarding the systemic release of drugs following absorption.

Oral nanoscale carriers

In general, nanoscale dimensions favour transport of particles across the mucosal epithelium. Desai et al. demonstrated that 100 nm poly(lactic-co-glycolic acid) (PLGA) particles diffused throughout the submucosal layers, whereas 10 mm particles were predominantly localized on the epithelial lining of the tissues [34]. Taken together, nanoscale carriers composed of biocompatible polymers are thought to be promising for the development of an oral delivery system for macromolecules. Representative nanoscale oral polymer carriers employed for oral peptide and protein drug delivery are shown in Table 2. Indeed, these nanocarriers show pharmacological effects of the incorporated biologicals following oral administration in vivo. The potential of chitosan nanoparticles for oral peptide administration has been recently reported by several researchers, as shown in Table 2. Insulin-loaded chitosan nanoparticles administered orally to diabetic rats reduced their glucose levels to a normal range for more than several hours [35,36].

Oral Colon-Specific Drug Delivery of Protein and Peptide Drugs(emergind tremmds)

An interesting approach is oral insulin delivery to the colon by using a coating of copolymers cross-linked with azoaromatic groups to form an impervious film that protects orally administered insulin from digestion in the stomach as well as the small intestine. In the large intestine, however, the indigenous microflora reduce the azo bonds, break the cross-links, and degrade the polymer film, thereby releasing the drug into the lumen of the colon for absorption[42,43]. A covalent functionality susceptible to cleavage by bacterial action is the azoaromatic group $R\text{-}C_6H_4\text{-}N{=}N\text{-}C_6H_4\text{-}R'$, which can be cleaved to $R\text{-}C_6H_4\text{-}NH_2 + R'\text{-}C_6H_4\text{-}NH_2$. One of the earliest works in this area was done by [44] who coated insulin with copolymers of styrene and hydroxy-ethylmethacrylate crosslinked with azo-bonds. Kopecek and colleagues[45,46,47] have worked on a biocompatible hydrogel system for colon targeting of drugs and peptides. One of their systems, for example, is based on the co-polymerization of N,N′-dimethylacrylamide with tertiary butyl acrylamide, acrylic acid, and crosslinking agents that contain aromatic azo-bonds[47]. [48] synthesized biodegradable pH-sensitive hydrogels with enzymatic degradable azoaromatic cross-links for colon-specific peptide and protein

delivery. The hydrogels contain an acidic co-monomer that ionizes in a high-pH environment and an azo-aromatic crosslink degradable by enzymes produced by the microbial flora of the colon. In the stomach, the gels have a slow equilibrium degree of swelling, and the drug is protected against the low-pH environment. The degree of swelling increases as the hydrogel passes down the GI tract to a higher pH environment. In the colon, the hydrogel reaches a degree of swelling that makes the cross-links accessible to azo-reductase activity (produced by colonic bacteria), and consequently the matrix degrades and the drug is released.

Oral nanoparticle (NP) drug carrier for protein and peptides

Carrier	Drug	Size (nm)	Animal	Outcome	Ref.
Poly(isobutylcyanoacrylate) NP	Insulin	220	STZ-induced diabetic rat	Long-lasting strong hypoglycemic response	[37]
Chitosan NP	Insulin	250–400	Alloxan-induced diabetic rat	Pharmacological availabilityb was 14.9%	[35]
Chitosan NP	Insulin	269, 339	STZ-induced diabetic rat	Pharmacological availabilityb was 3.2–5.1%	[36]
Chitosan-coated lipid NP	sCT	537.0	Rat	Long-lasting hypocalcemic response	[38]
Chitosan-coated PLGA NP	Elcatonin	650	Rat	Long-lasting hypocalcemic response	[39]
Nanocubicle	Insulin	220	STZ-induced diabetic rat	Strong hypoglycemic effect	[40]
Poly(N-isopropyl acrylamide) NP	sCT	148–895	Rat	Hypocalcemic response	[41]

[a]Abbreviations: PLGA, poly(lactic-co-glycolic acid); sCT, salmon calcitonin; STZ, streptozotocin.
[b]Pharmacological availability of peroral chitosan-insulin nanoparticles was determined based on the extent of hypoglycemic response relative to subcutaneous [35] or peritoneal [36]
insulin injection

Colonic delivery of insulin (colon rectal)

