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A Review: The Impact Of Excipient Selection On The Stability Of Biological Drugs

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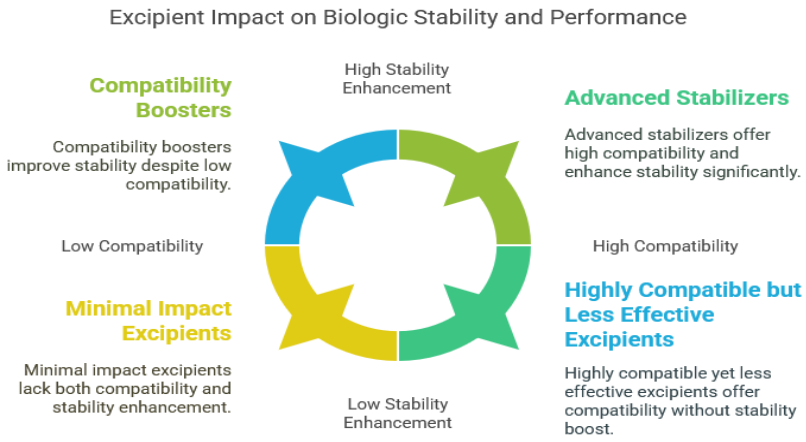
Abstract: Biologics, often known as biological medications, are important part of current therapies since they provide specialized therapy options for a variety of illnesses. However, there are several difficulties in formulating and developing them because of their high molecular size, structural complexity, and limited stability. One important element affecting the safety, effectiveness, and shelf life of biological medications is their stability. Various types of biologics such as monoclonal antibodies (mAbs), recombinant proteins and vaccines are often sensitive to environmental conditions, including temperature, pH and oxidative stress. Excipients added to drug formulations play a crucial role in enhancing the stability, efficacy and delivery of biologics to their respective action sites. In this review, the different kinds of excipients used in biological medication formulation and their effects on biologic stability and the difficulties relating to compatibility, excipient-drug interactions, and regulatory considerations are covered. New developments in excipient formulation are also emphasized as possible ways to improve biologics' performance and stability.

Keywords: Biological drugs, Excipients, Stability, Formulation, Development, Safety, Drug-excipient interactions.

Graphical Abstract:



Introduction: Pharmaceuticals known as biologics are made or extracted from living things using biological processes (including biotechnology techniques) as opposed to chemical synthesis. Because biological products are unique, they can be used to cure a variety of diseases by focusing on a specific gene or protein that is defective. Biologics first appeared on the market around thirty years ago, and since then, they have been successful commercially and improved patient care. Since then, millions of individuals have been treated with nearly 300 authorized biologics, and another 900 are now being developed [1].

The Food and Drug Administration (FDA) definition of "Biological Products" or "Biologics" can be summarized as "any virus, therapeutic serum, toxin, anti-toxin or analogous product applicable to the prevention, treatment or cure of disease or injuries if man" as 2 in CFR 600 [2]. Since the FDA authorized the first therapeutic monoclonal antibody (mAb), muromonab CD3 (Orthoclone OKT3), in 1986 and the first recombinant pharmaceutical, insulin (Humulin), in 1982, they have become indispensable parts of modern drugs. Throughout the past few decades, protein-based therapy for cancer, immunological disorders, infections, multiple sclerosis, and many other diseases has grown at an unparalleled rate thanks to advancements in pathophysiology of diseases, structural and molecular biology, biotechnology, and bioengineering [3,4]. Various biological products are peptides, fusion proteins, monoclonal antibodies, vaccinations, oligonucleotides, blood derivatives and somatic cell therapy. In contrast to tiny molecules produced chemically, these biomacromolecules are relatively large molecules with structural flexibility. For instance, proteins and peptides are classified as multi-domain biological polymers and are composed of residues with a wide range of polarity, hydrophobicity, and cationicity. These structural characteristics offer the advantage of specific binding to treatment targets for optimal safety and efficacy [4]. Comparing biologics to traditional chemically manufactured small-molecule medications, their applications in disease regulation and personalized therapy have contributed significantly to their success and demand. Biologics frequently reduce the possibility of off-target toxicity while optimizing target specificity, which improves the drug's capacity to change and end a disease state [4]. Biologics pose major development hurdles due to their vast size, high structural complexity, and limited stability, despite their inherent therapeutic benefits [5]. Biologics-based treatments have grown to be a significant segment of the pharmaceutical business and are expected to expand at a quick rate in the near future because of its many benefits, which include efficacy and specificity [6].

