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RECENT ADVANCES IN THE ORAL DELIVERY OF BIOLOGICS

Kunchala Malleswari[1*], Dr. Desireddy Rama Brahma Reddy[2], Addanki Jeevana Jyothi[3], Vatambeti Navya[4] and Sani Hymavathi[5]

[1]Associate Professor, Department of Pharmaceutics, Nalanda Institute of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, (V), Sattenpalli(M), Guntur Dist,-522438, A.P, India.

[2]Principal and Professor, Department of Phytochemistry, Nalanda Institute of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, (V), Sattenpalli(M), Guntur Dist,-522438, A.P, India.

[3,4,5]Student, B.Pharmacy, Nalanda Institute of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, (V), Sattenpalli(M), Guntur Dist,-522438, A.P, India.

***Corresponding Author: Kunchala Malleswari**

Associate Professor, Department of Pharmaceutics, Nalanda Institute of Pharmaceutical Sciences, Siddharth Nagar, Kantepudi, (V), Sattenpalli(M), Guntur Dist,-522438, A.P, India.

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ABSTRACT

Patients tend to prefer taking medicines orally as tends to be more convenient; however, oral administration is not currently possible for biologics. The physiological role of the gastrointestinal tract presents multiple barriers that limit the systemic absorption of complex macromolecules after ingestion. Biologics are not only highly sensitive to the harsh environment of the gastrointestinal tract, but, as very large molecules, their permeability across the intestinal mucosa is extremely poor. Research in the area of oral delivery of biologics has a long and rich history, and the proliferation of biologics in recent decades has further accelerated the research activity. Significant advances in drug research and development are herein reviewed first to set the background for a critical consideration of the economic sustainability of biologics and small molecules, why biologic drugs are more expensive, and how drug cost often influences patient access to one drug class over the other. Also strongly emphasized is the need for the drug-making, especially the biopharmaceutical, industry to consider a reassignment of priorities so that more patients can enjoy the great benefits that come with blockbuster drugs, many of which are of biological origin but extremely expensive. A balance between the efficacy of wonder-performing drugs and the patient's financial ability to access them must be established to obliterate the crippling effect of the high costs of drugs on the poor majority of patients – those who cannot afford them.

KEYWORDS: Biologics, small molecule drugs, biosimilars, antibody-drug conjugates, patient access to drugs, drug cost.

INTRODUCTION

Biologics are those medicines which influence various types of products from living organisms such as vaccines and recombinant proteins. They have ultimately revolutionized and help in the improvement of the management of various conditions such as diabetes, cancer and inflammatory diseases (e.g. Inflammatory Bowel Disease and Rheumatoid Arthritis). The development and use of biologics have increased dramatically over the past two decades, owing to advances in biotechnology with a new understanding of biology and disease processes.[3]

THE ROLE OF BIOLOGICS

Biologics are medicines that influence various products from living organisms such as recombinant proteins and vaccines. Biologics have ultimately revolutionized and improved the management of various conditions such as inflammatory diseases, cancer, and diabetes. Biologics generally have higher molecular weight and an inherent heterogeneous structure that differs from small molecule drugs.[4]

ADVANTAGES OF ORAL DELIVERY SYSTEM

The compliance of patients to oral formulations is generally higher than that of other parenteral routes such as intravenous, subcutaneous and intramuscular injections, as well as inhalation for asthma patients. Orally administered drugs can be targeted to particular regions within the gastrointestinal (GI) tract for localized treatment of pathological conditions such as stomach and colorectal cancers, infections, and inflammations. Typically, orally administered drugs are the most convenient for repeated and prolonged use. Patients can self-administer treatments in non-sterile conditions, which can be an added benefit for patient compliance.[4]

BENEFITS OF BIOLOGCS

Oral delivery of biologics is a challenging task, as these molecules are often large and highly sensitive to degradation in the gut. In spite of these obstacles, great strides have been achieved in the past several years in the development of technology that can facilitate the oral administration of biologics. If you're wondering why oral biologics could be better than injectable ones, here are a few potential benefits:

Biological drugs have produced extraordinary results in the treatment of diabetes, Crohn's disease, ulcerative colitis, rheumatoid arthritis, hepatitis, anemia, multiple sclerosis and cancer etc. Biologics, by altering the processes that regulate the disease, explicate their action.

