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Review

Recent advances in crystalline and amorphous particulate protein formulations for controlled delivery

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ABSTRACT

The number of particulate delivery systems for biologics is negligible compared to liquid dosage forms, signifying the complications associated with development of solid protein delivery systems. Particulate protein delivery systems can improve stability, reduce viscosity of suspensions at high protein concentration and allow for controlled drug release. This review discusses current advances in controlled delivery of particulate protein formulations. While the focus lies on protein crystals and delivery systems employing protein crystals, amorphous protein particles will also be addressed. Crystallization and precipitations methods and modifications allowing controlled delivery with and without encapsulation are summarized and discussed.

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1. Introduction

With the increasing number of biologics in the pipelines of pharmaceutical manufacturers, approaches enabling improved stabilization and delivery of these molecules are increasingly sought-after. Administration of biologics via the gastrointestinal tract frequently yields poor bioavailability because of low intestinal absorption and enzymatic and chemical degradation of proteins prior to absorption, although some progress has been made in the case of peptides [1–3]. Consequently, parenteral administration is still the most common route of administration for protein pharmaceuticals. The vast majority of biologics for parenteral application nowadays are marketed as liquid or lyophilized formulations, but both presentations are associated with specific advantages and also some drawbacks and intricacies. Specifically, liquid presentations are convenient to use but require meticulous optimization of formulation composition, especially with regards to formulation pH, ionic strength and stabilizing excipients to achieve optimal physical and chemical stability [4]. Lyophilized biologic drug products apart from optimization of the formulation

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often require product-specific development or optimization of the lyophilization process to safeguard product quality while achieving commercially viable lyophilization process durations. However, lyophilization often results in high physical and chemical stability enabling shelf life of 3 to 5 years and may also be advantageous if highly concentrated solutions must be administered (up-concentration by lyophilization) [5,6].

Moreover, several additional requirements regarding tolerability and applicability of the formulation have to be factored in when developing liquid or lyophilized drug products. Beyond sterility, appropriate tonicity and pH-value, protein concentration is a main parameter, especially when dealing with high doses administered by subcutaneous or intramuscular injection, where injection volume is strictly limited. Apart from detrimental effects on physical stability, increasing protein concentrations frequently result in increased viscosity and/or opalescence affecting the injectability of the formulation and complicating visual inspection [7,8].

In addition to the challenges associated with development and stabilization of biologics formulations, standard liquid and lyophilized forms result in almost all cases in immediate drug release. Frequent application due to the short circulation half-life of numerous therapeutic proteins represents a significant burden for patients and sustained drug release would be beneficial. However, low drug load, protein degradation during encapsulation and low stability of the encapsulated protein during storage and after administration complicate development of polymeric protein delivery systems [9,10].

Crystalline protein formulations may represent an interesting alternative as protein crystals are densely packed allowing high drug loading, they have a reduced surface area reducing interactions with the solvent and polymeric scaffolds and show improved stability compared to amorphous formulations [11–13]. Furthermore, dissolution rate of protein crystals can be controlled without requiring encapsulation into a polymeric system [14]. Processing and administration of protein drug products also benefits from crystalline forms: viscosity of suspensions is substantially lower than that of equally concentrated protein solutions, allowing higher drug loading and simplifying administration [15]. In addition, interactions with aqueous or organic media are reduced and the protein stability at elevated temperatures is improved [16]. Despite these advantages, the crystallization of proteins with and without subsequent encapsulation for controlled delivery is still in its infancy, and previous reviews on this topic mainly have dealt with general suitability [17] as well as the upscaling and characterization of protein crystals [16].

In this review, we present the latest developments in the crystallization of pharmaceutically active proteins as well as give an update on the progress in delivery and encapsulation methods of amorphous protein precipitates and protein crystals.

2. Particle production methods

Defining optimal conditions for protein crystallization and precipitation can be tedious, and the transfer of crystallization conditions between molecules is typically unsuccessful, leading to the notion that protein crystallization is rather art than science. In order to prepare protein crystals, a protein solution has to be transferred into a thermodynamically unstable supersaturated state which returns to equilibrium by development of a crystalline or amorphous phase. For crystallization, it is the goal to increase the interactions between two protein molecules so that a well ordered arrangement takes place while nonspecific aggregation is avoided [18]. In general, the native conformation is maintained during and often preserved effectively after crystallization (see chapter 2.3.). There exists a wealth of knowledge about protein crystallization with focus on purification or structure determination [19] but much less research efforts were made toward manufacturing of larger batches. For elucidation of the protein structure, only a few large but almost perfect crystals are needed, typically produced in very small scale. However, in order to produce crystalline protein drug substance at commercial scale, batch crystallization methods appear to be the most suitable option (chapter 2.1.). The formation of protein particles is a wide field with countless methods published, a selection of which is presented in chapter 2.2.

2.1. *Preparation of protein crystals by batch crystallization*

Batch crystallization is the production of uniform crystals in a large scale, preferably with a high yield [20]. In general, the strategy is to quickly reach a high level of supersaturation of the protein so that numerous crystallization nuclei are formed simultaneously followed by a growth phase, whereby all nuclei grow in parallel, reaching the same size (Fig. 1A). This process is often initiated by a liquid–liquid phase separation between the protein and the solvent, followed by a first nucleation within the protein droplets [23]. According to the classical nucleation theory, more nuclei are formed if the difference of Gibbs free energy (ΔG) is largely negative, i.e. the system reaches a lower free enthalpy. With the free enthalpy ΔG being related to the chemical potential by $\mu = \left(\partial G / \partial n\right)_{p,T}$ systems tend to spontaneously 'escape' to lower chemical potentials as this leads to a reduction of the free enthalpy if other parameters, particularly the pressure p and the temperature T are held constant. Thereby, supersaturated solutions are thermodynamically instable as the chemical potential in the supersaturated state is higher as compared to the solid aggregate state – hence, these systems tend to aggregate with crystals frequently forming the lowest free enthalpy state. Accordingly, dissolved proteins in a supersaturated state spontaneously aggregate and thereby form nuclei on which further protein will deposit. The speed and extend at which supersaturation is reached strongly affects nuclei size and size distribution [24], but if the degree of supersaturation is pushed too high, precipitation takes place [20]. Commonly, supersaturation is reached by mixing a solution containing a high concentration of precipitating agent to a protein solution or by a rapid temperature drop. For the crystallization of individual proteins, different buffers and precipitating agents like salts, glycol, alcohols or poly(ethyleneglycol)s are required [25,26]. Decreasing the solvation of the protein is the primary goal for crystallization. For example, 'salting out' a protein by the addition of kosmotropes (e.g. sodium, lithium,

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