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Shipping-Induced Aggregation in Therapeutic Antibodies: Utilization of a Scale-Down Model to Assess Degradation in Monoclonal Antibodies

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ABSTRACT

It is vital to understand the impact of transportation on monoclonal antibody (mAb) product quality during drug product development. Fully representative real-time shipment studies are resource intensive, so in this work, we studied laboratory agitation methods to mimic the effect of real-time shipment on aggregation, specifically subvisible particle formation. The agitation methods studied include a rotator, orbital shaker, vortexer, and shipping simulator vibration table. The simulator is able to predict the particle formation behavior during real-time shipment for a number of mAbs in vial and prefilled syringe configurations, with a correlation of about 90%, whereas the other methods of agitation were inconsistent. This study demonstrates that using a shipping simulator vibration table provides an opportunity for consistent and predictive development studies of shipping stress with minimal resource requirements during early- or late-stage drug product development.
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Introduction

Monoclonal antibodies (mAbs) are highly effective biopharmaceuticals with continually increasing importance in the pharmaceutical industry. However, they can be difficult to develop because of the propensity for physical and chemical degradation as a result of external stresses and intrinsic instability.[1,2] Aggregation is a major challenge as it has the potential to reduce the product's efficacy and may be a safety risk due to concerns around the immunogenicity of aggregate species.[3,4] Aggregates can be formed by many factors including elevated temperatures, light exposure, and processing such as mixing, freezing, and agitation/shipping.[5-7] In addition, aggregates may exist across many size ranges from dimers to subvisible and visible particles, leading to challenges in characterizing and predicting them.[6]

The aggregation caused by agitation is potentially due to the proteins' tendency to adsorb to and partially unfold at interfaces. Significant efforts are ongoing to mechanistically understand the details of how this adsorption leads to aggregate and particle formation,[8,9] and although much has been accomplished, there are still many unknowns. Small aggregate species may form at the interface or due to desorption of partially unfolded proteins, which may lead to the formation of larger aggregates in solution.[10] Gel formation at interfaces has been observed,[11,12] which can lead to particles when the gel is disrupted or broken. This breakage may be triggered by dilation forces[13,14] caused by the expansion or compression of surfaces or by surface tension forces such as between a moving bubble and a solid-liquid interface.[15] Vigorous agitation may also cause cavitation.[6] Different types of stress,[16,17] including different sources of agitation stress,[18-20] can have significant impact on the amount and character of the aggregates formed. Aggregate formation can also vary significantly for different molecules.[21] The complexity of particle formation even in simple agitation systems is further exaggerated in complex agitation such as vibration stress, the major component of shipping stress.[22]

Transportation-induced degradation is frequently mitigated by the addition of surfactants, such as polysorbate, to the formulation.[18,19,23,24] Surfactants protect mAb solutions by competitively binding to interfaces,[14] reducing protein adsorption and interfering with surface gelation, or by interacting directly with the protein.[23] However, the minimum required concentration to achieve these mitigating effects can be product dependent. In early development,

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shipping studies are frequently used to screen for optimal surfactant concentration in various drug product formulations. In later development, a shipping component is often included in long-term stability studies to ensure there is no impact on aggregate or particle formation rates. Throughout development, a robust, repeatable, and efficient method to study shipping stress is required.

Directly studying the impact of shipping stress for products in development has a number of challenges including resource requirements and consistency.[22] Design of an appropriate shipping route can be challenging because no single route could possibly cover every scenario that may be experienced during commercial distribution. To cover the most likely stresses, a shipping route should include both air and ground transportation, preferably with repetition of both types of shipment. Constraints associated with needing multiple sites to facilitate round-trip shipment and avoid customs or other long-term holds can create additional challenges. Once a route is designed, variability may still be a concern, especially if comparison of data between separate shipments is required. The variability can arise from differences in traffic, route choices, road conditions, handling, weather, wind patterns, and air turbulence, even if samples follow the same shipping path. Furthermore, these shipments often require cold chain, pallet shipment, and overnight shipments, all leading to high costs. In addition, to achieve sufficient shipping stress, these studies can be time consuming. These extensive resource requirements can be restrictive.

