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International Association for Pharmaceutical Technology
Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V.
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03 · 2021

APV NEWS

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What´s hot in European Journal of Pharmaceutics and Biopharmaceutics?

Elena Richert, Ludwig-Maximilians-Universität, D-München

Development and optimisation of simulated salivary fluid for biorelevant oral cavity dissolution

Joseph Ali, Jong Bong Lee, Sally Gittings Alessandro Iachelini, Joanne Bennett Anne Cram, Martin Garnett, Clive J.Roberts, Pavel Gershkovich

Drug release within the oral cavity can be of paramount importance for formulations that are designed for specific purposes such as taste-masking, faster onset of therapeutic action, localization of treatment or avoidance of first-pass metabolism. Preclinical methods for assessment of dissolution in the oral cavity are necessary for design and development of these formulation but currently there is no consensus on what variables should be defined to achieve biorelevance in these tests. In this study, biorelevant simulated salivary fluids (SSFs) that can be uniformly applied for oral cavity dissolution testing were developed. Unstimulated saliva (US) SSF and stimulated saliva (SS) SSF were separately developed since the two states significantly differ. Physicochemical properties including pH, buffer capacity, surface tension and viscosity were assessed during development and optimised to mimic human saliva (HS). In order to account for the salivary proteins in HS, use of bovine submaxillary mucin (BSM) and porcine gastric mucin (PGM) in SSFs was evaluated. Following optimisation of the SSFs, biorelevance of the developed SSFs to HS was assessed by their comparative physicochemical properties as well as dissolution profiles of three diverse model compounds (sildenafil citrate, efavirenz, and caffeine) which showed comparable profiles between the SSFs and HS. This work addresses the lack of uniformed biorelevant dissolution media for oral cavity dissolution studies and provides a basis for standardised dissolution tests that provide consistency and harmonisation in future oral cavity dissolution studies. We envisage that this will have a positive impact on the development of new medicines that require functionality in the oral cavity.

Screening of novel excipients for freeze-dried protein formulations

Tobias Palle Holm, Helena Meng-Lund, Jukka Rantanen, Lene Jorgensen, Holger Grohganz

The typical excipients used as bulking agents and lyoprotectants for freeze-drying are usually limited to only a few selected substances, such as sucrose and mannitol. Considering the sheer diversity amongst proteins, it is doubtful that this limited choice should, in every case, provide the best possible option in order to achieve the most stable product. In this work, a screening of 12 proteins with 64 excipients was conducted in order to increase the knowledge space of potential excipients. Three critical quality attributes (CQAs) of the freeze-dried products, namely the solid state, the cake appearance and the protein integrity based on changes in tryptophan fluorescence were investigated by high throughput X-ray powder diffraction, image analysis and intrinsic fluorescence spectroscopy, respectively. It was found, that in some cases the excipient had a dominating influence on the CQAs, whilst in other cases the CQAs were primarily protein dependent, or that the CQAs were dependent on the combination of both. In the course of this investigation, a general view of potentially relevant excipients, and their interplay with various proteins, was obtained, thereby furthermore paving the way for the use of novel freeze-drying excipients.

The combined disulfide cross-linking and tyrosine-modification of very low molecular weight linear PEI synergistically enhances transfection efficacies and improves biocompatibility

Michael Karimov, Dietmar Appelhans, Alexander Ewe, Achim Aigner

Efficient and non-toxic DNA delivery is still a major limiting factor for non-viral gene therapy. Among the large diversity of non-viral vectors, the cationic polymer polyethylenimine (PEI) plays a prominent role in nucleic acid delivery. Since higher molecular weight of PEI is beneficial for transfection efficacy, but also leads to higher cytotoxicity, the biodegradable cross-linking of low-molecular PEIs, e.g. through disulfide-groups, has been introduced. Another promising strategy is the chemical modification of PEI, for example with amino acids like tyrosine. In the case of small RNA molecules, this PEI grafting has been found to enhance transfection efficacies and improve biocompatibility.

In this paper, we report on the combination of these two strategies for improving DNA delivery: the (i) cross-linking of very small 2 kDa PEI ("P2") molecules through biodegradable disulfide-groups ("SS"), in combination with (ii) tyrosine-modification ("Y"). We demonstrate a surprisingly substantial, synergistic enhancement of transfection efficacies of these SSP2Y/DNA complexes over their non- or mono-modified polymer counterparts, accompanied by high biocompatibility as well as favorable physicochemical and biological properties. Beyond various cell lines, high biological activity of the SSP2Y-based complexes is also seen in an ex vivo tissue slice model, more closely mimicking in vivo conditions. The particularly high transfection efficacy SSP2Y/DNA complexes in 2D and 3D models, based on their optimized complex stability and DNA release, as well as their high biocompatibility thus provides the basis for their further exploration for therapeutic application.

Powder suspensions in non-aqueous vehicles for delivery of therapeutic proteins

Christoph Marschall, Madlen Witt, Bernhard Hauptmeier, Wolfgang Friess

Formulating biopharmaceuticals is a challenging task due to their complex and sensitive nature. Protein drugs are typically marketed either as an aqueous solution or as a lyophilizate. Usually aqueous solutions are preferred as neither drying nor reconstitution are required. But it may be unfeasible if the protein features low stability. An interesting alternative to

avoid at least reconstitution are protein powder suspensions in non-aqueous vehicles. Such formulations combine the ready-to-use approach with the high protein stability in the solid state. Additionally, protein powder suspensions offer a potentially lower viscosity compared to aqueous solutions at high protein concentrations. Besides injection, other application routes might also benefit from the protein powder approach such as topical or inhalational delivery.
Protein powders, which can be dispersed in the non-aqueous suspension vehicle, are usually prepared by spray-drying or freeze-drying with an additional milling step, but other techniques have also been described in literature. An ideal powder preparation technique results in minimum protein damage and yields particle sizes in the lower micrometre range and homogeneous particle size distribution enabling subcutaneous or intramuscular injection through hypodermic needles.
As suspension vehicles traditional non-aqueous injectable liquids, such as plant oils, may be selected. But they show an inherent high viscosity, which can lead to unacceptable glide forces during injection. Furthermore, the vehicle should provide high product stability with respect to protein integrity and suspension resuspendability.
This review will describe how proteins can be formulated as protein powder suspensions in non-aqueous vehicles for subcutaneous injection including potential vehicles, protein powder preparation techniques, protein and suspension physical stability, as well as the use in the field of high concentration protein formulations.

Impressum:

Redaktion
Prof. Jörg Breitkreutz (Präsident der APV)
Dr. Martin Bornhöft (Leiter der Geschäftsstelle der APV)

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Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e. V. (APV)
Kurfürstenstr. 59 · 55118 Mainz · Germany
Telefon +49 6131 9769-0
Telefax +49 6131 9769-69
email apv@apv-mainz.de
web www.apv-mainz.de

Verlag
ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH
Baendelstockweg 20 · 88326 Aulendorf · Germany
Telefon +49 7525 940-0
Telefax +49 7525 940-180
email info@ecv.de
web www.ecv.de

Druck
Holzmann Druck GmbH & Co. KG
Gewerbestr. 2 · 86825 Bad Wörishofen · Germany

Satz
Anna-Maria Pötzl · APV e.V.

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