Concept of Excipient: Drug products are made up of both active and inactive components. In the US, the Code of Federal Regulations (CFR) provides definition of "Active ingredient means any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals"[7].

The U.S. Food and Drug Administration (FDA) defines excipients as "any inactive ingredients that are added intentionally to therapeutic or diagnostic products, but they are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery" [8]. A typical medication product has one or two active pharmaceutical ingredients (APIs) and several excipients. Excipients can account for approximately 50% of solid medication forms and 90% of liquid dosage forms [9]. Excipients are utilized to get rid of the API's problems, namely its poor stability, permeability, and solubility. Excipients can have functional properties such as solvents, stabilizers, buffers, freezing agents, emulsifiers, antimicrobials, etc. Chemically, excipients can include proteins (like human serum albumin), polymers (like polysorbate 80), inorganic salts (like NaCl), organic small molecules (like sorbitol), and water for liquid dosage forms [9].

Regulatory review of excipients: When a new drug application (NDA), investigational new drug application (IND), or biological license application (BLA) is filed, the FDA reviews the excipients in connection with the drug product. There isn't a specific evaluation process for excipients at the moment. In other words, excipients are created and utilized in conjunction with new pharmaceutical products because the FDA does not evaluate them outside of an IND, NDA, or BLA [9].

Functional roles in pharmaceutical dosage form: (i) alter the solubility and bioavailability of the active ingredient or ingredients; (ii) enhance the stability of the drug or ingredients in completed dosage forms; (iii) assist active ingredients in maintaining a preferred polymorphic form or conformation; (iv) preserve the pH and osmolarity of liquid formulations; (v) function as antioxidants, emulsifying agents, aerosol propellants, tablet binders, and tablet disintegrants; (vi) inhibit aggregation or dissociation; (vii) alter the immunogenic response of active ingredients (e.g., adjuvants) and numerous other substances [10].

Challenges and Strategies for Enhancing Protein Therapeutic Stability: Over the last few decades, recombinant technology has resulted in an increase in licensed biotechnology medications and an eventual move toward creating biologically active molecules by cloning and fermentation [11]. The obstacles that must be overcome for recombinantly generated proteins to be effectively used as therapies are stability during manufacture and long-term storage, as well as effective delivery methods that prevent unfavorable immunological adverse effects [12, 13]. Protein therapeutic formulation presents particular issues due to their macromolecular structure, including structural instability, chemical instability, immunogenicity, and delivery route/dosage form issues [14]. Stability of proteins can be improved using a variety of techniques, such as altering the protein's external environment or its intrinsic characteristics. For instance, innate qualities can be changed by chemical modifications like PEGylation, which stabilizes proteins against denaturation and aggregation, or by site-directed mutagenesis, which replaces labile amino acids with ones resistant to chemical decomposition. These changes are difficult, though, and they might impair the protein's biological function. Determining the characteristics of the environment surrounding the protein is therefore the simplest and most popular way to stabilize it. In achieving this, excipients plays crucial role.

C**lasses of excipients used for biotechnology products:** Many excipients have been incorporated into formulations in order to reduce injection discomfort, stabilize proteins, function as antimicrobials, assist in the production of the dosage form, and control or target drug distribution [12, 13]. Aside from the excipients' safety, toxicity, and immunogenicity, the selection of excipients should be informed by the active drug product's degradation routes and the ways in which certain excipients alleviate those instabilities. Preserving the native structure of a protein is the first step of a well-proven generic method that optimizes solution conditions and excipient selection to limit structural modifications and decrease intermolecular interactions. Consequently, changes must be made to the manufacturing and formulation conditions in order to remove phase or interfacial instabilities, if they are contributing factors to protein instability [13, 15].

