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A perspective on high-concentration spray-dried monoclonal antibody suspensions for subcutaneous delivery

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Abstract
There is a growing demand in the subcutaneous delivery of monoclonal antibodies (mAbs) to reduce treatment burden for both patients and healthcare systems when compared to intravenous administration. However, it poses significant challenges in formulation development primarily due to high viscosities in highly concentrated solutions of mAbs for subcutaneous injection, which impacts injectability and effective dosing. Advances in protein spray drying have enabled the production of solid protein powders with enhanced stability. When suspended in non-aqueous media, these spray-dried powders facilitate the achievement of protein concentrations far exceeding 200 mg/mL to overcome challenges associated with high-concentration formulations for biologics such as solubility, viscosity, and aggregation. This perspective aims to discuss recent studies showcasing the successful application of spray-dried proteins to achieve high protein concentrations; key formulation aspects of protein spray drying with respect to subvisible particles; formulation considerations for spray-dried protein suspensions in non-aqueous media; technical and regulatory challenges for subcutaneous delivery of non-aqueous suspensions for mAbs; their knowledge gaps in clinical translation; and the need for patient-centric studies to enhance patient experience, providing insights into how future research can better balance quality and compliance. Finally, with the growing exploration of drying technologies, this article discusses the future outlook for high-concentration suspensions of therapeutic proteins.

Keywords Spray drying, Monoclonal antibodies, High-concentration formulations, Non-aqueous suspensions, Subcutaneous delivery

Introduction

Monoclonal antibodies (mAbs), since the approval of the first therapeutic mAb in 1986, muromonab-CD3 (OKT3), have revolutionized the pharmaceutical industry over the past decades by offering a more effective, safer, and targeted therapeutic option for multiple disease areas (Chan et al. 2025). The landscape of therapeutic mAbs is advancing rapidly beyond the standard immunoglobulin G (IgG) format, with alternative antibody formats such as antibody–drug conjugates (ADCs) and bispecific antibodies (Chan et al. 2025). This progress has led to the approval of over 212 antibody therapeutics and the treatment of millions of patients to date (Chan et al. 2025). An economic analysis has revealed that the global market revenue of mAbs is projected to reach half a trillion dollars in 2030 (Stone et al. 2024). Traditionally, proteins are formulated as liquid aqueous formulations to facilitate intravenous infusion and directly deliver the drug into

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systemic circulation, but it can pose heavy burdens from patients' perspectives: A qualitative study found that hospital patients had decreased feelings of quality and safety due to issues upon receiving intravenous infusions, including the nuisance of infusion pump alarms, the lack of mobility, and associated discomfort due to pain and irritation relating to cannulation (Wheeler et al. 2020). These challenges can negatively impact patient compliance and adherence to prescribed mAbs, ultimately impacting health outcomes. Therefore, the development of alternative delivery methods for mAbs from a patient-centric perspective is critical to enhancing the patient experience and broadening accessibility to life-saving treatments.

Subcutaneous delivery of mAbs offers several advantages over traditional intravenous infusion, including improved patient convenience, reduced healthcare costs, and the potential for self-administration. The growing demand for subcutaneous administration is mainly driven by the patient and healthcare provider preference to reduce treatment burden (Ghosh et al. 2025). According to a recent survey, patients reported greater satisfaction, increased convenience, and less impact on daily activities with subcutaneous administration of oncology therapies compared to intravenous administration (George et al. 2025). For subcutaneous delivery of mAbs with high doses, it typically requires formulations with high protein concentrations because of small injection volumes (e.g. < 2 mL injection volume) (Shire et al. 2004; Davis et al. 2024). This has motivated the development of high-concentration protein formulations to predominantly enable this route of administration. A recent report highlights that 76% of the total approved numbers from 1998–2021 for therapeutic antibodies with high-concentration formulations (≥ 100 mg/mL) are developed for subcutaneous administration (Wang et al. 2021a). However, at elevated concentrations, mAbs are more prone to self-association, which can cause several issues, including increased solution viscosity and a higher risk of protein aggregation (Zarzar et al. 2023). These challenges are problematic in compromising the drug product quality of mAbs, leading to reduced therapeutic efficacy and potential safety issues. One key focus area in the development of high-concentration liquid formulations is managing viscosity. A number of different formulation approaches such as viscosity-reducing excipients, formulation pH optimization, and ionic strength modulation are effective strategies for viscosity mitigation (Banik et al. 2022; Cruz et al. 2025; Prašnikar et al. 2025). Another promising approach is to leverage hyaluronidase by breaking down hyaluronic acid in the extracellular matrix, thus enabling the administration of higher drug doses and increasing dose volume in subcutaneous tissues (Guo et al. 2025). While these strategies have proven effective to some extent, achieving protein concentrations far exceeding 200 mg/mL with sufficiently low viscosity remains a considerable challenge. A recent survey from a group of formulation experts reported that challenges in the development of high-concentration formulations for biologics such as solubility, viscosity, and aggregation could result in delays in clinical trials or product launches (Desai et al. 2025). High viscosity formulations can lead to practical issues in manufacturing and dose administration, such as reduced syringeability and increased injection force, which can negatively impact patient compliance and acceptance (Wang et al. 2025). On the other hand, suspending spray-dried powders of mAbs in non-aqueous media emerged as a potential alternative in achieving high protein concentrations (Bowen et al. 2012; Ren 2025). However, the clinical use of spray-dried proteins remains limited, critical gaps still exist in bridging preclinical data on spray-dried protein suspensions and human clinical applications.