A laboratory method to provide agitation stress has many advantages because of the minimal resource requirements and the improved reproducibility created by applying the identical stress profiles in each run. However, it can be difficult to determine the amount and character of the stress experienced by proteins, so laboratory methods may not accurately reflect the real-life situation.[6] Different types of agitation, such as shaking and stirring, have been observed to impact protein solutions differently, impacting both the extent of particle formation and the characteristics of the particles.[17-19] In this work, we study the extent of particle formation in various mAb solutions under different stress conditions to find suitable equipment and appropriate settings to predict real-time shipment results.

This work focuses on a comparison to an established shipping route used for development characterization purposes. The route comprised 4 cross-continental shipments, where each one includes air and ground transportation. Three bench-top methods are evaluated along with a shipping simulator vibration table. Bench-top methods are chosen to cover a broad range of commonly used methods, including a vortexer, orbital shaker, and rotator. Testing multiple methods provides an opportunity of determining if the type of motion is important to a methods' predictive capability.

This work does not consider the temperature and pressure components of shipment, although they may also have an impact. Real-time shipments and studies on the shipping simulator were executed with passive temperature control to maintain a cold environment, regardless of external conditions. Bench-top studies were run at room temperature. The real-time shipments experienced all ambient pressure variations, especially during air transport. Bench-top and shipping simulator studies were run at ambient pressure. Further studies are required to understand the impact of the temperature and pressure components of shipment.

Physical degradation of multiple mAbs in various formulations and vial and syringe configurations are compared to determine the most predictive method and settings. Chemical degradation is not considered. The formulations studied are optimized for each mAb but did not contain polysorbate as the fully optimized formulations with polysorbate are protected from particle formation during shipment. A polysorbate screening study was conducted for the best agitation method to verify the comparison to real-time shipment.

Materials and Methods

Monoclonal Antibody Solutions

Previously optimized formulations of mAbs were used in these studies, including 5 IgG1 and 1 IgG4 subtype. Only one formulation and protein concentration is examined for each antibody included in the study; the impact of varied composition is not studied. However, the formulations encompass a wide range of protein concentrations (6-150 g/L) and multiple excipients, including sugars and amino acids. Unless specifically noted, the formulations did not contain surfactants to induce degradation and differentiate models.

A fill volume of 1.5 mL in a 3-cc vial is used for most samples. For Mab F, a 2.0-mL fill in a 10-R vial was used. For Mabs A and C, a 1.0-mL fill in a 1-mL long prefilled syringe is studied in addition to the 3-cc vial configuration. Details of the formulations and configurations studied are provided in Table 1.

Agitation Stress

Vials and syringes are agitated in a horizontal orientation to allow stopper contact and maximize the air-water interface in the vial and to promote bubble movement in the syringe, to ensure the worst-case degradation. For the bench-top methods, including vortex, rotator, and orbital shaker, the samples are secured directly to the agitation surface. For the real-time shipment and shipping simulator, samples are stored securely in sample boxes, which are then packaged into a larger box which is placed inside an insulated transportation tote with ice and cold packs to maintain temperature control. The tote is secured to the vibration table of the shipping simulator, or to a pallet for real-time shipment, to ensure the sample orientation is maintained. The equipment used and the direction of motion are shown in Figure 1.

Table 1
Formulations and Configurations Studied

mAb	IgG Subtype	Protein Concentration, g/L	Excipient Type	Container	Fill Volume, mL
Mab A	IgG1	20	Sugar	3-cc Vial	1.5
				1-mL Syringe	1.0
Mab B	IgG1	100	Sugar	3-cc Vial	1.5
Mab C	IgG1	100	Sugar	3-cc Vial	1.5
				1-mL Syringe	1.0
Mab D	IgG4	6	Sugar/amino acid	3-cc Vial	1.5
Mab E	IgG1	150	Sugar/amino acid	3-cc Vial	1.5
Mab F	IgG1	50	Sugar	10-R Vial	2.0

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