Common Excipients:

Excipient	Mechanism	Examples
1. Antioxidants as Chemical Stabilizers	Prevent oxidation of sensitive drugs and preserve active ingredient from chemical degradation.	Methionine, Methyl hydroxybenzoate, Propyl gallate, Butylated hydroxyanisole, ascorbyl palmitate, Ascorbic acid, Fumaric acid and maleic acid [17].
2. Buffering Agents, Tonicity Agents	Maintain the formulation's pH.	Citric acid, Dibasic sodium phosphate, Hydrochloric acid, Lactic acid, Monobasic sodium phosphate, Potassium citrate, Tartaric acid, diethanolamine, glycerin, mannitol, monoethanolamine, potassium Chloride, Triethanolamine and sodium chloride [18].
3. Chelating Agents	Works as Complexing agents. Metal binding compounds.	Edetic acid and Edetates, cyclodextrines,
4. Photo stabilizing Agents	Excipients used in photo stabilization may function by means of the idea of spectral overlay that entails combining of substance whose Ultra Violet absorption range overlap (or considerably overlaps) with active ingredient to compete with it for the photons coming through source of radiation [19].	Oxybenzone, Titanium dioxide etc.
5. Preservatives	Prevent the growth of microbes [16].	Benzene carboxylic acid, Phenylmethanol, Alkylbenzyldimethylammonium chloride, Benzylparaben, Alkyltrimethylammonium bromide, Chloretone, p-Chloro-m-cresol, Cresylic acid, Ethyl alcohol, Ethylparaben, Glycerine
6. Solubilizers	Solubilizers are chemicals that form micelles with medicinal agents at crucial concentrations, altering important physical features.	Benzyl alcohol, benzyl benzoate, cremophor, cyclodextrines, ethanol, glycerol monostearate, lectine, polypropylene glycol.
7. Ant-frictional Agents and Anti- adherents	Avoid friction between two surfaces while Manufacturing [16].	Hydrophobic: Calcium stearate, fumaric acid, hydrogenated vegetable oil, magnesium stearate, stearic acid, and zinc stearate. Hydrophilic lubricants are: sodium lauryl sulfate, polyethylene glycol 4000 or 6000, sodium stearyl fumarate, and starch.
8. Binders	Enhance the cohesion and aggregation of a substance mixture [17].	Acacia, Alginic acid, bentonite, Dextrin, Ethylcellulose, Hydroxypropyl cellulose, Sodium starch glycolate, starch,

		maltodextrin, magnesium aluminum silicate [18].
9. Viscosity-Enhancing Agents	Viscosity boosting chemicals have a significant function in raising viscosity in aqueous systems and stabilize active drugs in emulsions and suspensions [16].	Gum Arabic tree, Goat's thorn, alginates, starch and xanthan gum, water soluble celluloses Methylcellulose, Hydroxyethylcellulose, Hydroxypropylmethylcellulose (HPMC), Carmellose sodium

Challenges in the Formulation Development of Biotechnology products or Biologics:
The use of therapeutic proteins made from recombinant sources has raised concerns about stability during manufacture and preservation, as well as effective administration strategies that minimize immunologic side effects. Biotechnology products often have comparable efficacy and safety requirements as small molecule therapies. Immunogenicity, in addition to protein instability, is a key barrier to clinical success for new protein therapies [21]. A significant factor to consider in the development of biosimilars is immunogenicity. For instance, many interferons (IFNs) treated patients generate neutralizing antibodies (Abs) that severely limit the biological activity of the IFNs (22, 23).
A further obstacle in the development and choice of excipients for protein therapeutics is the unique administration methods and formulations that are essential or desirable. When handling and storing liquid formulations, certain proteins might not be sufficiently stable this will leads to deterioration of product [24].

