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Editorial Board Member of *World Journal of Clinical Oncology*, Boulaiz Houria, PhD, Doctor, Professor, Department of Human Anatomy and Embryology, Institute of Biopathology and Regenerative Medicine, School of Medicine, University of Granada, Granada 18012, Spain

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MINIREVIEWS

Formulation strategies in immunotherapeutic pharmaceutical products

Yajie Zhang, Robert O Williams III, Haley Oana Tucker

ORCID number: Yajie Zhang (0000-0001-5570-5436); Robert O Williams III (0000-0003-4993-6427); Haley Oana Tucker (0000-0001-7735-2862).

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Yajie Zhang, Robert O Williams III, Division of Molecular Pharmaceutics and Drug Delivery, College of Pharmacy, The University of Texas at Austin, Austin, TX 78712, United States

Haley Oana Tucker, Departments of Bioengineering and Molecular Biosciences, The University of Texas at Austin, Austin, TX 78712, United States

Corresponding author: Haley Oana Tucker, PhD, Professor, Departments of Bioengineering and Molecular Biosciences, The University of Texas at Austin, 1 University Station A5000, Austin, TX 78712, United States. haleytucker@austin.utexas.edu

Abstract

Development of immunologic-based biopharmaceutical products have strikingly increased in recent years and have made evident contributions to human health. Antibodies are the leading entity in immunotherapy, while chimeric antigen receptor T cells therapies are the advent of a novel strategy in this area. In order to enable antibody candidates or cells available as products, formulation is critical in terms of stabilize molecules or cells to achieve practical shelf life, storage and handling conditions. Here we provide a concise and contemporary review of ongoing formulation strategies and excipients used in approved antibodies and cellular therapeutic products. Excipients are categorized, and their function in formulations are discussed.

Key words: Immunotherapeutic; Pharmaceutical products; Formulation; Excipients; Cell therapy; Antibody

Core tip: In this review, we have focused on the formulation strategies and excipients that have been used in commercialized antibody products as well as the formulation concerns for immuno-cell therapy. Development of immunologic-based biopharmaceutical products have strikingly increased in recent years and have made evident contributions to human health. Antibodies are the leading entity in immunotherapy, while chimeric antigen receptor T cells therapies are the advent of a novel strategy in this area.

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INTRODUCTION

The approval of the first therapeutic monoclonal antibody (mAb) in 1986, Orthoclone OKT3, "opened the gate" of antibody therapy. Since then, more than 70 mAbs has been approved continuously and applied in both diagnose and therapeutics[1]. The performance of these products has proved to be remarkable in terms of minimized adverse effect and outstanding efficacy, which results from their unparalleled specificity and avidity. Yu *et al*[2] reported that progression-free survival and overall survival were greatly improved in lung cancer patients by immunotherapies as compared to chemotherapy without suffering the associated adverse reactions of chemo-patients. In addition, the half-life of mAbs are typically much longer than small molecules. For instance, the half-life of the anti-IgE mAB omalizumab (Xolair®) is 26 d[3]. This allows for once-monthly dosing, thereby avoiding the need of twice-daily doses of antihistamine agents for chronic idiopathic urticaria patients[3].

The year 2017 was celebrated within the pharmaceutical industry because of the approval of the first gene therapy product and the first two cellular therapy products, Yescarta and Kymriah™[4]. This historic action not only set forth the application of cellular immunotherapy but buttressed the success of biotechnology in disease treatment. Yescarta™ and Kymriah™, developed by Kite and Novartis, respectively, were based on chimeric antigen receptor (CAR) T-cell therapy of hematological cancers. In CAR T-cell therapy, patient's autologous T cells are collected and genetically modified by either viral or non-viral methods to express CARs specific for given tumor antigens. The modified cells are subsequently sorted and expanded *ex vivo* before re-infusion back into patients. CAR is a fusion of two domains: An extracellular domain for tumor antigen recognition and an intracellular signaling domain that mediates T-cell activation[5]. Recently, anti-CD19 CAR T cells have been demonstrated to be remarkably effective for the treatment of relapsed or refractory B-cell malignancies in pediatric and adult patients[5,6].

