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AN INNOVATIVE SMART ORAL DELIVERY TECHNOLOGY FOR PROTEINS AND PEPTIDES

Andrea Engel, PhD, Head of Particle Formulation Laboratory; Anne Benedikt, PhD, Head of Biopharmaceutical Laboratory; and Hans Baer, MSc, Senior Project Manager, all of Evonik, explain how their recently introduced new modular platform technology for improving the oral bioavailability of peptides may offer a feasible solution to the problem of compliance with peptide drugs. These can be highly beneficial for conditions such as diabetes, oncology and metabolic disorders but the fact they have to be delivered as injections has limited their appeal, a problem which may be solved by technology that enables it to be used as a tablet.

During the last few decades the use of therapeutic proteins and peptides for applications in medicine and biotechnology has gained high interest. Peptide drugs can be highly beneficial in major diseases such as diabetes, oncology and metabolic disorders. The global peptide market is expected to increase up to US\$25.4 billion (£19.2 billion) in 2018.¹ Therapeutic peptides in general are known to be highly selective, efficacious, safe and well tolerated.

overall inconvenient therapy concept.

For patients and medical practitioners alike, compliance is often a determining factor in the choice of medication. It has a significant impact on how widely a drug is prescribed. A study revealed patients' preferences for different routes of administration, showing the majority of patients preferred daily tablets over monthly injections.² Nevertheless, various formulation approaches for oral protein

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Most pharmaceutical proteins and peptides are considered to be BCS Class III drugs, thus having a good solubility but poor permeability, which leads to an overall poor bioavailability. Furthermore, poor stability and short plasma half-life are major drawbacks. Therefore, most of the protein and peptide drugs in the market today are administered parenterally as injections. Patients receiving protein and peptide injections often experience discomfort and pain, which results in an

and peptide delivery considered in the last decades have not constituted the desired breakthrough.³

In order to offer a feasible solution, Evonik recently introduced a new modular platform technology for improving the bioavailability of peptides. Evonik's EUDRATEC™ PEP technology allows treatment in capsule form, replacing unpleasant injections and therefore tremendously enhancing patient compliance. The technology provides all the advantages



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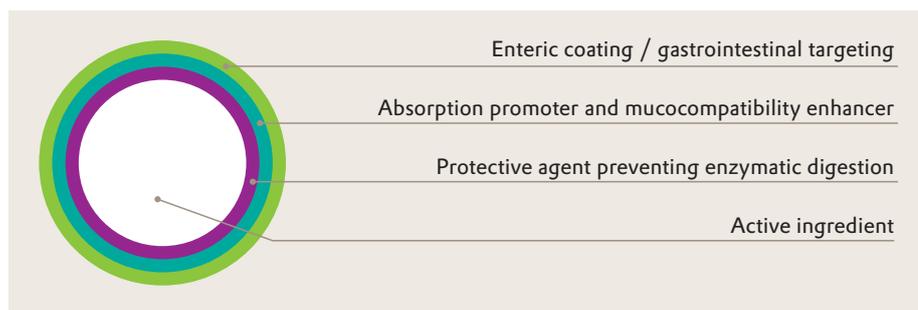


Figure 1: Typical EUDRATEC™ PEP particle design.

of oral solid dosage forms for poorly permeable active pharmaceutical ingredients such as, but not limited to, proteins and peptides. Due to its modular approach, the finished dosage form can be tailored to the drug's special needs.

EUDRATEC™ PEP TECHNOLOGY

Various aspects have to be considered during formulation development including the stability, solubility and permeability of proteins and peptides, the site of absorption and the compatibility with the mucus. The innovative EUDRATEC™ PEP technology is a modular multiparticulate platform technology.

The formulation approach uses conventional oral solid dosage form manufacturing technologies and can therefore be integrated easily in existing manufacturing concepts. The drug products

are formulated on the basis of either microparticles or mini-pellets, wherein the particles contain various thoroughly selected modules of the EUDRATEC™ PEP system that are required for the specific active.

