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Review

Histidine as a versatile excipient in the protein-based biopharmaceutical formulations

Jia-Yi Lv [a b c 1], Rahul G. Ingle [a d 1], Hao Wu [e], Cuihua Liu [f], Wei-Jie Fang [a b g h]

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Abstract

Adequate stabilization is essential for marketed protein-based biopharmaceutical formulations to withstand the various stresses that can be exerted during the pre-

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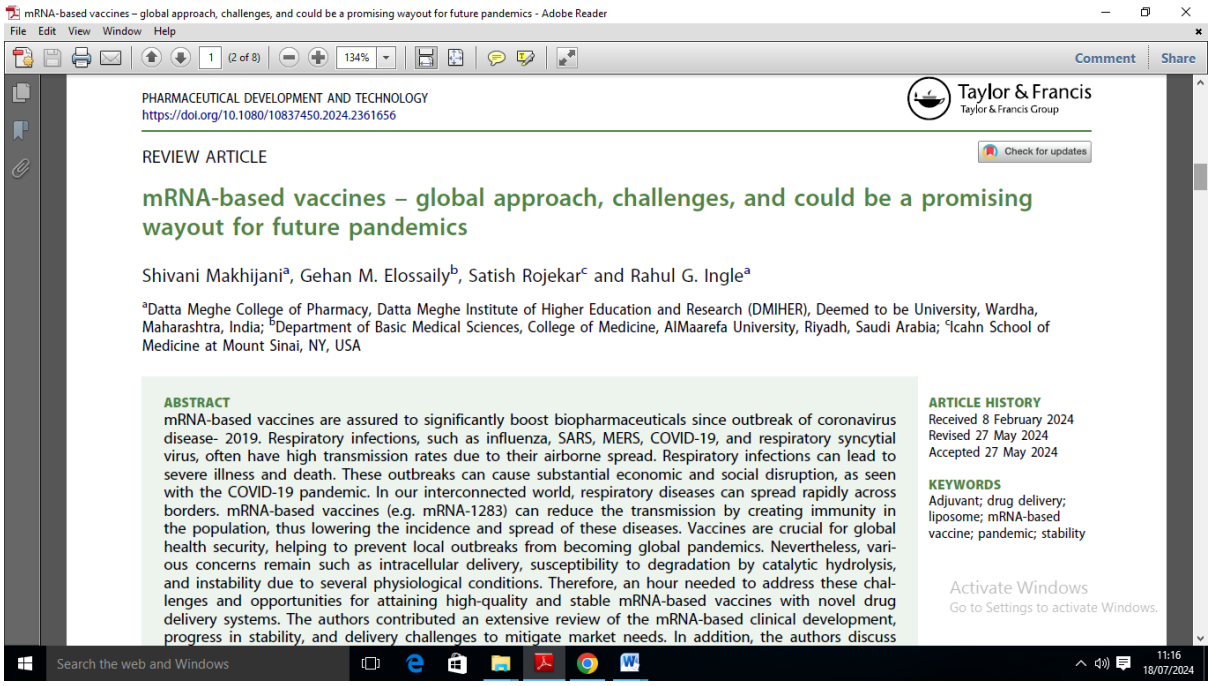

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REVIEW ARTICLE

mRNA-based vaccines – global approach, challenges, and could be a promising wayout for future pandemics

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ABSTRACT

mRNA-based vaccines are assured to significantly boost biopharmaceuticals since outbreak of coronavirus disease- 2019. Respiratory infections, such as influenza, SARS, MERS, COVID-19, and respiratory syncytial virus, often have high transmission rates due to their airborne spread. Respiratory infections can lead to severe illness and death. These outbreaks can cause substantial economic and social disruption, as seen with the COVID-19 pandemic. In our interconnected world, respiratory diseases can spread rapidly across borders. mRNA-based vaccines (e.g. mRNA-1283) can reduce the transmission by creating immunity in the population, thus lowering the incidence and spread of these diseases. Vaccines are crucial for global health security, helping to prevent local outbreaks from becoming global pandemics. Nevertheless, various concerns remain such as intracellular delivery, susceptibility to degradation by catalytic hydrolysis, and instability due to several physiological conditions. Therefore, an hour needed to address these challenges and opportunities for attaining high-quality and stable mRNA-based vaccines with novel drug delivery systems. The authors contributed an extensive review of the mRNA-based clinical development, progress in stability, and delivery challenges to mitigate market needs. In addition, the authors discuss