With the increasing demand for mAbs to be formulated in high concentrations that enable patient-friendly subcutaneous injections, this perspective focuses on the broad challenge and addressing gaps for clinical translations of spray-dried protein suspensions. The following sections will first examine the specific formulation challenges with respect to subvisible particles associated with spray-dried proteins and highlight emerging trends in utilizing spray-dried proteins to facilitate subcutaneous delivery of mAbs, supported by examples from the development of high-concentration spray-dried protein suspensions (Fig. 1). Specifically, this article aims to pose the following questions: What is our current understanding of subvisible particles for spray-dried proteins? What are the key considerations and knowledge gaps for formulation development of spray-dried protein suspensions for mAbs? Furthermore, how do pharmaceutical scientists work collaboratively with regulatory agencies to bridge the use of spray-dried protein suspensions from preclinical to clinical settings?

Spray drying of monoclonal antibodies

The history of spray drying dates back over 150 years ago, when Samuel Percy developed the first documented method in 1872 for transforming liquid into powder through atomization, laying the groundwork for modern spray drying technology (Jafari and Samborska 2021; Milanesi et al. 2025). Initially, spray drying found its early success in the food industry and the production of milk powders during the early twentieth century, which was conducive in enhancing their storage stability and shelf life (Milanesi et al. 2025). The role of spray drying in industrial applications began expanding rapidly in the mid-twentieth century with advancements in atomization technology and the development of more efficient

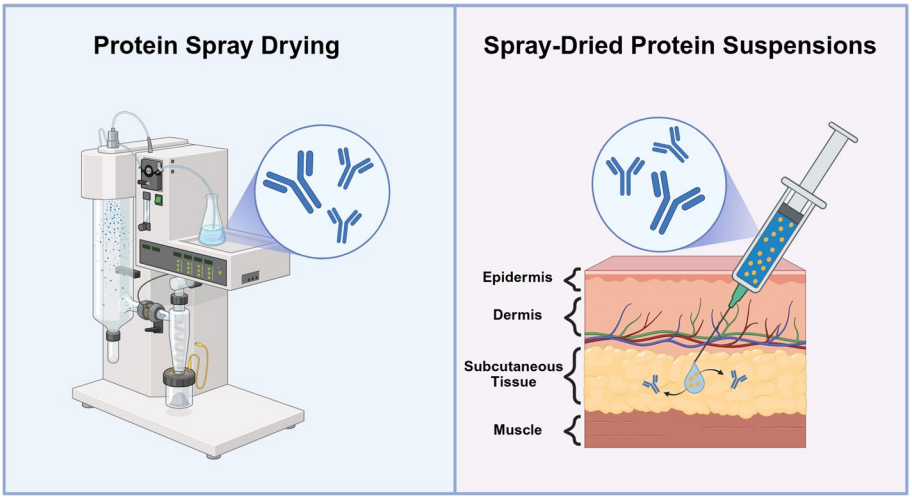

Fig. 1 Applications of spray-dried protein suspensions for subcutaneous delivery of mAbs