Several synergistic modules include the active ingredient, a permeation promotor, a bioavailability promoting agent and a polymeric coating for the gastrointestinal targeted release. Depending on the type of active ingredient, additional modules can be applied to achieve further customised and beneficial functionalities. Each particle is essentially a complete pharmaceutical system, typically comprised of four basic modules (Figure 1).

The following standard modules are applied:

- Gastrointestinal targeting
- Absorption promotor
- Enzymatic protection
- Mucocompatibility.

The following advanced modules can be applied additionally:

- Anti-aggregate
- Release control
- Active ingredient specific components, e.g. stabiliser.

Figure 2: From liquid for injection only to solid oral dosage form.



THE MODULES AT A GLANCE

Up to now, parenteral administration remains the most common application route for therapeutic macromolecular active ingredients like proteins and peptides due to their poor oral bioavailability. However, considering patient acceptance and long-term compliance, the oral administration route is preferred, resulting in an increase in the therapeutic value of the drug. The formulation of proteins and peptides as oral dosage forms requires advanced drug delivery strategies to overcome physiological challenges of the gastrointestinal tract, including enzymatic degradation, poor permeability and large molecular size⁴ and thus ensuring proper bioavailability (Figure 2).

Gastrointestinal Targeting

Proteins and peptides require protection from the gastric fluid to avoid degradation induced by the stomach's acidic environment. When entering the upper small intestine, the environmental pH increases and the protective functionality shall disappear. Such functionalities are offered by commonly used enteric coatings. Over more than 60 years, anionic EUDRAGIT® polymers have been the industry standard for delayed-release coatings, preventing the release of the active pharmaceutical ingredient in the stomach. The poly(meth)acrylate chemistry behind EUDRAGIT® polymer systems provides an exceptionally versatile platform for designing drug delivery to match the specifics of individual pharmaceutical actives and treatments. The polymers used in EUDRATEC™ PEP are impervious to the stomach's acidic environment, but dissolve rapidly at specific higher pH values.

Absorption Promotor

The absorption of proteins and peptides is very limited due to their size and the intestinal barrier. An absorption promotor mediates enhanced permeation over the intestinal barrier via the paracellular pathway. The efficacy of penetration enhancers depends on several factors, including peptide type, nature of the enhancer, physicochemical properties of the delivery system as related to the drug release, and the site of application. In order to provide a successful concept, the enhancer must be released either simultaneously with or shortly before the peptide.⁵ Several absorption enhancers are discussed in the literature, but a key aspect of absorption promotors is to act reversibly and without persistent impairment.

Enzymatic Protection

One of the main obstacles limiting oral bioavailability of proteins and peptides is caused by luminal or brush border membrane-bound proteolytic enzymes such as pepsin, trypsin, chymotrypsin and pancreatin, leading to a severe pre-systemic degradation in the gastrointestinal tract. An enzymatic inhibitor has to be selected for peptide protection from proteases. It is dependent on the amino acid composition and on the position of the amino acids within the active peptide as well as the pH value.⁶

Mucocompatibility

The luminal surface of the intestinal membrane is covered by a layer of mucus which effectively protects the epithelial surfaces. Excipients interfering with mucus can increase the residence time at certain absorption windows. Such local increases in combination with high concentrations of proteins and peptides generate a favourable diffusion gradient to support the permeation through the mucus barrier.