Indeed, the growing market of Ab-based drugs and the advent of CAR T cell therapy have illustrated the success of the application of basic immunology to disease treatment. However, several issues have to be addressed to improve the "drugability" of new entities and to develop more candidates into products. An approved drug product must possess stable shelf-life and to endure the stresses of handling and transportation. Thus, stability and preservability have become a major challenge to Abs and cell therapies due to their relative unstable nature. Biologics are sensitive to external conditions, such as temperature changes, agitation, moisture (for solid forms), pH changes, and exposure to interfaces or denaturants[7]. Therefore, appropriate formulation is needed to enhance the stability of active pharmaceutical ingredients to maintain their potency and safety by directly or indirectly interacting with the active pharmaceutical ingredient to prevent them from being damaged by harmful factors.

In this review, we have focused on the formulation strategies and excipients that have been used in commercialized Ab products as well as the formulation concerns for immuno-cell therapy.

FORMULATIONS AND EXCIPIENTS IN ANTIBODY-BASED BIOPHARMACEUTICAL PRODUCTS

As shown in Table 1, Ab formulations are mostly in liquid form and occasionally in solid forms such as lyophilized powders. The excipients selected for Ab formulations can be categorized into 5 classes: Sugars and polyols, amino acids, surfactants, buffer and tonicifying agents, and others (preservatives, antioxidants, and chelators) (Figure 1).

Sugars and polyols

Sugars have been identified as one of the intracellular solutes (osmolytes) that stabilize microorganisms under harsh conditions such as serious dehydration and elevated temperature. Being wisely utilized in pharmaceutical industry, sugars and polyols are effective in stabilizing therapeutic Abs thereby protecting them from aggregation, denaturation and other degradative pathways in both dried and solution states.

In solution, sugars can stabilize Abs *via* increasing their melting temperatures (Tm), raising water surface tension, excluded volume effects, and preferential hydration at high concentrations[8,9]. For instance, sorbitol has been shown to increase the Tm of human IgG and reduce its aggregation during the heating process, which is employed for viral inactivation[10]. Sek[11] studied the effect of polyols in increasing the unfolding

Table 1 List of antibody products approved by the United States Food and Drug Administration in 2018 and through May 2019. Information source: www.fda.gov and each product's package insert

Trade name	API	Yr	Sponsor	Excipients[1]	Form	Storage condition
Skyrizi	Risankizumab-rzaa	2019	Abbvie	Disodium succinate hexahydrate, polysorbate 20, sorbitol, and succinic acid	Liquid	2-8 °C, avoid light/shake/freeze
Evenity	Romosozumab-aqqg	2019	Amgen	Acetate, calcium, polysorbate 20, and sucrose	Liquid	2-8 °C, avoid light/shake/freeze
Cablivi	Caplacizumab-yhdp	2019	Ablynx/Ablynx	Citrate dihydrate, polysorbate-80, sucrose, and trisodium citrate dihydrate	Lyophilized Powder	2-8 °C, avoid light /freeze
Trogarzo	Ibalizumab-uiyk	2018	TaiMed Biologics/ Theratechnologies	L-histidine, polysorbate 80, sodium chloride, sucrose	Liquid	2-8 °C, avoid light/shake/freeze
Ilumya	Tildrakizumab	2018	Sun pharma	L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose	Liquid	2-8 °C, avoid light/shake/freeze
Crysvita	Burosumab-twza	2018	Ultragenyx pharmaceutical/kyowa hakko kirin	L-histidine, L-methionine, polysorbate 80, D-sorbitol	Liquid	2-8 °C, avoid light/shake/freeze
Aimovig	Erenumab-aooe	2018	AmgenNovartis	Acetate, polysorbate 80, sucrose	Liquid	2-8 °C, avoid light/shake/freeze
Poteligeo	Mogamulizumab-kpkc	2018	Kyowa hakko kirin	Citric acid monohydrate, glycine, polysorbate 80	Liquid	2-8 °C, avoid light/shake/freeze
Takhzyro	Lanadelumab	2018	Dyax/ Shire	Citric acid monohydrate, L-histidine, sodium chloride, sodium phosphate dibasic dihydrate	Liquid	2-8 °C, avoid light/shake/freeze
Lumoxiti	Moxetumomab pasudotox-tdfk	2018	AstraZeneca	Glycine, polysorbate 80, sodium phosphate monobasic monohydrate, sucrose	Lyophilized Powder	2-8 °C, avoid light/shake/freeze
Ajovy	Fremanezumab-vfrm	2018	Teva	Disodium ethylenediaminetetraacetic acid dihydrate (EDTA), L-histidine, L-histidine hydrochloride monohydrate, polysorbate-80, sucrose	Liquid	2-8 °C, avoid light/shake/freeze
Emgality	Galcanezumab-gnlm	2018	Eli Lilly	L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sodium chloride	Liquid	2-8 °C, avoid light/shake/freeze
Libtayo	Cemiplimab-rwlc	2018	Regeneron/Sanofi	L-histidine, L-histidine monohydrochloride monohydrate, sucrose, L-proline, polysorbate 80	Liquid	2-8 °C, avoid light/shake/freeze