The discovery of insulin rapidly led to its clinical application for treating insulin dependent diabetes mellitus (IDDM). The therapeutic impact of insulin on the treatment of IDDM is dramatic. Patients suffering from this disease are able to control their blood glucose to a point where they can lead normal lives. The need to deliver the drug by injection is acceptable when compared with the consequences of not taking insulin. Current therapy consists of once or twice daily injections of insulin, including mixed intermediate or rapid-acting insulins [49]. Even so it is recognized that this therapy is not a complete solution as, for example, with aging, a variety of conditions become prevalent in diabetic patients. The most common of these are retinopathy, nephropathy, neuropathy and cardiovascular disease [50]. These conditions are a consequence of incomplete control of blood glucose levels leading to long-term adverse side

effects [51,52]. Recent clinical studies have shown that careful monitoring of blood glucose coupled with intensive insulin administration can lead to a significant reduction in these side effects [49]. To be successful oral insulin at the very least must provide therapeutic equivalency to the current therapies but ideally would provide the ability to tightly control glucose levels. To achieve this, control of insulin administration is key to both achieving the correct acute hypoglycemic response and reeducate chronic morbidity associated with the disease. Atchison et al. [53], studied the colonic absorption of radiolabel led insulin using non-everted sacs of rat colon. The percentage of intraluminal insulin degradation and the transport of insulin into the surrounding media was determined. They showed that transepithelial flux of insulin was consistently less than 0.3% of the dose. In addition, significant degradation of insulin (64%) was found within 15 min of exposure. Given the difficulty in predicting when an insulin dose would reach the colon and be transported across the epithelium it is difficult to imagine an oral dosage form reaching the market soon. Nevertheless, activity in this tield is enormous. More practical approaches to oral delivery may result in a diabetic patient taking fewer injections and thus lead to an improved quality of life rather than complete respite from the needle.

Delivery of calcitonin

The rationale for -considering oral delivery of peptides for therapeutic purposes is based on patient compliance. In the case of diabetes, the disease characteristics and the consequences of not taking insulin force the patient into accepting the injectable formulations. In contrast to this, peptides indicated for prophylactic treatment of a non-terminal disease are poorly tolerated by the patients because of the need for injections to dose the drug. This is well illustrated by calcitonin. Historically, calcitonin has had a relatively narrow usage in Paget's disease and control of hypercalceamia associated with cancers. both treated with injectable formulations. Although it has been recognized for many years that it is effective in retarding the progress of osteoporosis, current formulations limit the use of calcitonin in this indication. In responding to market needs many delivery routes have been considered. Nasal delivery has had some success showing therapeutically significant endpoints whilst avoiding injectable administration. However it is considered that ultimately an orally administered formulation will be the optimal solution. The therapeutic regimen for calcitonin in treating osteoporosis differs markedly from the treatment of IDDM with insulin. Calcitonin has a large therapeutic window. In the treatment of osteoporosis. Calcitonin is influencing the outcome of a long onset disease by down-regulating osteoclast activity. There is no requirement for precise dosing either regarding the amount absorbed or the timing of the administration. The requirement is that a therapeutic dose is delivered in the order of once a day. This therapeutic profile greatly simplifies the dosing requirements and makes calcitonin a particularly attractive peptide fog GI tract delivery. [54] used direct administration of human calcitonin into a colonic loop in anaesthetized rats to examine the bioavailability of human calcitonin. This was compared to the pharmacodynamic effect. detectable in normal juvenile animals, of a reduction in plasma calcium levels in response to human calcitonin. They demonstrated the bioavailability achieved after intracolonic dosing of three different doses compared to an i.v. dose. These were: 0.5% at 5.0 mg kg ' , 0.9% at I .O mg kg- ' and 0.2% at 0. I mg kg '. In addition, intracolonically

administered human calcitonin at doses of 0. I-5.0 mg kg -' resulted in a dose-dependent reduction in plasma calcium levels. These doses achieved reductions in plasma calcium levels of 12?6 to 382.5%. The reference i.v. dose of 1.25 kg kg ' achieved a calcium reduction of 29.24%. Moreover. Immunohistochemistry showed that human calcitonin transport across the rat colon was rapid and a significant amount was via a transcellular pathway. In a subsequent report, [55] studied the influence of eyuimolar monoolein/sodium taurocholate enhancer formulations on the absorption of human calcitonin and two markers of intestinal permeability, HRP and polyethylene glyco], MWt 4000 (PEG 4000). Human calcitonin, HRP and PEG 4000 were all absorbed across the colonic mucosa to a limited extent. The use of a 40 mM monoolein/40 mM sodium taurocholate mixed micellar formulation significantly ($p < 0.001$) enhanced (9.0t I.O-fold) the absorption of all three molecules with no acute damage to the mucosal tissue as judged after light microscopy. At concentrations of 20 mM and below, the monooleini sodium taurocholate formulation did not enhance the absorption of human calcitonin. HRP or PEG 4000. HRP immunohistochemistry showed an intracellular localisation suggesting that a transcellular pathway was involved in absorption across the epithelium. The increased absorption of human calcitonin in the presence of the 40 mM enhancer formulation was able to elicit a maximal hypocalcaemic response. Whereas no significant effect was observed in the absence of the enhancer. The authors concluded that the absorption enhancer used in this study can increase intestinal absorption of a range of molecules without causing major tissue damage, albeit after acute treatment. These formulations may offer advantages as they enable pharmacodynamic responses to be elicited from reduced doses of therapeutic peptides and proteins. It is important to understand the relevance of these results to the potential pharmacokinetic and pharmacodynamic effects after dosing to the unligated colon of conscious man Fukunaga et al. [56] showed that liposomally entrapped salmon calcitonin produced a hypocalcaemic effect in rats when dosed orally, but did not determine the mechanism or intestinal location of the absorption.