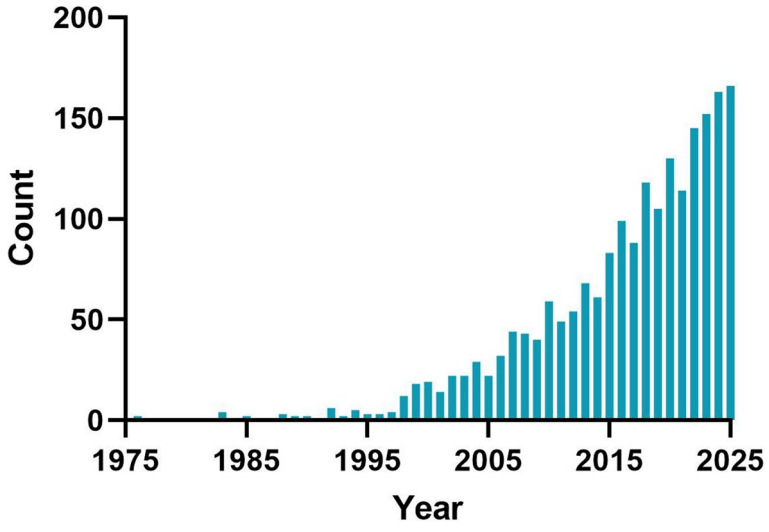

Fig. 2 Publication count of the keyword "protein spray drying" on PubMed® from 1975 to 2025

designs for spray dryers, including improvements in nozzle designs, and the optimization of drying chambers and process controls (Cal and Sollohub 2010). While early applications of spray drying were primarily focused on food preservation, the successful applications of spray drying to generate stable protein powders for heat-sensitive enzymes and therapeutic proteins in the early 1990 s marked a paradigm shift in how spray drying can be applied to biopharmaceuticals (Mumenthaler et al. 1994; Broadhead et al., 1994). As highlighted by the exponential increase in the number of publications using the keyword "protein spray drying" retrieved from PubMed® over the past five decades (Fig. 2), scientific research on this field has greatly expanded in both academia and the pharmaceutical industry. This trend reflects not only the widespread recognition of the importance of spray drying in biopharmaceutical development but also the increasing demand for innovative formulation technologies that enhance the stability, manufacturability, and delivery of complex therapeutic proteins.

Compared to the conventional drying method via lyophilization, spray drying has a number of advantages due to its effectiveness in converting liquid protein formulations into stable, free-flowing dry powders with controlled particle size and morphology (Chen et al. 2021; Milanesi et al. 2025). Additionally, the rapid atomization and drying steps in spray drying are highly scalable and cost-effective, allowing a seamless transition from lab to large-scale production (Pinto et al. 2021). However, mechanical stresses induced by the spray drying process and the high operating temperatures used to remove aqueous solvent could be detrimental to protein stability. Consequently, spray-dried proteins have a greater propensity to generate subvisible particles upon

reconstitution in aqueous media compared to lyophilized solids (Gikanga et al. 2017). To maintain protein stability during spray drying, formulation compositions must be carefully designed in order to withstand stresses such as heat, air–liquid interfacial, and shear. Controlling critical process parameters, including drying temperature, drying rate, droplet size, and solution feed concentration, is essential to achieve target particle morphology while preserving protein integrity (Vehring 2008). The spray drying process can also impart static charges to particles through various stages (Murtomaa et al. 2004). Formulation approaches, such as optimizing protein-to-excipient ratios and incorporating hydrophobic shell-forming excipients, can reduce powder tackiness and improve powder flowability (Bowen et al. 2013; Wang et al. 2021b; Arte et al. 2024). Additionally, enhancing solid-state stability of spray-dried proteins is a crucial strategy to extend the shelf life of drug products, making them more suitable for various drug delivery applications (Chang et al. 2015; Tam et al. 2026). Nonetheless, no spray-dried solid formulations for therapeutic mAbs are yet available on the market (Wang et al. 2021a). As noted, one key limiting factor lies in the risk of forming soluble and insoluble aggregates caused by the harsh operating conditions during spray drying.