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Review

An Overview of the Stability and Delivery Challenges of Commercial Nucleic Acid Therapeutics

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Abstract: Nucleic acid (NA)-based biopharmaceuticals have emerged as promising therapeutic modalities. NA therapeutics are a diverse class of RNA and DNA and include antisense oligonucleotides, siRNA, miRNA, mRNA, small activating RNA, and gene therapies. Meanwhile, NA therapeutics have posed significant stability and delivery challenges and are expensive. This article discusses the challenges and opportunities for achieving stable formulations of NAs with novel drug delivery systems (DDSs). Here we review the current progress in the stability issues and the significance of novel DDSs associated with NA-based biopharmaceuticals, as well as mRNA vaccines. We also highlight the European Medicines Agency (EMA) and US Food and Drug Administration (FDA)-approved NA-based therapeutics with their formulation profiles. NA therapeutics could impact future markets if the remaining challenges and requirements are addressed. Regardless of the limited information available for NA therapeutics, reviewing and collating the relevant facts and figures generates a precious resource for formulation experts familiar with the NA therapeutics' stability profile, their delivery challenges, and regulatory acceptance.

Keywords: drug delivery; excipient; formulation; mRNA vaccine; nucleic acid therapeutics; stability

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1. Introduction

Biopharmaceuticals are at the supreme level of the pharmaceutical market due to their high efficacy, high specificity, and low toxicity profiles [1]. Recently, nucleic acid (NA) therapeutics have emerged as promising candidates for several severe diseases and disorders. NAs are present in all living organisms, including humans, animals, and plants [2]. NAs are naturally occurring chemical compounds; certain small NAs are also synthesized in the laboratory. NAs can be broken down into sugars, phosphoric acid, and a mixture of organic bases (e.g., purines and pyrimidines). NAs have been developed as therapeutic agents and carefully characterized to provide the intended quality, efficacy, and safety profile. NAs are complex and delicate molecules that require sophisticated processes with clever handling during manufacturing, which makes these drugs more expensive. The stability of NAs during manufacturing, handling, shipping, and long-term storage is a major subject of discussion. Excipients play a key role in designing NA therapeutics by improving the manufacturability, stability, quality, and safe delivery of the products [3].

Due to their complex nature, NAs require special attention as active pharmaceutical ingredients (APIs). The alteration in NA quality as a result of physicochemical degradation makes their formulation development challenging. Therefore, several aspects must be considered, including active drug concentration, excipients, delivery routes, and novel drug delivery systems (DDSs). The use of excipients at optimized concentrations aims to maintain the stability of NA therapeutics [4]. However, a key obstacle for the formulation expert is to formulate stable NA therapeutics with the narrow range of excipients usually employed in parenteral settings. Therefore, the launch of novel and ideal excipients to

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Lessons Learned

Freeze-Dried Monoclonal Antibody Formulations are Unexpectedly More Prone to Degradation Than Liquid Formulations Under Shaking Stress

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ABSTRACT

Liquid biopharmaceuticals including monoclonal antibodies (mAbs) have been widely acknowledged to undergo various stresses during shipping/handling and long-term storage. Several mechanical stresses including shaking during shipping has been widely known to cause protein aggregation and sub-visible particle (SbVP) formation in liquid biopharmaceutical formulations. However, shaking-induced degradation of freeze-dried (FD) biopharmaceuticals has seldomly been reported in the literature and therefore this type of stress is widely overlooked in industry due to their presumed high stability, especially when the formulations and freeze-drying processes are fully optimized. In this Lessons Learned article, we report an interesting phenomenon in which the optimized FD biopharmaceutical formulations of three typical mAbs showed much degradation and SbVP formation under shaking stress compared with their liquid counterparts. This is a striking deviation to the notion that mAbs are generally more stable in the FD formulations than in the liquid ones. Therefore, shaking stress experiment should be considered a critical stress condition for early-stage selection of liquid versus FD mAb formulations.