[1]Water for injection and pH adjusting reagents, such as hydrochloric acid and/or sodium/potassium hydroxide, are not specified here. API: Active pharmaceutical ingredient.

temperature of several Abs and reported that the extent of stabilization improved with increasing polyol concentration or with larger polyols conferring greater stability[11].

It has been widely demonstrated that solidifying biologics can improve the long-term storage stability of the biopharmaceutical product as well as ease shipping and storage related problems. Lyophilization or freeze-drying is the most commonly used technique to produce protein and peptide solids[12]. There are three major steps during lyophilization: Freezing, primary drying and secondary drying. During the processes, sugars and polyols can exert significant stabilizing effects *via* mechanisms such as water replacement and vitrification[13]. Moreover, sugars and polyols act as bulking agent to maintain the integrity of lyophilized "cake" structures[14].

Sucrose, trehalose, mannitol, and sorbitol are the most frequently selected additives for protein formulations, acting as the stabilizer in both solid and liquid forms as well as lyoprotectants and/or bulking agents in solid form[15]. Reducing sugars, comprised of monosaccharides and most disaccharides (including glucose, lactose, fructose, maltose, and maltodextrins) should be avoided in Ab formulations. This group of compounds can degrade Abs *via* the Maillard reaction during storage which leads to degradation and deactivation of the Abs[16,17].

Amino acids

The amino acid seems an ideal excipient in pharmaceutical development due to its natural origin, safety within the human body, and other functions that benefit formulations. Thus far, the most frequently used amino acids that stabilize Ab molecules in pharmaceutical products include histidine, arginine, and glycine. Amino acids have been reported to stabilize proteins by various mechanisms, including buffering capacity, thermal stabilization, antioxidant properties, preferential hydration and direct/indirect interaction with proteins[9,18,19].

For example, the stabilizing effect of an equimolar mixture of L-Arg and L-Glu on colloidal and conformational stability of four monoclonal antibodies (mAb1–mAb4) at different pH was examined[20]. L-Arg and L-Glu increased the aggregation temperature of all four mAbs in a concentration-dependent manner and elevated the unfolding temperature of the least thermally stable mAb3, without direct effects on the Tm1 of other mAbs. Consequently, aggregation is suppressed with increasing temperature/pH and, importantly, under accelerated stability conditions at weakly acidic to neutral pH[20].

Surfactants

Surfactants are one of the routine additives in biopharmaceutical products (Table 1). Non-ionic surfactants are formulated with Abs to specifically assist protein refolding and non-specifically suppress surface interaction-related aggregation against various stresses, including increasing temperature, freezing, dehydration, rehydration, and agitation. The fundamental pathway of the surfactant stabilization effect is to prevent surface adsorption and subsequent denaturation of Abs *via* competing with the protein for container surface, air-water interface, ice-water interface, solid-air interface and any other non-specific adsorption[9,21-23]. Certain surfactants also can directly and specifically bind noncovalently to the hydrophobic region of Abs. Stabilization results when the binding of the surfactant ligand is weaker in the non-native state than in the native state. This allows binding to hydrophobic sites of the protein to protect it from interacting with other Abs or surfaces[24]. Most commonly added surfactants are polysorbate 20, polysorbate 80, and poloxamer 188, regardless liquid or solid forms[25].