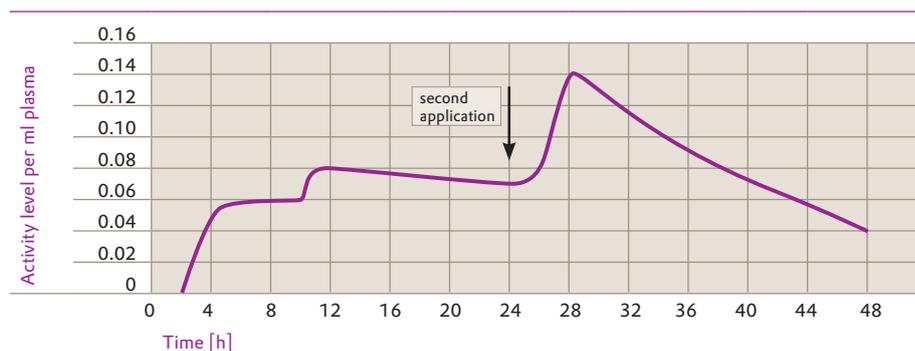
Multiparticulate Dosage Form

In EUDRATEC™ PEP formulations, the therapeutic dose is distributed over a large number of particles which are assembled into a capsule as a multi-unit dosage form. The final dosage forms are manufactured by using polymers and materials that are physiologically safe in conventional production processes, and can also be used in GMP compliant production processes.

BIOAVAILABILITY ENHANCEMENT PROVEN IN VIVO

Several *in vivo* studies emphasise the therapeutic benefits of the EUDRATEC™ PEP technology. It was applied for an anionic glycosidic drug which does not show any oral bioavailability when used unformulated. The drug is typically administered parenterally. A study in monkeys revealed that the activity of the drug could be measured in plasma. Furthermore, very promising pharmacokinetics providing a prolonged and adjustable plasma profile could be obtained through repeated application (Figure 3).

In addition to that the EUDRATEC™ PEP system was used to enhance the bioavailability of a commercially available oral peptide formulation. The technology led to a seven-fold increase of relative bioavailability of the peptide in a mini-



oral reference is not shown since the profile is on 0-level

Figure 3: EUDRATEC™ PEP mean activity profile in a monkey study (n=3), second application after 24 hours.

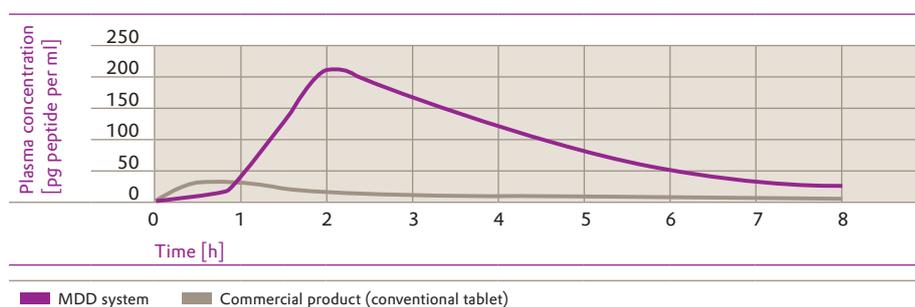


Figure 4: Mean plasma profiles in a mini-pig cross-over study (n=8).

“Overall, Evonik’s proprietary EUDRATEC™ PEP smart formulation toolbox for oral administration of macromolecular active pharmaceutical ingredients provides a unique concept for tailor-made drug delivery profiles.”

pig cross-over study compared to the conventional tablet (Figure 4).

BENEFITS OF EUDRATEC™ PEP

As a modular, multiparticulate platform technology, customised functionalities can be achieved successfully. EUDRATEC™ PEP formulations increase the oral bioavailability of proteins and peptides as well as other small and medium-sized biopharmaceuticals. The system enables parenterally administered medicines to be replaced by oral dosage forms. *In vivo* studies confirmed the suitability to enhance the bioavailability of drugs and the safety advantage of the system *versus* parenteral formulations.

Evonik’s absorption enhancers were

well tolerated in animal studies. EUDRATEC™ PEP formulations have shown superior results in pig and monkey studies employing a peptide drug and an anionic glycoside drug, respectively.

As a technology provider, Evonik offers a well-designed concept for the customised formulation development, starting with the selection of suitable EUDRATEC™ PEP modules and materials based on the physicochemical characteristics of the protein or peptide used. The chosen modules and materials are then evaluated within a systematic compatibility study.