Nowadays, biopharmaceuticals especially monoclonal antibodies (mAbs) are at the supreme level of pharmaceutical market due to high efficacy, high specificity, and low toxicity, and have been used for the treatment of various severe diseases such as autoimmune diseases, cancers, and infections.[1] Like most biopharmaceuticals, mAbs are inclined to chemical and physical degrdation during manufacturing, handling, shipping, and long-term storage.[2, 3] Aggregation and sub-visible particle (SbVP) formation of mAb formulations have been widely recognized as potential concerns that affect the safety and efficacy profile of the biopharmaceuticals.[4] It is also widely recognized that freeze-dried (FD) biopharmaceuticals, especially with optimized formulations and/or freeze-drying processes, afford superior stability during shipping, handling, and long-term storage compared with their liquid counterparts.[5] Therefore, to increase biopharmaceutical stability, labile biopharmaceuticals are generally formulated in the FD state.

Shaking induced degradation of liquid biopharmaceutical formulations due to interfacial and shear stresses has been widely known.[6] On the contrary, shaking induced degradation of freeze-dried biopharmaceuticals including mAbs has only been reported once in literature. Telikepalli and coworkers reported the physical degradation of a FD mAb formulation after accelerated shipping-like stress.[7] Surprisingly, no further work was reported on similar scenario. In this Lessons Learned article, we report an interesting phenomenon in which the optimized FD biopharmaceuticals of three mAbs (either commercialized or in late-stage development) are much more prone to degradation and SbVP formation during shaking compared with their liquid counterparts. This is in dramatic contrast to what we have generally assumed that optimized FD biopharmaceutical formulations are always more stable than liquid formulations.

Model mAbs (mAb-1, mAb-2, and mAb-3) were manufactured using a mammalian cell (Chinese Hamster Ovary) expression system by Zhejiang Bioray Biopharmaceutical (http://www.bioraypharm.com/, Zhejiang, China), which was spinned off from Zhejiang Hisun Pharmaceutical (Zhejiang, China) in late 2019. mAb-1 has been recently approved by the National Medicinal Products Administration

Abbreviations: CHO, Chinese hamster ovary; DLS, dynamic light scattering; FD, freeze-dried; IgG, immunoglobulin G; mAb, monoclonal antibody; MFI, micro-flow imaging; NMPA, National Medicinal Products Administration of China; OD_{320}, optical density at 320 nm; PS, polysorbate; SbVP, sub-visible particle; SE–HPLC, size exclusion –high performance liquid chromatography; UV–Vis, ultraviolet–visible.

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Review

Prefilled dual chamber devices (DCDs) – Promising high-quality and convenient drug delivery system

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ABSTRACT

Prefilled dual chamber devices (DCDs) are combination products containing freeze-dried drug and diluent in two separate chambers of the device. DCDs provide high stability and convenience to patients and doctors, thus significantly improving product quality, patient compliance and market competitiveness. DCDs should also provide seal integrity, sterility and compatibility with biopharmaceuticals and avoid leachability and needle stick injuries. DCDs are promising alternatives to traditional containers or devices for biopharmaceuticals. The regulatory and medical practice to choose plastic DCDs as better alternatives over well-established glass syringes will be addressed here. The impact and major issues during processing, manufacturing, and storage of DCDs are also highlighted. Further discussion clears its business potential, composition, stability testing, and quality standard requirements to deal with market competition. It also covers major role of extractables and leachables in storage stability of the product.

1. Introduction

Prefilled dual chamber devices (DCDs) are combination products containing freeze-dried drug and diluent in two separate chambers of the device (Candido and Winnie, 1992; Lin et al., 2002). DCDs have been show many advantages over the traditional drug-delivery systems (DDSs) such as accurate dosing, easy handling, seal integrity, and high stability, and therefore are promising alternatives to these DDSs. DCDs show upsurge market scenario with many processing and manufacturing challenges addressed here. Nowadays, DCDs such as Mix jet, Vetter Lyo-Ject (Fig. 1), and LyoTwist are becoming popular choices for physicians and patients in need of instant acting and safe delivery (i.e., free of needlestick injuries and airborne bacterial contaminants) (Ninomiya et al., 2001; Mitrano et al., 1986; Gurman et al., 2014), significantly improving patient compliance by easily applying pressure to the end plunger after mixing and dissolving of freeze-dried powder. Compared with the traditional prefilled syringes (PFSs), DCDs could improve long term (bio)pharmaceutical stability by storing them in freeze-dried form before administration and therefore are becoming more popular specially for those unstable (bio)pharmaceutical products. It is glue free to eradicate the risk of interaction with drug product and cannot be reused which makes it safe for disposal. The development of DCDs, for a drug and flush solution instead of catheter seems to be an important step to facilitate good clinical practices in many hospitals. It avoids patient's complications such as phlebitis or infection due to the catheters and becomes handy to the medical staff (Parreira et al., 2020a,b). A brief comparison and necessary steps before administration among traditional vials, PFS/Cartridges, and DCDs are shown in Table 1 and Fig. 2 respectively. Conventional injectables that involve vials and ampoules cannot serve this purpose to administer the same drug. These are the main reasons why DCDs are gaining a significant upsurge in the market as emerging DDS for injectables. DCDs move towards a purpose of individualized treatment regimens and improve quality of life (Michaels, 1988; Kafal et al., 2018; Ma et al., 2012). However, the