(i) High specificity and affinity;

(ii) Long-acting pharmacokinetics;

(iii) Less toxicity and side effects, but close to these advantages, very expensive development and production.[5]

DISEASES TREATED BY ORAL BIOLOGICS

1. INFLAMMATORY BOWEL DISEASES

Inflammatory bowel disease (IBD) is defined as a systemic, autoimmune, relapsing-remitting chronic disease of the gastrointestinal system.

JANUS KINASE INHIBITORS: Tofacitinib, a non-selective Janus kinase (JAK) inhibitor, was approved in Europe in 2018 for UC treatment. Although this small molecular drug can orally administered, it presents some considerable adverse effects such as thromboembolism, infections, and hyperlipidemia. Filgotinib and upadacitinib are JAK1 inhibitors and have just finished the phase II studies, and phase III randomized clinical trials are currently under way As tofacitinib, both are orally administered.[6]

2. RHEUMATOID ARTHRITIS

Janus Kinase inhibitors (JAKi) have been approved for the treatment of Rheumatoid Arthritis (RA) for several years. They are the first oral advanced treatment with efficacy similar to, if not greater than, biologic agents. Recently, concerns over their safety was raised by the results from Oral Surveillance trial suggesting that tofacitinib, one of the JAKi, was associated with higher cardiovascular adverse events and malignancies than TNF inhibitors (TNFi).When TNFi are contraindicated and in certain RA patients, especially when an oral drug is preferable, JAKi have significant advantage providing patients are involved in the decision-making process.

Rheumatoid arthritis is a chronic [long lasting] autoimmune disease that mostly affects joints. Drugs used for RA, Disease-modifying antirheumatic drugs (DMARDs) are a class of drugs indicated for the treatment of several inflammatory arthritides, including rheumatoid arthritis (RA), DMARDs are immunosuppressive and immunomodulatory agents and are classified as either conventional DMARDs or biologic DMARDs. Commonly used conventional DMARDs include methotrexate, leflunomide. Some of these drugs are monoclonal, chimeric humanized fusions antibodies, while others are receptors that have been fused to a part of the human immunoglobulin or small molecules such as Janus kinase (JAK) inhibitor.

DRUGS USED FOR RA TREATMENT

upadacitinib (rinvoq), baricitinib (olumiant), tofacitinib(xeljanz) leflunomide (arava).[7]

BIOLOGICAL BARRIERS TO ORAL DRUG DELIVERY SYSTEMS

On account of its easy application, being painless, low expense, wide drug assimila tion/distribution, and high patient compliance, the oral route is the most common way for patients. However, the efficiency of many oral medicines is still limited due to various physiological barriers, resulting in low permeability, and drug degradation The limitation of oral drug delivery can be summarized by anatomy factors, biochemistry factors, and physiology factors in GIT.

1. ANATOMICAL BARRIERS

Anatomically, the GIT consists of the oral cavity, oesophagus, stomach, small intestine colon, each part having different factors that affect drug delivery. The different anatomical characteristics of GIT show varying effects on drug absorption. However, the limited surface of oral cavity, saliva, and enzymatic composition are the main barriers of drug delivery in mouth, Due to the low permeability and short residence time of drugs, the oesophagus is not a prime target for drug delivery. The stomach exhibits the harshest barrier to drug absorption. I The tight junctions beneath the intrinsic barrier also limit the drug absorption. The small intestine has a huge surface area due to the villi and microvilli in the intestinal lumen.

2. BIOCHEMICAL BARRIERS

Different pH environments and digestive enzymes were regarded as the main bio chemical barriers for oral drug delivery systems. The pH varies distinctly in different parts of the GIT, it rises gradually from the stomach to the colon in the range from 1 to 8. There are over 400 different species of aerobic and anaerobic microorganisms in the colon.

3. PHYSIOLOGICAL BARRIERS

The GIT exerts a low permeability to the bloodstream and extraneous substances, which restricts the bioavailability and absorption of drugs. The physiological barriers mainly consist of epithelium cellular barrier and the mucus barrier. The gastrointestinal epithelium is a phospholipid bilayer membrane, which allows the penetration and absorption of lipophilic macromolecules, while it is a primary absorbtion barrier for hydrophilicity and macromolecules. Mucus is a dynamic semipermeable barrier, which restricts the direct interaction of drugs with epithelial cells. Mucus is a strong barrier to entrap

foreign particles and eliminate potentially harmful compounds and bacteria.[8]