Buffer agents and tonicifying agents

Buffer systems are typically comprised of two chemical species that are related to a change in protonation state. The major function of a buffering agent system in a formulation is to provide a relatively consistent pH at which the active ingredient is physically and chemically stable. Several chemical degradation pathways are pH dependent for example, deamidation and oxidation. An arginine-acetate buffer was found to stabilize an IgG1 Ab against deamidation and aggregation at pH 4.5 to 6.0[26]. In addition, buffer agents also influence the electrostatic interaction both inter- and intra-molecularly by controlling solution pH. Otherwise, intramolecular charge repulsion can compromise the native structure of Abs, leading to protein unfolding[27]. Alternatively, intermolecular charge repulsion can protect the native structure, resulting in increasing Ab colloidal stability and solution phase stability[27,28]. Commonly used salt buffer systems are listed in Table 2.

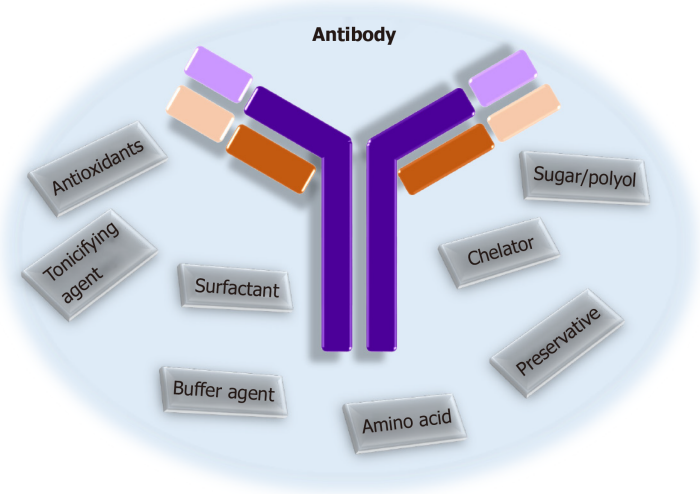

Figure 1 Cartoon of antibody formulations and excipients. Heavy chain (purple) and light chain (brown) constant regions; heavy (purple) and light (brown) antigen-binding variable regions. Excipients are depicted as gray rectangles which associate with Abs in noncovalent fashion.

Besides maintaining pH, as mentioned above, salts also can act to resolve "tonicity" (*i.e.*, osmotic pressures differences between two solutions). Sodium chloride is the most commonly used of the iso-tonicizing agents. Other than salts, excipients like mannitol, lactose, and glycerin, are also incorporated into Ab formulations (mostly parenteral) to prevent tonicity related symptoms, including pain, irritation or tissue damage at the administration site[21].

Preservatives, antioxidants, and chelators

Chelators and antioxidants are typically used to prevent the oxidation of Abs and other excipients. Several conserved amino acid residues encoded within Abs, such as methionine and cysteine, are prone to oxidative degradation. During stages of production, purification, formulation, and storage, three sources can provide oxidative molecules to product formulations, including trace metal ions from containers or handling tools (during the extended production process), hydrogen peroxide from sanitizing agents, and additional oxidant impurities from other excipients[29,30]. Besides, antimicrobials are typically added to the formulations, especially when employing multi-dose vials, as preservatives to inhibit microbial proliferation. These frequently employed antioxidants, chelators and antibiotics include edetic acid/or edetate salts (*e.g.*, EDTA), glutathione, metacresol, phenol, benzyl alcohol, benzalkonium chloride, and certain amino acids such as methionine and cysteine[25].