Followed by the manufacturing of first preclinical prototypes, Evonik performs standardised *in vitro* characterisation of the prototypes employing compendia test methods. Besides pharmacopoeial dissolution test methods, investigations with bio-relevant media are a core competency of Evonik. In addition, biopharmaceutical *in vitro* assays, such as the well-established Caco-2 transport assay, are performed in order to gain first indications of the drug transport across the intestinal barrier. After a successful prototype screening, Evonik can provide samples for preclinical studies and clinical development.

Overall, Evonik's EUDRATEC™ PEP smart formulation toolbox for oral administration of macromolecular active pharmaceutical ingredients provides a unique concept for tailor-made drug delivery profiles.

THE FUTURE

EUDRATEC™ PEP provides valuable opportunities for the lifecycle management of parenteral protein and peptide formulations. The unique technology generates advanced pharmacokinetics and economic advantages compared with conventional oral formulation concepts by significantly reducing the quantity of drug required and thus lowering product costs.

Compliance is significantly improved thus increasing the therapeutic success of the specific protein or peptide.

ABOUT EVONIK

Evonik, the creative industrial group from Germany, is a world leader in specialty chemicals, operating in the Nutrition & Care, Resource Efficiency and Performance Materials segments. The company benefits from its innovative prowess and integrated technology platforms. In 2015 more than 33,500 employees generated sales of around €13.5 billion and an operating profit (adjusted EBITDA) of about €2.47 billion. The Nutrition & Care segment is a strategic partner for producers of

pharmaceuticals, nutritional supplements and medical products. Its Health Care business line provides a wide range of functional pharmaceutical excipients, drug delivery technologies, development services, and GMP manufacturing for oral and parenteral formulations.

The EUDRATEC™ portfolio of proprietary technologies for oral targeted drug delivery systems enables specific release profiles tailored to medical needs and drug requirements and thus provides smart formulation solutions for value added therapies.

REFERENCES

1. Fosgerau K et al, "Peptide therapeutics: current status and future directions". *Drug Discov Today*, 2015, Vol 20(1), pp 122-128.
2. Fallowfield L et al, "Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer". *Ann Oncol*, 2006, Vol 17(2), pp 205-210.
3. Hassani L et al, "Oral peptide delivery: Technology landscape & current status". *ONdrugDelivery*, 2015, Issue 59, pp 12-17.
4. Shaji J et al, "Protein and Peptide Drug Delivery: Oral Approaches". *Indian J Pharm Sci*, 2008, Vol 70(3), pp 269-277.
5. Lee VH et al, "Mucosal penetration enhancers for facilitation of peptide and protein drug absorption", *Crit Rev Ther Drug Carrier Syst*, 1991, Vol 8(2), pp 91-192.
6. Bernkop-Schnuerch A, "Multifunctional matrices for oral peptide delivery". *Critical Reviews*, 2001, Vol 18(5), pp 459-501.

ABOUT THE AUTHORS

Andrea Engel is a pharmacist and laboratory manager in the Drug Delivery Group at Evonik Nutrition & Care. She acts as project manager and scientific lead in various projects and activities referring to innovative drug delivery technologies and formulation development. She holds a PhD in pharmaceutical technologies and biopharmacy from the University of Münster, Germany. There, she investigated bioabsorbable nanoparticles for therapeutic photosensitisers used for the treatment of cell carcinoma.

Anne Benedikt is a laboratory manager in the Drug Delivery Group at Evonik Nutrition & Care. She acts as project manager and scientific lead in various projects and activities referring to biopharmaceutical analysis and cell culture applications. Before joining Evonik, she received her PhD in pharmaceutical biology from the University of Frankfurt, Germany. There, she investigated multi-protein complexes for the evaluation of the mechanism of acute lymphatic leukaemia.

Hans Baer has more than 12 years' experience in industrial R&D, including several scientific and business positions at Evonik Nutrition & Care. Currently, he acts as Senior Project Manager responsible for the project portfolio of the Oral Drug Delivery Segment. He holds a Bachelors degree in Pharmaceutical Process Engineering from the University of Applied Science in Bingen, Germany, and a Masters degree in Pharmaceutical Medicine from the University of Duisburg-Essen, Germany.



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