During atomization, the protein solution is dispersed into tiny droplets, significantly increasing the air–liquid interfacial area (Ameri and Maa 2006). Since protein molecules exhibit surface activity, they tend to compete with other excipient molecules such as surfactants to adsorb at the air–liquid interface (Koepf et al. 2018). Protein-surface interactions are intensified by the extremely high specific surface area of fine droplets during spray drying, which can disrupt intramolecular hydrogen bonds, leading to partial unfolding and exposing hydrophobic residues typically buried within the structure of the protein (Maa and Prestrelski 2000). The exposure of hydrophobic patches can potentially increase the likelihood of non-specific protein–protein interactions, triggering aggregation and leading to the formation of insoluble aggregates or subvisible particles (Ameri and Maa 2006). While the exact mechanisms behind this phenomenon are still being investigated, a previous study by Tao et al. demonstrates that the spray drying process could have exposed the hydrophobic residues in the heavy chain, wherein hydrophobic interactions upon reconstitution of spray-dried proteins could lead to the formation of insoluble aggregates (Tao et al. 2023). The formation of subvisible particles in spray-dried proteins poses a challenge in satisfying stringent regulatory requirements for drug product quality. Subvisible particles in mAb formulations are not merely a regulatory concern but also pose potential safety risks, which can evoke immunogenic responses in patients. Ahmadi et al. has demonstrated that a minute amount of subvisible aggregates for trastuzumab can become a potent inducer to elicit immunologic reactions (Ahmadi et al. 2015). Therefore, reducing or preventing the formation of subvisible particles in spray-dried proteins is critical to ensuring both product quality and patient safety.

Selecting appropriate excipients for protein stabilization during spray drying is crucial for mitigating the risk of subvisible particle generation. In general, sugars are commonly used as stabilizers to maintain stability of proteins upon drying. The classic theories of the protection mechanism are primarily based on vitrification and water replacement (Mensink et al. 2017; Brom et al. 2023): (1) The vitrification theory posits that during dehydration, sugars can form a rigid, glassy polymer matrix due to their ability to form a thermodynamically stable amorphous solid state (Mensink et al. 2017; Brom et al. 2023). The glassy state significantly reduces molecular mobility, thereby suppressing motions of protein molecules (Mensink et al. 2017; Brom et al. 2023). This immobilization prevents unwarranted interactions between protein molecules, and therefore dramatically minimizes aggregation and denaturation. (2) The water replacement theory focuses on the molecular interactions between sugars and proteins. Water is crucial for protein stability since it provides a hydrating environment and is integral to forming hydrogen bonds and maintaining the three-dimensional structure of the protein (Brom et al. 2023). During drying, the removal of water can reveal new epitopes or induce conformational changes that differ from their native state, potentially increasing the risk of aggregation by facilitating intermolecular hydrophobic interactions (Prestrelski et al. 1993; Rojekar et al. 2025). Since sugars such as trehalose, sucrose, and mannitol exhibit numerous hydroxyl groups which are capable of forming hydrogen bonds, they can replace the hydrogen bonds that water molecules typically form with polar groups on the protein, thereby stabilizing the protein structure during drying (Mensink et al. 2017; Brom et al. 2023). A study performed by Grasmeijer et al. suggested that at glass transition temperatures below the storage temperature, protein stabilization is primarily governed by the vitrification mechanism (Grasmeijer et al. 2013). By contrast, when the glass transition temperature is well above the storage temperature, degradation can take place when there is either enough free volume or insufficient protein–sugar interactions, thus the primary stabilization is dominated by the water replacement mechanism (Grasmeijer et al. 2013). While the two theories are often discussed independently, they are not mutually exclusive (Olgenblum et al. 2020; Brom et al. 2023). Nonetheless, the effectiveness of stabilization can also be influenced by the types of sugars used and the drying methods employed (Brom et al. 2023).

Among various sugars used as protein stabilizers, trehalose has attracted increased attention due to its distinctive physicochemical properties. It possesses superior glass-forming ability, a relatively high glass transition temperature, and remarkable chemical stability (Olgenblum et al. 2020; Brom et al. 2023). These features make trehalose particularly effective in stabilizing proteins during spray drying and ensuring physical and structural integrity of proteins over storage, even at elevated temperature (Rajagopal et al. 2013, 2019). Despite its numerous advantages, amorphous trehalose exhibits a notable drawback due to its susceptibility to recrystallization when exposed to increased relative humidity (Heljo et al. 2012; Jójárt-Laczkovich et al. 2016). When trehalose is used as a cryoprotectant for mAbs, recrystallization of trehalose can lead to phase separation and compromise its protective properties, which consequently promote protein aggregation (Connolly et al. 2015). Exposure of spray-dried mAbs using trehalose as excipients to high humidity conditions has been shown to induce trehalose recrystallization, which has been identified as a potential factor contributing to the formation of subvisible particles (Tam et al. 2025). The use of cyclodextrins has shown promise in delaying or inhibiting trehalose recrystallization in spray-dried proteins, which results in improved protein stability and reduced cumulative count of subvisible particles (Tam et al. 2025). In addition, the incorporation of moisture-resistant hydrophobic amino acids such as leucine have been shown effective in inhibiting trehalose recrystallization under high humidity conditions while maintaining protein stability (Zhang et al. 2024; Arte et al. 2025). These strategies highlight the importance of selecting appropriate formulation components to maintain the amorphous state of spray-dried proteins and enhance long-term solid-state stability.