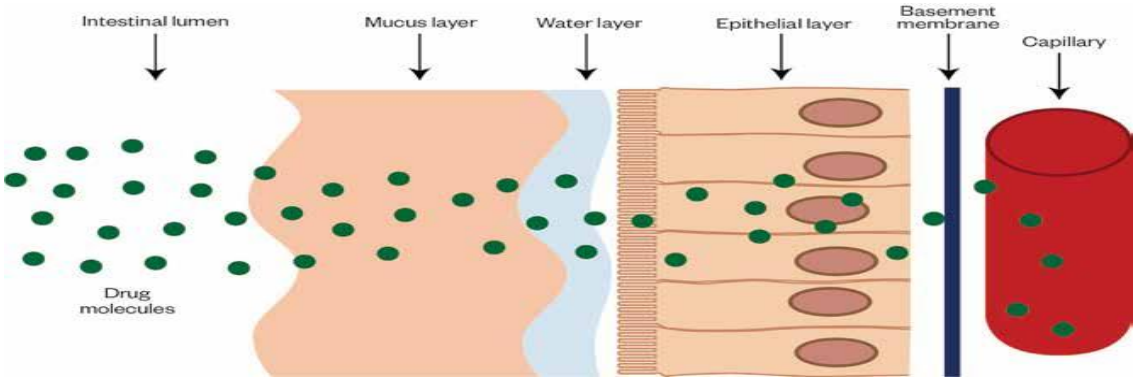

FIG: 1 Physiological barriers to the absorption of biologics in the intestine.

DEVICES USED FOR DELIVERING OF ORAL BIOLOGICS

1. **NANOFITINS:** Our present strategy to enhance the transport of biologics across the intestinal barrier relies on Nanofitins targeting the LepR (anti-LepR Nanofitins), which offer a combination of protein robustness, modularity, and tunable specificity. Importantly, they maintain the stability of their parental protein, including resistance With their N- and C-termini located on opposite faces of their binding site, they can be easily assembled to a cargo molecule. anti-LepR Nanofitin candidate as an efficient carrier for transporting functional cargo proteins across the intestinal barrier.[9]

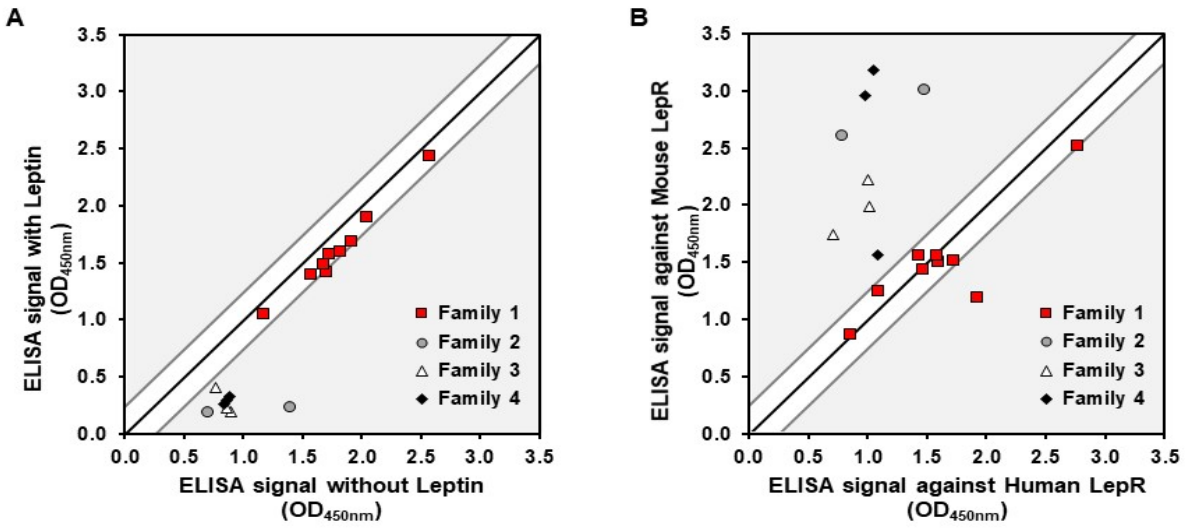

Fig. 2: Characterization of Nanofitins targeting the LepR.(A)Signals obtained in a competition ELISA with NanoftinstestedonimmobilizedrhLepRinthepresenceorabsenceofleptin.(B)Signals obtained with across reactivity ELISA with Nanofitins test on immobilized rhLepRor rmLepR.Signal ratio of1:1is indicated by a black line,with a delimitation of ±0.25absorbanceunits.

