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RECENT ADVANCES IN THE ORAL DELIVERY OF BIOLOGICS

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ABSTRACT:

Oral route of drug administration is most favorable for most of the patients. It is easiest, convenient, patient compliance, non-invasiveness method and is preferred by most of the physicians. The oral administration of biologics yet not beneficial compared to other routes due the various gastrointestinal barriers, mucosal permeability also it limits the systemic absorption of macromolecules that are complex after ingestion. Biologics contribute in significant treatment of therapeutic interventions such as chronic ailments, metabolic disease ageing and inflammatory disorders but are highly sensitive to the harsh environment of the gastrointestinal tract; the large molecular size causes the permeability across the intestinal mucosa to become extremely poor for biologics.

Various drug discovery, intensive research and design have enhanced the growth of biologics in recent decades' and have further accelerated in the way we administer the medication in a clinical settings. . Different drug delivery systems pharmaceutical technologies that include micelles, nano carriers, lipid-based carriers, and cyclodextrins have been explored to enhance oral drug absorption. This article will first address the physiological barriers to oral delivery of biologics and discusses different strategies to improve the effectiveness of oral delivery. Additionally, this discussion will extends to the various advantages and limitations of drug delivery systems as well as the overall opinion and potential of this future clinical field.

Keywords: drug delivery, oral delivery, biologics, gastrointestinal barriers

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, almost 100 years in case of insulin they have also been used in clinical settings. Biologics were the eight out of ten top selling drugs (global sales in US dollars) in 2018.

Due to advancement in the field of biologics its development and efficiency have also been improved, they are different from chemically derived 'conventional' medicines with implications on clinical efficacy, production, administration, and cost. Comparing with drugs such as aspirin, biotherapeutics which are generally small-molecule drugs having significant inherently heterogeneous structure and higher molecular weight. Biologics are extremely sensitive to large and complex molecules, the physical and chemical conditions of the Gastrointestinal (GI) environment. With a few exceptions the biologics are currently administered by injection due the sensitivity in gastrointestinal environment.

Although oral administration is taking place for almost a century and is considered as most convenient and preferable method of drug administration. Ingestion provides the benefit when it is compared with administration by injection, for example, the physiology of endogenous insulin secreted by the pancreas closely mimics the oral administration of insulin, which leads to minimizes hypoglycemic episodes, weight gain and decreased levels of systemic insulin problems. It also reduces needle-related complications and costing problems.

The current clinical reality remains unchanged in terms of therapeutic administration despite research into the oral delivery of biologics. However, the research activity on proliferation of biologics available on the market has also intensified. Research into the oral delivery of biologics is increasingly producing more clinically relevant drug-delivery technologies having recent advances in materials also the potential to make oral administration of biologics a viable option.

This article will give the overview of the drug delivery of biologics and recent advances in this field. The process of producing biologics is not in the scope of this article.

PHYSIOLOGICAL BARRIERS TO ORAL DELIVERY OF BIOLOGICS:

Multiple physiological barriers in the GI tract (GI)is a major challenge in achieving clinically relevant oral delivery of biologics which are designed to prevent the uptake of foreign materials, including harmful pathogens, acid, proteolytic enzymes in the gut lumen and at the brush border membrane, the mucus layer, the bacterial gut flora and the epithelium, from the external environment.

The entry of macromolecules and particulate matter from the external environment into the body, the GIT mucosa act as a selective barrier, the mucosal surface is not completely impenetrable there is a restriction on the penetration of harmful pathogens and toxic materials. The understanding of absorption of macromolecules and particulate matter is important if biological transport mechanisms are to be exploited for oral delivery of biologics facilitated by a variety of mechanisms.

Amino acids, dipeptides and tripe tides are a major chemical barrier in the pH-induced proteolysis of proteins. Proteolytic enzymes in the gut lumen (e.g. pepsin, chymotrypsin and trypsin), proteolytic enzymes at the brush border membrane (i.e. end peptidases) and efflux pump P-glycoprotein are some of the biochemical barriers.