Commercial challenges

The problems facing oral delivery of peptides and proteins have been approached from many different angles, several of which have claimed that an increase in GI absorption of peptides and proteins can be readily achieved. One might, therefore, ask why none of the technologies has yet been fully developed into an oral dosage form for peptide and protein drugs? The answer is that there are many other criteria that must be fulfilled to bring an oral peptide or protein drug to the market. For example, bioavailability is very low for most oral protein delivery systems. This might be acceptable for peptide drugs that are both cheap and safe, such as the oral dosage form for desmopressin, but low bioavailability implies a large variation in absorption and a high manufacturing cost, which are both unacceptable for the development of most peptide and protein drugs.

Even if a dosage form is developed to produce a reasonable bioavailability, reproducibility is another potential problem. For drugs such as insulin that have a relatively narrow therapeutic window, the effects on GI absorption of age, genomic factors,

pathophysiological conditions and other individual variations must be carefully investigated. With some of the oral delivery technologies, an accurate prediction of bioavailability might prove to be very difficult. Finally, most peptide and protein drugs require chronic administration and hence the effects of long-term oral administration of absorption carriers on both the GI and systemic physiology must also be carefully evaluated.

TOXICITY AND SAFETY OF PROTEIN THERAPEUTICS:

The quality, safety and efficacy of biotechnology products for therapeutic use are intricately linked, far more so than for conventional medicinal products, leading to the need for increased communication between those responsible for ensuring product quality and those responsible for non-clinical safety testing. Safety issues include microbiological safety (due to the use of biological materials either during the manufacturing process or as an integral part of the products), pharmacological/ biological toxicity (due to excessive primary pharmacology or undesirable secondary pharmacology), immunogenicity and potential tumourigenicity (for example, for growth factors, immunosuppressive monoclonal antibodies and cell therapy products). Genotoxicity and intrinsic chemical toxicity are less of a problem for biotechnology Products [57].

Immunogenicity:

Immunogenicity is one of the major Concerns in the development and application of biotherapeutics. The patients can mount sustained Immune responses to protein therapeutics with the production of neutralizine antibodies that can compromise efficacy or safety of this drugs[58].The Immunogenicity of protein drugs can be ascribed to a few Immunodominant helper T lymphocyte epitopes , and that reducing the MHC binding affinity of these HTL epitopes contained within these proteins can generate drugs with lower Immunogenicity[59] Recently method for Investigation of the Immunogenicity of a protein drugs has been developed with the help of Equilibrium dialysis and liquid chromatography/ tandin mass spectroscopy.

Key points to consider before commercial development of protein delivery methods

Key point	Considerations
Manufacturing	Costs of manufacturing process, scalability, yields
Protein quality	Effect of processing and delivery on protein
Bioavailability	Fraction of total drug delivered to circulation
Safety/toxicity	Impact of delivery method on clinical toxicology of the protein and the site of administration