2. **NATURALLY DERIVED ORAL DELIVERY DEVICES:** Biotic components and living organisms can be harnessed or mimicked for the construction of oral delivery devices. for example, animal exosomes, plant pollen grains, microbial cell walls and bacterial extracellular vesicles. Such biological components, and in particular plant pollen grains and bacteria, exist in large quantities, thereby enabling the large-scale manufacturing of naturally derived oral delivery devices.

3. **EXTRA CELLULAR VESICLES FROM ANIMAL SOURCES:** Extracellular vesicles are nano-sized bilayer phospholipid vesicles secreted by cells for information transfer and inter cellular communication. The four major types of extracellular vesicles are exosomes, microvesicles, apoptotic bodies and virus-like particles. Exosomes have a size range of 30–200 nm and a specific endocytosis–fusion–secretion biogenesis pathway. Exosomes can transport cargo across plasma and cell membranes, acting as drug carriers.

4. **PLANT DERIVED BIOTIC COMPONENTS:** Plant-derived biotic components mainly include pollen grains, spores, leaf materials and extracellular

vesicles. Pollen grains are robust microscopic objects that accommodate and protect plant gametes and associated proteins. Because of their resistant shells, pollen grains have a high tolerance to mechanical force, high temperatures and extreme chemical conditions such as acids, alkalis, enzymes and organic solvents.

5. **MICROBIAL SOURCES:** Bacterial ghosts, fungal cell walls, microalgae shells, bacterial spores and bacterial OMVs can be obtained from microorganisms and applied as oral delivery devices. Bacterial ghosts are microscale capsules that remain when bacterial cell content is removed through lysis or chemical processing. The hollow bacterial ghost can be loaded with drug formulations through physical or chemical interactions. Bacterial ghosts preserve the surface structure, immunogenicity and adhesiveness of the original bacteria, which enables them to serve as carriers for vaccine delivery.[10]

ROADMAP FOR PRODUCT DEVELOPMENT AND MANUFACTURING OF BIOLOGICS

DEFINING THE ROADMAP FOR DRUG DEVELOPMENT

The aim of biopharmaceutical development is to design a quality product and manufacturing process to consistently deliver the intended performance of the product and meet the needs of the patient and discussed in more detail in the following sections. The roadmap was designed based on a Quality by Design (QbD)-like approach and experience from developing drug products at the clinical and commercialization stages, regulatory guidance's to industry from worldwide regulatory agencies, and recent reviews on manufacturing and DP development. Central to defining the roadmap is a recognition of common challenges encountered during development of the different DP formats, such as liquid and lyophilized drug products in vials and pre-filled syringes. Common issues are highlighted based on the examples of therapeutic proteins. To enable early clinical studies, a platform formulation and manufacturing process, requiring minimal development, may be used in clinical phases I and II. Novel modalities, where little prior-art knowledge and no platform formulation is developed yet, may require more extensive formulation studies for early clinical phases I and II. As product development progresses to the clinical phase III and commercialization stages, additional studies are performed based on alignment with updates to the QTPP to define an optimized formulation for maintenance of drug quality and stability during commercial manufacturing, storage, and clinical administration. An important aspect of the DP development studies is drug substance (DS) process and the resulting quality/purity of the DS. The source of the materials for the sequence of studies used for the DP development and characterization are highlighted in the example of a mAb. Changes to upstream production such as fed-batch to intensified fed-batch to continuous process production for mAbs can all affect impurity profiles, introducing changes in the host cell proteins, such as peptidases and esterases that can effect the product.

