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Challenges of Oral Protein Administration

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Keywords: Peptide, protein, oral, formulation

1. Introduction

Therapeutic proteins are important in the treatment of several diseases due to their specificity and bioactivity. These proteins and peptides are usually delivered by invasive routes such as subcutaneous route because of their low oral bioavailability [1]. However, oral administration would be better because of its higher patient acceptance and compliance [2]. Therefore, huge efforts have been made over the last decades to develop oral formulation of proteins and peptides [3]. Many advantages can be mentioned, for example patients are able to avoid pain and possible infections associated with injections. Special techniques and modification are required during formulation to improve oral bioavailability as proteins and peptides have several unfavorable properties. The aim of this short discussion is to summarize the possibilities of pharmaceutical formulation procedures.

. Aspects of pharmaceutical formulation

Enzyme inhibition

The pharmacon must be protected against the gastrointestinal metabolic barrier since endopeptidases and exopeptidases are physiologically degrading the amino acid chains of peptides in the GIT. The most common proteolytic enzymes are trypsin, chymotrypsin, elastase, pepsin and carboxypeptidases [4]. As a golden standard, serpins should be chosen first from the protease inhibitors. They are able to protect the protein from protease enzymes as they form covalent complexes with the target protease. Though, we must consider the fact that long term administration of these inhibitors might result in the deficiency of proteases.

Adsorption enhancers

The objective of penetration enhancer applications is to increase the pharmacon absorption across biological membranes. [5] Therapeutic peptides and proteins, since their morphology and size, do not have therapeutically sufficient bioavailability. Amphiphilic molecules are the most frequently used penetration enhancers. Not only because surfactants are able to stabilize proteins in different stages of formulation starting from drug incorporation until the release at the site of delivery, but also application of surface active agents are able to decrease the self-association and absorption of therapeutic peptides or proteins on hydrophobic interface of delivery matrix [6]. From the other hand, permanent modification of membrane integrity might result in toxicity. [7] Therefore, accurate biocompatibility screening required to ensure the maximum safety of the applied excipients. [8]

Innovative drug delivery systems

The aim of innovative carrier system development is complex. The challenge of pharmaceutical technology is not only to protect the active compound from acidic milieu and luminal proteases of the gastrointestinal tract but also to transfer the active molecule to the appropriate place in the required condition. Several formulation strategies investigated to select the possible delivery systems to overcome these barriers. At this point, nanoparticles as drug delivery systems are the most advantageous carriers to deliver therapeutic peptides or proteins orally. [9] It has been concluded that nanoparticles are absorbed unscathed by the gastrointestinal epithelium. [10] Nanoparticles as delivery systems of proteins and peptides are more resistant against enzymatic degradation since their structure. Moreover, many factors affecting posi-

tively the pharmacon uptake such as the surface charge, the size of the particles, or even the dynamic nature of particle interaction in the gut. The only known disadvantage of nanoparticles in drug delivery is the erratic nature of nanoparticles absorption. It has shown that ratio of undamaged particles reaching systemic circulation was found to be below 5%. [11].

3. Conclusions

In the previous decades, oral administration of therapeutic peptides was considered to be unaccomplishable. Nevertheless, new researches revealed many important context to overcome these difficulties. Despite of great efforts, stability problems and low bioavailability of therapeutic proteins remains in the focus. It must be concluded that there is still no major breakthrough in oral peptide medication. However, several aspects reached a new stage of understanding, golden standard of formulation has not been evaluated yet.

4. Acknowledgement

The research was financed by the Higher Education Institutional Excellence Programme of the Ministry of Human Capacities in Hungary, within the framework of the Research and Development on Therapeutic purposes thematic programme of the University of Debrecen. 20428-3/2018/FEKUTSTRAT and this work were also supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult” project and EFOP-3.6.2-16-2017-0000 KLI-K-K project.

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