High-concentration spray-dried monoclonal antibody suspensions for subcutaneous delivery

As alluded to earlier, to address the challenges associated with high-concentration liquid formulations, a solid suspension approach utilizing powder-based suspensions in non-aqueous media has been increasingly investigated in recent years (Marschall et al. 2021; Ren 2025). Early studies have demonstrated the potential of crystalline suspensions in addressing both viscosity and stability concerns. For example, Yang et al. reported that crystalline suspensions of mAbs achieved low viscosity formulations while maintaining protein stability under various storage conditions (Yang et al. 2003). Nonetheless, the large size and structural complexity of mAbs make crystallization a challenging and resource-intensive process, limiting its broader applicability (Chattaraj et al. 2025). In contrast, suspensions of spray-dried protein powders in non-aqueous media present an appealing alternative. Advancements in spray drying technology have shown promising progress, with recent studies demonstrating the potential to achieve extremely high protein concentrations surpassing 400 mg/mL by suspending spray-dried protein powders in non-aqueous media (Jons et al. 2025; Yadav et al. 2025). The ability to formulate high-concentration protein formulations is extremely beneficial for the development of therapeutic mAbs tailored for the subcutaneous route of administration.

The selection of suspension vehicles is one of the essential criteria that influences the rheology, injectability, and physical stability of the formulation. Non-aqueous vehicles, such as vegetable oils, esters, and medium chain triglycerides, are frequently utilized in high-concentration spray-dried protein suspensions due to their inert nature and ability to prevent water-mediated degradation pathways of mAbs such as hydrolysis (Marschall et al. 2021). Admixtures of various suspension vehicles offer additional possibilities in optimizing the suitable physical properties of spray-dried protein suspensions for mAbs (Bowen et al. 2012). However, the molecular interactions between the mAbs, the excipients that stabilize them, and the non-aqueous milieu are not yet well understood. Further questions need to be addressed with additional research such as how does the solid-oil interface impact the solid-state stability of spray-dried proteins in non-aqueous media and what specific interactions govern protein stability upon dissolution from a suspension into the liquid phase. Different studies have demonstrated that the residual moisture levels can impact the solid-state stability of spray-dried proteins, and different polarity environments in non-aqueous solvents can be detrimental to protein stability (Toba and Merz 1997; Maa et al. 1998). On the other hand, the presence of impurities such as free radicals and various secondary oxidation products from poly-unsaturated fatty acids found in some vegetable oils can negatively impact protein stability via oxidation (Marschall et al. 2021). These interactions may also vary greatly depending on specific physicochemical properties, such as different charged or hydrophobic patches on the mAb surface, making it challenging to develop a platform formulation approach across various macromolecular formats. An effective screening tool to identify the optimized suspension vehicles would be conducive in early formulation screening. Hence, the compatibility of spray-dried proteins with suspending non-aqueous vehicles remains an area that warrants further investigation.

Injectability is a vital factor for the development of spray-dried protein suspensions intended for self-administration in autoinjectors or other drug delivery devices, as this greatly influences patient experience and the feasibility of subcutaneous delivery. One distinct advantage of spray-dried protein suspensions is their tendency

to exhibit non-Newtonian shear-thinning behavior (Marschall et al. 2021). During injection, suspension viscosity decreases with an increased shear rate, thus enabling a faster flow and a low injection force (Marschall et al. 2023). For instance, spray-dried mAb suspensions at 280 mg/mL showed remarkably lower glide forces below 20 N (which are generally considered an ideal target for self-administration to ease patient comfort (Watt et al. 2019)) using a 25-gauge needle when compared to their liquid formulation counterparts (Marschall et al. 2023). Interestingly, Yadav et al. reported that although the viscosity in formulations with protein concentrations approaching 400 mg/mL can exceed 100 cP, the corresponding injection force using a 24-gauge needle remained manageable below 20 N (Yadav et al. 2025). In addition, particle morphology and size distribution play crucial roles in determining suspension characteristics. Jons et al. highlighted that a smooth surface morphology of spray-dried protein particles reduces interparticle friction, resulting in the formation of flowable suspensions rather than thick pastes, which lowers the glide force required for injection (Jons et al. 2025). Therefore, controlling the morphology and particle size distribution of spray-dried proteins is crucial to enhance formulation injectability of highly concentrated suspensions.