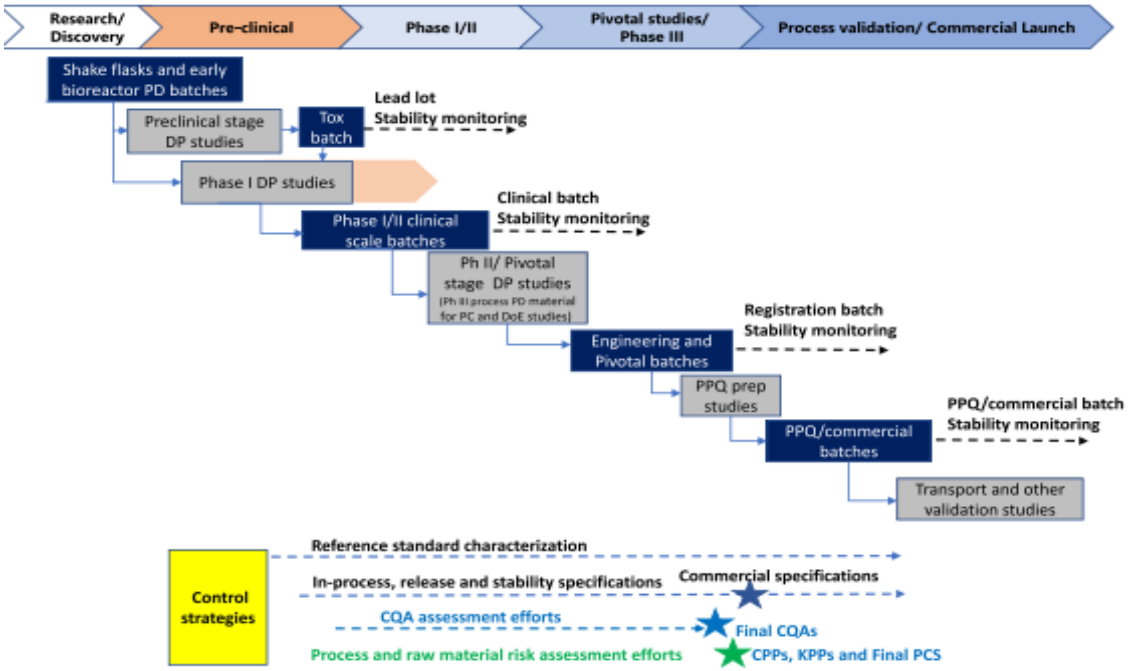

FIG. 3: Timeline and material for biologics drug product development, characterization and qualification studies. Solid Arrows point to sequence of material flow and activities.

REGULATORY AUTHORITIES OF BIOLOGICS

These guidelines can also be used to the well determined proteins with their functionate substance existed through DNA recombinant technology. The similar biologics are formulated with reference biologic product that has approved in India. If it is not licensed in India, it should have marketed and allowed for minimum of 4 years with sufficient and significant safety and efficacy data. The similar biologics can be examined only when it proves the same quality attributes that of reference biologic product.

APPLICABLE REGULATIONS AND AUTHORITIES

These biologics are regulated under the Drugs and Cosmetics Act 1945 and based on the regulations for the production, usage, import, export of micro-organisms genetically engineered organisms 1989. Some of those guidelines are: Recombinant DNA safety guideline, 1990 Guidelines for generating pre-clinical and clinical data for RDNA vaccines, 1999 Guidelines and Handbook for Institutional Bio-safety committee CDSCO guidance for industry, 2008:

a) Capitulation of CTA for Evaluating Safety and Efficacy

b) Requirements for acceptance of New Drugs Approval

c) Post approval changes in biological products: Quality, Safety and Efficacy Documents

d) Establishing the requirements of the Quality Information for Drug Submission for New Drug Approval: Biotechnological/Biological Products.

PRINCIPLE INVOLVED IN SIMILAR BIOLOGICS

1. Selection of reference biologic

It is necessary for development of similar biologic. It depends upon the DBT & CDSCO. The reference biologic should be Licensed in India and should be discoverer product. If it is not licensed in India, it should be widely distributed for minimum of 4 years in accordance with their regulatory guidelines. The same reference biologic product should be utilized to fill the complete of the whole study.

2. Manufacturing process

a) Molecular biologic considerations: The information based on the host cell cultures, vectors, gene sequences, promoters are used in the manufacturing of similar biologics. If there is any up-right translational manufacturing such as glycoylation, oxidation should be detailed.

b) Fermentation process development: Three batches should carry out the replicate fermentation Fermentation process must be operated in a controlled environment Factors such as PH, temperature and dissolved oxygen should be noted Production should be replicatable and scalable. Data should remain sustained for all the batches.

- In case of submitting the clinical trial application. A proper GMP should be maintained during the manufacture and production process. The data includes.

Detailed description of drug substance, Critical quality attributes of product, Critical process parameters, Stability data, Comparability of product manufactured at clinical scale against reference biologics. Data from consistency batches and /or process validation batches as applicable.[12]

CONCLUSION

Despite tremendous advancements, research on the oral administration of biologics has not yet had a substantial influence in clinical settings. The limited success in translating therapeutic applications in this field, which is partly due to the formidable physiological barriers in the gastrointestinal tract (GIT), is sometimes attributed to concerns about the safety of drug delivery methods. Nevertheless, the growing understanding of physiological obstacles, together with remarkable recent advancements in materials, are driving progress in this field and are expected to enable the practical use of oral administration for biologics.

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