Abbreviations: BD, Becton Dickinson; CCI, Container-Closure Integrity; CCS, Container Closure System; COC, Cyclic Olefin Copolymer; COP, Cyclic Olefin Polymer; CZ, Crystal Zenith; DCC, Dual Chamber Cartridge; DCD, Dual Chamber Device; DCS, Dual Chamber Syringe; DDC, Drug-Device Combination; DDS, Drug-Delivery System; DTP-IPV, Diphtheria-Tetanus-Whole Cell Pertussis with Inactivated Poliovirus Vaccine; E&L, Extractables and Leachables; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; GC-HS, Gas Chromatography-Headspace; ISO, International Organization for Standardization; PFS, Prefilled Syringe; PRP-T, Polyribosylribitol Phosphate Conjugated to Tetanus Toxoid; USP, United States Pharmacopoeia.

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ORIGINAL RESEARCH ARTICLE

The Effects of Excipients on Freeze-dried Monoclonal Antibody Formulation Degradation and Sub-Visible Particle Formation during Shaking

Meng-Jia Jin[1,2] · Xin-Zhe Ge[1,2] · Qiong Huang[1,2] · Jia-Wei Liu[1,2] · Rahul G. Ingle[3] · Dong Gao[4] · Wei-Jie Fang[1,2,5,6]

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Abstract

Purposes We previously reported an unexpected phenomenon that shaking stress could cause more protein degradation in freeze-dried monoclonal antibody (mAb) formulations than liquid ones (J Pharm Sci, 2022, 2134). The main purposes of the present study were to investigate the effects of shaking stress on protein degradation and sub-visible particle (SbVP) formation in freeze-dried mAb formulations, and to analyze the factors influencing protein degradation during production and transportation.

Methods The aggregation behavior of mAb-X formulations during production and transportation was simulated by shaking at a rate of 300 rpm at 25℃ for 24 h. The contents of particles and monomers were analyzed by micro-flow imaging, dynamic light scattering, size exclusion chromatography, and ultraviolet – visible (UV–Vis) spectroscopy to compare the protective effects of excipients on the aggregation of mAb-X.

Results Shaking stress could cause protein degradation in freeze-dried mAb-X formulations, while surfactant, appropriate pH, polyol mannitol, and high protein concentration could impact SbVP generation. Water content had little effect on freeze-dried protein degradation during shaking, as far as the water content was controlled in the acceptable range as recommended by mainstream pharmacopoeias (i.e., less than 3%).

Conclusions Shaking stress can reduce the physical stability of freeze-dried mAb formulations, and the addition of surfactants, polyol mannitol, and a high protein concentration have protective effects against the degradation of model mAb formulations induced by shaking stress. The experimental results provide new insight for the development of freeze-dried mAb formulations.

Keywords aggregation · freeze-dried/drying · monoclonal antibody · shaking stress · sub-visible particle

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Abbreviations

DLS	Dynamic light scattering
HES	Hydroxyethyl starch
His-HCl	Histidine-HCl
k_D	Diffusion interaction parameter
mAb	Monoclonal antibody
MFI	Micro-flow imaging
NMPA	National Medicinal Products Administration of China
PDI	Distribution coefficient
PES	Polyethersulfone
PS	Polysorbate
SbVP	Sub-visible particle
SE – HPLC	Size exclusion high-performance liquid chromatography
UV – Vis	Ultraviolet – visible spectroscopy