Particle settling is another important consideration for the successful development of spray-dried protein suspensions for mAbs. The uniform dispersal of suspended particles is necessary to maintain formulation homogeneity and ensure consistent dosing. During storage, the settling of solid particles within non-aqueous media can occur, which can lead to phase separation and an increased likelihood of syringe clogging during administration (Kowsari et al. 2024). Although higher viscosities can reduce particle sedimentation by increasing the resistance to gravitational settling, excessive viscosities may render the suspension difficult to mix, which further exacerbates the risk of product instability. Evaluating sedimentation rates and selecting suspension vehicles with densities higher than that of spray-dried powders can help mitigate the risk of particle settling (Marschall et al. 2023). On the other hand, the ability to uniformly resuspend spray-dried particles after settling is essential. Creating a smooth spherical particle morphology can assist redispersion (Jons et al. 2025). Other mixing aids such as incorporating a small glass ball to facilitate resuspension inside the syringe may be required similar to an insulin pen-cartridge device (Shnek et al. 1998). In addition, sugar excipients used to stabilize spray-dried proteins tend to be hygroscopic, which can induce particle agglomeration (Arte et al. 2024). The morphology and size distribution of larger agglomerated particles could be drastically different from the initial spray-dried formulations, potentially impacting their resuspendability and injectability in non-aqueous media. Efficient mixing techniques and the incorporation of appropriate stabilizing agents are therefore vital to minimize the risk of particle agglomeration in the development of spray-dried protein suspensions.

However, the successful adoption of this technology requires addressing significant gaps in our understanding of the long-term stability of mAbs in such complex systems. Comprehensive data on how long-term storage of spray-dried mAbs within the unique physical and chemical environment of non-aqueous media affects the drug product quality attributes remains scarce. For instance, Huang et al. investigated the stability of spray-dried proteins recovered from a suspension after storage at 4 °C for 3 days, with the rationale of suspending the spray-dried powders before use (Huang et al. 2022). Patients may need to follow precise instructions to ensure proper mixing in a vial and carefully withdraw the required dosage, which may impose additional caveats of underdosing or overdosing due to improper mixing. To simplify the process of combining the powder with the appropriate solvent in the same compartment, specialized devices such as dual-chamber syringes or customized transfer systems may be required (Werk et al. 2016). For other paste-like suspension formulations that are stored in prefilled syringes or autoinjectors, the interplay between protein stability and varying concentrations of silicone oils and tungsten levels in these configurations still warrants comprehensive analysis (Murphy et al. 2023). Additional forced degradation studies are critical to evaluate how physicochemical stability of mAbs responds to stressors such as elevated temperatures, light exposure, and mechanical agitation associated with spray-dried protein suspensions to establish product shelf life (Hawe et al. 2012; Basle et al. 2020).

Considerations for clinical translations

The development of a high-concentration subcutaneous formulation for mAbs necessitates rigorous evaluation to ensure it meets clinical and regulatory standards. However, clinical studies on spray-dried protein suspensions for mAbs are sparse, leaving gaps in our understanding of their pharmacokinetics, biodistribution, safety, and efficacy compared to their liquid formulation counterparts. Conducting a bioequivalence study is an important stage in the approval process, which plays a central role in establishing that the new formulation has the same therapeutic effect as the traditional formulation of an approved product (Chow 2014). These studies are essential for demonstrating comparable pharmacokinetics and pharmacodynamics, thereby confirming that the new formulation or device delivers the intended clinical benefits without compromising safety or efficacy (Midha and McKay 2009). Furthermore, these studies

serve to streamline the drug development process, avoiding the need for extensive clinical trials which are both time-consuming and costly. While the literature has vastly discussed bridging studies from intravenous to subcutaneous administration, the transition to a new delivery device or novel formulation is equally critical. One example is the introduction of an established autoinjector platform for ofatumumab, which demonstrated bioequivalence to the prefilled syringe presentation of ofatumumab in the pivotal phase 3 study and successfully bridged a phase 2 trial utilizing the autoinjector platform (Bittner 2023). Another example is the co-formulation with hyaluronidase, where a phase 1 trial demonstrated that efgartigimod co-formulated with hyaluronidase in a prefilled syringe was bioequivalent to its traditional vial presentation, facilitating other clinical trials of efgartigimod in a prefilled syringe for various indications (Guo et al. 2025). Thus, such an approach can expedite the timeline for bringing the product to market, enabling quicker access for patients and healthcare providers.