Pharmaceutical and biotechnological industries

New formulations may be patentable and can therefore extend a drug's life cycle. For these reasons, pharmaceutical and biotechnology companies are researching and testing new delivery methods for protein drugs, according to Market Research. Some companies on the

cutting edge of protein and peptide drug delivery include American Peptide, SurModics Pharmaceuticals (formerly Brookwood Pharmaceuticals), Emisphere, PolyPeptide, and 3M Drug Delivery Systems. Emisphere's core business strategy is to use its proprietary Eligen® Technology to develop novel oral forms of injectable drugs or poorly absorbed compounds. The broadly applicable Eligen® Technology and Emisphere's current product candidates in the pipeline represent the foundation of the company's value proposition and create significant opportunities for growth. Emisphere's pipeline includes product candidates that have reached clinical development as well as a variety of preclinical research and development programs. Emisphere is currently active in the area of peptide delivery through partnerships with Novartis for the oral delivery of salmon calcitonin and parathyroid hormone, and with Novo Nordisk for delivery of its proprietary GLP-1 analogs."An Eligen® carrier is co-formulated with the molecule of interest to form a reversible drug/carrier complex. After oral administration in tablet form, the complex is transported across the gastric mucosal membrane by the action of the carrier in transiently altering gastric epithelial permeability. Eligen® carriers also protect molecules from degradation in the GIT in the interval before absorption occurs. This is a most important feature where proteins and peptides are concerned, says Dr. Riley. Several Eligen® formulations are in late development. A vitamin B12 formulation is expected to be marketed in 2011, and the Novartis Eligen®/salmon calcitonin products for osteoporosis and osteoarthritis are currently in late Phase III testing in approximately 6,000 patients. These products are expected to reach the market in approximately 2012.[60]

REGULATORY CONSIDERATIONS FOR ORAL PROTEIN DELIVERY

Preclinical and toxicological studies must be performed in accordance with guidelines set by the FDA to eliminate formulations that are too toxic for human or animal use and to indicate whether an oral DDS, for example, biodegradable nanoparticles or microspheres containing protein drugs are effective and safe. To gain FDA approval for any oral DDS formulation, it is necessary to consider the presence of residual solvents and polymers that might remain after delivery as well as preclinical and toxicological studies. Virtually all DDS processes require the use of an organic solvent such as dichloromethane or ethyl acetate for maintaining polymer solubility during fabrication. These solvents may pose significant health risks for long-term exposure. Acceptable residual amounts of these solvents may vary among regulatory agencies. For example, the International Conference on Harmonization (ICH) guideline for permissible dichloromethane is 6 mg/day unless it can be shown that the residual solvent is released in a sustained fashion for several days. The FDA requires the safety and biocompatibility of all polymeric materials used for medica and dental applications to be established prior to use. The tests used to establish safety will depend on the type of device, the drug to be delivered, and its application. In vivo and in vitro testing of polymeric materials should be designed to investigate the polymer mucosal interface reactions, effects on subsurface tissue, and systemic effects. After oral delivery, bioabsorption studies would begin with animals at predetermined time periods along with mucosal tissue isolation and preparation for immunohistochemical or cytochemical analysis. Scoring systems have been used based on the number of specific cell types within a specific area of detected DDS to

effectively compare the biocompatibility of polymers.[61–63].Skin patch tests are common tests for delayed type hypersensitivity evaluation.190 Hence, acute toxicity could generally be measured by applying a test material comprised of the encapsulated contents onto shaved intact or abraded skin. Various biological parameters such as body weight, mortality, and gross pathological evaluation would also be assessed includes multiple doses over longer periods of time to recognize both acute and chronic toxicity of DDS components.[64] Evaluation of biocompatibility of polymers via tissue culture techniques are based on analysis of cellular growth, division, enzyme levels, and synthesis of important macromolecules.[65,66]

National and international status

The report points out that the protein engineering market in 2006 was worth almost $67 billion (10% of total pharma sales) and is forecast to rise to $118 billion (12% of pharma sales) in 2011. Despite their remarkable success, protein drugs continue to suffer from drawbacks, especially with respect to their delivery (subcutaneously or intravenously injected). The past 3 years have seen approvals of products for non-parenteral delivery, alongside advances in parenteral protein and peptide drug delivery. The increased use, development, and discovery of protein therapeutics will lead to increasing opportunities for drug delivery companies. Pharma companies need to use these technologies to gain a competitive edge in an increasingly crowded therapeutic protein market. The protein therapeutic market is largely immediate release, but there is a trend moving toward increased sustained release formulations.

CONCLUDING REMARKS

Peptide and protein drugs are currently used as parenteral therapies because of their poor bioavailability from different alternative routes of administration, including the p.o. route. Poor intestinal absorption of these drugs is due to their unfavorable physicochemical properties, such as high molecular weight, susceptibility to enzymatic hydrolysis, and high hydrophilicity. Moreover, there are several biological barriers to intestinal absorption of peptide and protein drugs across the GI tract. These include hydrolysis in the stomach, proteolytic degradation across the GI tract, and bacterial fermentation in the colon. Development of an effective oral delivery system, therefore, will require a thorough understanding of these barriers as well as the mechanisms involved in their absorption across the GI tract.

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