IMMUNO-CELL THERAPY FORMULATIONS

Currently, the typical CAR-T manufacturing process involves blood collection, apheresis, T-cell activation, gene modification, cell expansion, formulation and packaging, cryopreservation, and eventually injection into patients[31]. During these steps, cells experience multiple transportation. They also are exposed to processes such as separation, transduction, expansion and freeze-thaw. Each of the several steps of synthesis and operation require specific environments for the cells which expose them to different compositions in the formulation[32,33]. Similar to other biopharmaceutical products, cells need ancillary materials to provide necessities for stability, including non-oxidative/reducing environment, proper pH, and other critical factors[34]. However, unlike biologics, cell-based products also need nutritional components to keep them alive and to maintain robust metabolism as well as cryoprotectant agents (CPA) to protect them from the stresses caused by dramatic temperature fluctuations during their processing.

CPAs are typically necessary in cell-based products to support cells for surviving freeze-thaw processes that facilitates transportation. Often non-electrolytes are added as CPAs, including low molecular molecules such as sugars, glycerol (trehalose and sucrose) and dimethyl sulfoxide (DMSO), as well as large polymeric molecules (*e.g.*, polyvinylpyrrolidone and hydroxyethyl starch)[35]. Since the discovery of the

Table 2 Non-amino acid buffer systems frequently used in antibody parenteral products

Buffer system	Controlled pH range (25 °C)	Acid	Base	Example product
Phosphate	5.8-7.8	Monosodium phosphate	Disodium phosphate	Tysabri®
Acetate	3.8-5.8	Acetic acid	Sodium acetate	Amgevita®
Citrate	3.0-7.4	Citric acid	Sodium citrate	Humira®
Succinate	3.3-6.6	Succinic acid	Sodium succinate	Kadcyla®
Tris	7-9	Tris-HCl	Tris	Besponsa®

cryoprotective property of DMSO in 1959[36], it has been investigated and routinely employed as a cryoprotectant in cellular products. For example, DMSO is used in majority of mostly approved cell products, HPC cord blood, as well as current CAR-T cell formulations to enable short term storage and transportation between the hospital and the CAR-T cell manufacturer[37].

There are a number of potential issues that concern drug developing organizations and regulatory agencies for CAR-T cell application[38,39]. The exposure of cells to a variety of formulations during the multiple steps of processing and manufacturing may cause the final product to carry residual amounts of the unintended components. These could be potential hazards in a drug product and thus, requires risk assessment. Yet, the limited shelf life of some cellular products and the impact of extensive tests on their quality hinders the removal, or at least the assessment, of the residuals[39-41].

Another issue results from the complexity of ancillary materials or excipients. Even subtle change within culture supplies can be influential to cellular physiology and may lead to the changes in their functional characteristics and performance. Also, serum and recombinant proteins might carry pathogen contamination. Therefore, the quality and stability of ancillary/excipient materials are crucial and need to be strictly controlled[42]. Further studies to improve excipient/ancillary materials, both systemic and detailed, are urgently needed. These include determination of the correlation of excipient with cell density and process parameters (primarily freezing and thawing) as well as container-excipient compatibility. Finally, the developments of novel excipient and even new dosage forms for CAR T-cells are anticipated. For example, a recent patent reported that T cells can be kept activated *via* cross-linking when mixed with biodegradable nanospheres/microspheres[43].

CONCLUSION

The discovery and invention of immunotherapies is a milestone in the history of the battle between humans and diseases. Inactive ingredients (*e.g.*, excipients) are critical component of a successful immune-biopharmaceutical product. This review offers a brief and concise introduction to the currently used excipients and formulation strategies for antibody drugs and immune cell-based therapeutics. Knowledge about formulation compositions for Abs injectables has significantly matured, and the understanding of mechanisms of excipients is increasing. However, more dosage forms are anticipated for mAbs, especially the ones that are less or not invasive to patients, resulting in an improved patient compliance. For example, administration routes such as nasal, respiratory and oral can be promising options. As mentioned previously, the development of immune cell therapy is only in its infancy, future investigation remains. There are still many aspects of issues urgently need to be addressed by formulation scientists, such as manufacture process optimization, excipient choice, and stability of formulation or environment cells are exposed to.

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