ICH Q5C Stability Testing of Biotechnological/ Biological Products: The ICH Q5C guideline, released in 1995, supplements guideline Q1A (R2) by focusing on the distinctive properties of biological medications compared to small molecule drugs. Over the past two decades, the biotechnology industry has introduced numerous innovative biological therapies and vaccines to the market. Biological medicines are becoming important to both traditional "pharmaceutical" and biotechnology organizations [25, 26]. Biological products are more complex than tiny molecules due to complex biological processes influenced by environmental and genetic factors. The final products are a combination of variations with somewhat different structures but similar biological activity. Variants in proteins can be caused by post-translational modifications (e.g., glycosylation) or breakdown during production and storage. Modifications to a molecule can have a cumulative and synergistic effect on its stability. Biological macromolecule medications may pose additional challenges in stability modeling, data extrapolation, and shelf-life prediction compared to manufactured small molecular drugs [25, 26]. The Q1A (R2) and Q5C recommendations refer to various types of stability investigations. These experiments will likely utilize various storage conditions. The studies and storage conditions studied have numerous purposes throughout product development and life cycle. It is vital to understand each stability study's goals and design. Studies may require certain storage conditions and a GMP setting, depending on their objective [27]. There are mainly three types of stability parameters that are considered while selecting the excipients physical stability, chemical stability and biological stability.

Excipient related challenges and solutions

Excipient-drug interaction: Excipients are typically regarded as inactive ingredients in product formulations. However, after being combined to create a parenteral solution, the excipients might interact with the medicinal component. Potential interactions can generally be categorized as chemical, physical, or biological interaction [28]. Interactions, which can happen via a number of processes such as adsorption, complexation, or incompatibility, may affect the stability and bioavailability of medications. For example, complexing agents may combine with a drug to form a complex, altering the drug's behavior, or drug molecules may adsorb onto excipient surfaces, affecting drug absorption and particle size [29]. Chemical Reactions such as Oxidation, Hydrolysis and pH Modulation are affects the formulation stability. Proteins can be oxidized by surfactants

such as polysorbate 80, which causes them to aggregate and degrade. In pH modulation the protein instability or aggregation may result from buffers like citrate that change the pH [30].

- **Excipient compatibility:** Ensuring the compatibility of excipients with biologic pharmaceuticals is critical to preserve the stability and functionality of the formulation. The API and certain inactive ingredient interact, changing the drug's physical or chemical properties or causing deterioration.

  Solution: Preformulation Studies: To find possible interactions early in the development process, thorough preformulation studies that evaluate each excipient's compatibility with the biologic medication are essential.

  Application of Analytical Methods: High-performance liquid chromatography (HPLC), size-exclusion chromatography (SEC), and differential scanning calorimetry (DSC) are examples of sophisticated analytical methods that can be used to identify incompatibilities and evaluate how excipients affect protein stability.

  Formulation Optimization: If incompatibilities are found, excipient concentrations should be optimized, or alternative excipients should be selected to reduce unfavorable interactions with the API [31].
- **Regulatory consideration:** Due to variations in raw materials, production methods, and sourcing, excipients can differ in quality and performance, which can impact the final product's quality and performance. Strict standards for excipient quality have been established by regulatory bodies including the FDA and EMA. For excipients, manufacturers can use sustainable sourcing methods including utilizing renewable or plant-based resources. Manufacturers are required to implement strict quality control procedures like Good Manufacturing Practice (GMP), Excipients supplier qualifications, Good Distribution Practice (GDP) Guide for Pharmaceutical Excipients, International Pharmaceutical Excipients Auditing, Inc. (IPEA) etc. Companies may be obligated by regulatory bodies to disclose the environmental consequences of their excipient sourcing and disposal practices. [32].

Emerging excipient technologies:

- **Excipients derived from nanotechnology:** These are essential for drug delivery systems because they offer advantages such as improved solubility, stability, and targeted distribution. Examples of excipients for nanomedicines that are used to enhance absorption or control the release of the drug component include polymers, targeting agents, coating agents, and lipids. These excipients are essential for assembling structures and stabilizing the final medicinal product [33]. Their unique properties allow medications to be given to target areas more specifically and steadily, improving the effectiveness of treatment. Furthermore, nanotechnology has revolutionized diagnostic and imaging methods, which has facilitated the development of precise and accurate medication delivery systems. Nanoparticles, which have unique properties that may be modified for various applications, are the building blocks of drug delivery systems including nanoshells and nanobubbles. Nanoshells, which have a silica core and an outer layer of metal, are utilized for drug targeting, but nanobubbles, which are created at the nanoscale and can be stabilized at normal temperature, present prospects for a range of medical uses [34]. Nanotechnology-based drug delivery systems have made great strides in the field of nanobiotechnology, with a focus on mitigating the shortcomings of traditional delivery methods. Nanoparticles may improve tissue engineering applications, biosensors, and medication administration due to their unique properties and small size. By using nanotechnology techniques to drug design, it might be able to overcome existing limitations and enhance the effectiveness of drug delivery systems [35].
- **Natural and biodegradable excipient:** Natural and biodegradable excipients are gaining significant interest in the pharmaceutical and biomedical sectors due to their Eco-friendly, reduced environmental