Another key gap pertains to understanding the in vivo stability of administered spray-dried mAb suspensions in a subcutaneous environment. The complex subcutaneous space consisting of extracellular matrix and adipose tissues may impact the structural and conformational stability of injected suspensions containing spray-dried mAbs (Jogdeo et al. 2024). Factors such as interfacial stresses, changes in pH, and changes in ionic strength that proteins experience when transitioning from a solid state to liquid in subcutaneous tissues could potentially influence their aggregation mechanisms. Changes in conformational stability of therapeutic mAbs can exacerbate protein unfolding and aggregation (Lundahl et al. 2021). Gaining an understanding of what drives protein aggregation in the subcutaneous space is crucial for developing spray-dried protein suspensions for mAbs. Stability of spray-dried protein suspensions under a simulated in vivo subcutaneous environment may need to be further investigated to better inform the risk of protein aggregation, and this could potentially be used to predict bioavailability of subcutaneously administered mAbs (Bown et al. 2018; Jogdeo et al. 2024). Insoluble aggregates of therapeutic mAbs, especially in the range of 2—10 μm, can be highly immunogenic (Joubert et al. 2012). Larger particles that are trapped in the subcutaneous space can potentially affect protein absorption and enhance interactions with immune cells (Turner and Balu-Iyer 2018). The induction of an anti-drug antibody (ADA) mediated immune response often results in loss of efficacy, altered pharmacokinetics of the administered mAb, and lead to serious adverse events (Joubert et al. 2012; Krishna and Nadler 2016). For example, aggregate-containing formulations of trastuzumab and rituximab have been shown to enhance inflammatory responses as compared to their non-aggregated monomer formulations (Lundahl et al. 2021). Regulatory bodies, such as the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), have imposed rigorous standards which emphasize the necessity of comprehensive analytical characterization to ensure product safety and efficacy of therapeutic protein products (Rojekar et al. 2025). Pinpointing the molecular triggers and stress conditions that lead to aggregation of spray-dried proteins in an non-aqueous environment as well as subsequent exposure in subcutaneous tissues requires deeper analytical characterization using advanced methodologies such as hydrogen–deuterium exchange mass spectrometry (HDX-MS), nuclear magnetic resonance (NMR), or molecular dynamics simulations (Kortkhonjia et al. 2013; Kumar et al. 2019; Bramham et al. 2021; Lai et al. 2022). Further investigation into these aggregation pathways in the subcutaneous space could provide insights into optimizing protein stability as non-aqueous suspensions.

Unlike traditional liquid formulations, suspension-based formulations inherently contain particles, which may require specific guidance on particle characterization regarding particle levels. In the case of spray-dried protein suspensions, it is worth noting the differentiation between the spray-dried solid powders in the suspension and the particles formed due to the degradation of the proteins or excipients. The particle limits for visible particles and subvisible particles are defined by USP < 790 >/EP5.17.2 and USP < 788 >/EP2.9.19, respectively (Saggu et al. 2021). As previously mentioned, the risk of subvisible particle formation upon reconstitution of spray-dried proteins poses an intrinsic challenge, as it can affect protein stability and increase aggregation propensity, both of which are known to impact immunogenicity. Optical techniques such as light obscuration and flow microscopy are valuable for characterizing subvisible particles, but both exert their own limitations (Demeule et al. 2010; Scherer et al. 2012). Additionally, the degradation of non-aqueous media is of major concern, as the resulting byproducts can compromise protein stability. For instance, hydrolytic degradation of triglycerides can produce free fatty acids, which can lead to the formation of insoluble particles and potentially inducing the formation of proteinaceous particles for mAbs (Driscoll 2006; Saggu et al. 2021; Zhang et al. 2022). To address these challenges, it is important to establish robust particle characterization techniques such as Raman spectroscopy, Fourier-Transform Infrared (FTIR) spectroscopy, and mass spectrometry to define the product quality attributes of suspension-based formulations for mAbs (Saggu et al. 2021; Zhang et al. 2022).