influence, and biological compatibility. Many natural polymers have been extensively researched for their potential in drug delivery systems, including chitosan, albumin, alginate, and hyaluronic acid. Because these polymers have improved bioavailability, biodegradability, and biocompatibility, they can be utilized in targeted and personalized drug delivery systems [36].

Emerging Trends

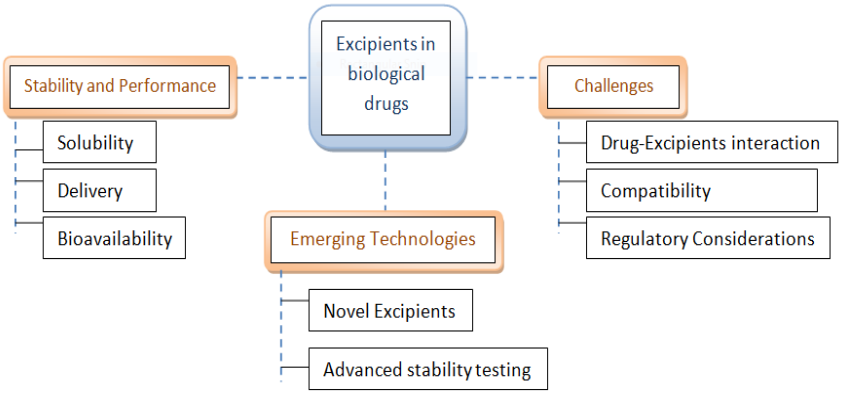
Co-processing for Multifunctional Excipients: Technique of co-processing multifunctional excipients creates a single, improved multifunctional excipient by combining 2 or more preexisting excipients at sub-particle level. Enhanced disintegration ability, compressibility, compatibility, and flow are a few of these characteristics. The demand for excipients with improved capabilities has increased along with tablet manufacturing techniques, leading to a greater interest in co-processed excipients [37]. The advantages of using natural components in coprocessing and the potential for developing unique, designer excipients to meet particular formulation needs have been shown by research. The creation of high-functionality co-processed excipients is seen as a major prospect due to the growing expense of developing novel chemical entity and first choice for direct compaction methods [38]. Creation of single multifunctional excipients as opposed to using several distinct excipients in formulations is a recent and developing trend in excipient technology. In summary, coprocessing multifunctional excipients offers a practical solution to the increasing need for higher-quality excipients in tablet manufacture [39].

Conclusion: The choice of inactive ingredient is crucial on behalf of the stability and performance of biological drugs. Excipients not only enhance the solubility, bioavailability, and delivery of biologics but also play a key role in preventing instability, aggregation, and immunogenicity. The stability of biological drugs is highly dependent on the excipients used in their formulation. As the biologics market continues to grow, optimizing excipient selection will be essential for overcoming the stability challenges associated with these complex drugs. A comprehensive understanding of excipient-drug interactions and the regulatory considerations surrounding excipient selection is essential for developing effective, stable biologic therapies. Further research into excipient-drug interactions, regulatory frameworks, and novel excipient technologies will help to ensure the safe and effective development of biologics. Emerging excipient technologies and advanced stability testing methods are expected to further improve the formulation and shelf-life of biologics, facilitating their broader clinical application.

Biological drugs or biologics are an essential component of modern therapeutics, offering targeted treatment options for a wide range of diseases. However, their large molecular size, structural complexity and limited stability present significant challenges in their formulation and development. The stability of biological drugs is a critical factor influencing their efficacy, safety and shelf life.

This review discusses various types of inactive ingredients used in the formulation of biological drugs and their impact on the stability of biologics. Moreover, the challenges associated with excipient–drug interactions, compatibility and regulatory considerations are discussed. Emerging technologies in excipient formulation are also highlighted as potential solutions to enhance the stability and performance of biologics.

Graphical Conclusion:



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