From a patient-centric perspective, at-home self-administration of therapeutic mAbs provides substantial advantages in terms of both convenience and cost

savings. Patients are relieved of the need to travel to healthcare facilities, which can be especially beneficial for those living in remote areas or individuals with mobility challenges. Data from the National Health Interview Survey highlighted that transportation barriers hugely impact adherence to medical appointments and can even prevent individuals from seeking care (Wolfe et al. 2020). This issue may pose a serious challenge for patients with chronic conditions (Wolfe et al. 2020). Beyond the convenience factor, the shift to enable at-home self-administration can also significantly reduce the indirect costs associated with other expenses, such as transportation costs, paid-time off, and caregiver support. By reducing the required dose volume, these spray-dried protein suspensions can enable the integration of high-concentration mAbs into devices designed for at-home self-administration. Examples include autoinjectors and on-body wearable injectors, which feature intuitive, user-friendly mechanisms that enable patients to safely and effectively administer their treatments in the comfort of their homes (Sunstrom and Sunstrum 2025). However, injection site reactions following subcutaneous injection can be manifested by various adverse events including erythema, itching, pain, swelling, or bleeding (Zhi et al. 2025). Increased injection pain resulting from high viscosities or prolonged self-administration times can impact patient experience. Additional considerations regarding the isotonicity of the spray-dried formulation with mAbs at high concentrations need to be taken into account to minimize injection site pain and prevent tissue or cell damage at the injection site (Gikanga et al. 2015). Therefore, patient-centric evaluations are essential during clinical development and usability studies to ensure ease of use and minimize discomfort.

Conclusion and future outlook

In conclusion, the application of spray-dried protein suspensions offers an alternative approach to the formulation and delivery challenges of high-concentration formulation for mAbs, with the potential to lessen the burden of treatment for patients and improve global access to critical therapeutic proteins. Additionally, innovative autoinjector technologies are now capable of administering highly viscous formulations with viscosities exceeding 200 cP (Simpson 2025). Other alternative drying technologies, such as spray freeze drying, supercritical fluid drying, electrospinning, microwave-assisted freeze drying, thin-film freeze drying, electrostatic spray drying, microglassification, solvent-based dehydration, and solvent precipitation have demonstrated successes in maintaining the stability of mAbs in a dried solid state (Maa et al. 1999; Gitter et al. 2019; Domján et al. 2020; Mutukuri et al. 2021; Hufnagel et al. 2022; O'Sullivan et al. 2022; Chandrababu et al. 2024; Koynov et al. 2025; Zheng et al. 2025).

Scaling up the manufacturing of spray-dried proteins in an aseptic environment is a vital but challenging aspect of commercializing spray-dried protein suspensions, especially for mAbs. Achieving aseptic conditions during large-scale spray drying is of great importance due to the stringent regulatory requirements for sterility and contamination control. This involves the integration of high-temperature-resistant high-efficiency particulate air (HEPA) filters, sterile liquid filters combined with contamination-free atomization, aseptic handling of spray-dried powders, and sophisticated equipment design to minimize microbial contamination throughout the production process (Arpagaus 2023). Prior approvals of spray-dried non-mAb protein products such as topical fibrin sealant Raplixa® and the first inhaled insulin product Exubera® have paved the road for the feasibility of producing sterile spray-dried proteins on a large manufacturing scale (Sharma et al. 2021). Additionally, ensuring uniformity and reproducibility of spray-dried proteins at high volumes requires optimization of not only the spray drying process parameters but also the formulation compositions, including the choice of excipients for protein stabilization. On the other hand, the downstream process of the powder mixing step with selected non-aqueous media and subsequent filling into syringes or other delivery devices demands careful consideration and specialized handling. Therefore, while protein spray drying holds great promise for enabling high-concentration formulations of mAbs as suspensions, it requires overcoming substantial technical and operational hurdles to ensure a balance between efficiency, quality, and compliance. Taken together, these challenges emphasize the need for multidisciplinary research to bridge the gap between the technological promise of high-concentration spray-dried protein suspensions and their clinical viability for subcutaneous delivery of mAbs.

Abbreviations

mAbs	Monoclonal antibodies
IgG	Immunoglobulin G
ADCs	Antibody-drug conjugates
ADA	Anti-drug antibody
HDX	Hydrogen-deuterium exchange
MS	Mass spectrometry
NMR	Nuclear Magnetic Resonance
FTIR	Fourier-Transform Infrared
FDA	Food and Drug Administration
EMA	European Medicines Agency
USP	United States Pharmacopeia
EP	European Pharmacopeia
HEPA	High-efficiency particulate air

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YTT contributed to conceptualization, visualization, writing the original draft, reviewing and editing the manuscript. The author read and approved the final manuscript.

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The datasets generated and/or analysed during the current study are available in PubMed® (https://pubmed.ncbi.nlm.nih.gov/).

Declarations

Competing interests
The author declares no competing interests.

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