Physiological barriers to the absorption of biologics in the intestine

The oral administration, systemic absorption of biologics is limited by several physiological barriers which include the stomach acid and enzymes .Moreover, mucus hinders the diffusion of macromolecules. Usually Intestinal epithelium is not penetrable by hydrophilic macromolecules. The capillary endothelium and extracellular matrix-based basement membrane may present additional barriers to intestinal absorption of biologics.

However, the intestinal epithelium is a single cell thick, the cells are arranged to form a near-continuous cell membrane barrier facing the lumen and for absorption of biologics the intestinal epithelium is the largest and most important barrier. The layer of the mucus having thickness (depending on the region of the gut) which sits above the epithelium also may act as a barrier, hindering the diffusion of biologics to the underlying epithelium. The Basement membranes located between the epithelia and connective tissue which are thin and specialized sheets of extracellular matrix can hamper the penetration of macromolecules into the space beneath the epithelium, thus limiting systemic absorption. Some of these factors significantly contribute to biopharmaceuticals having oral bioavailability.

Several physiological barriers to effective oral delivery of biologics although exist, however we will only refer to mucus and the BM, with the latter being a relatively uncharacterized barrier which is less commonly discussed in the literature.

Mucus layer:

Mucus is a thick substance which composed of water, lipids and proteins with the main structural component being mucin. Mucin is highly glycosylated protein with oligosaccharide side chains including sulphate residues that give an overall negative charge it has an extensive intermolecular interactions forming a mesh-like structure (average pore size 5-500 nm) and is responsible for the viscoelastic nature of mucus. These are some of the characteristics which allows mucus to act as a natural barrier against certain material diffusing to the underlying epithelium, mucus layer also covers the intestines, which usually have a range of about 10 to 100-200 μm thick (jejunum to colon), it forms a single layer in the small intestine and a double layer in the colon the inner mucus layer firmly attached to the epithelium.

The lubricating properties of mucus play a key role in providing protection against invasion by foreign agents. It expedite as the passage of food through the digestive tract. But in terms of drug delivery the mucus gel has a linear, glycosylated mucin fibers entwined within a dense network and can result in particle entrapment and restriction of their movement from the intestinal lumen to the underlying epithelium.

Basement membrane:

Basement membranes (BMs) are found between epithelia and connective tissue in the human body having thin, specialized sheets of extracellular matrices (ECM). BMs composition includes laminin, type IV collagen, nitrogen and heparin sulphate proteoglycans (HSPGs). The main protein of ECM is collagen which is covalently linked by multiple bonds including hydrogen and disulphide bonding that gives tensile strength to basement membrane, along with the

laminin which is strongly associates to cell surface, provides additional organized structural support to basement membrane. Basement membrane serves as a filter function due to a selective passage of molecules across this barrier also it have essential role in controlling a variety of epithelial phenomena, including cell attachment, growth, migration and differentiation.

Advantages of Oral Delivery Systems:

Oral delivery compliance of patients to oral formulations is generally higher than that of other parenteral routes such as subcutaneous, intravenous and intramuscular injections, as well as inhalation for asthma medications.

Administration of drug orally (e.g. capsules, tablets, solutions, syrup, emulsions, powders, suspensions, etc.) are placed in the mouth and swallowed. The oral administration of 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. It provides an effective option for treating various fatal diseases because of its several benefits such as ease of patient compliance, administration and cost-effectiveness.

About 90% is the current estimation which indicates the global market share in oral pharmaceutical formulations intended for the human source. 84% is the best-selling pharmaceutical products that are orally administered and are currently valued at $35 billion. Oral administration of drugs is the most convenient for the patients for repeated and prolonged use as they can self-administer treatments in non-sterile conditions, which can be an added benefit for patient compliance.

Strategies for Improving Oral Delivery of Biologics:

1. Protect the biologic from acid and enzymatic degradation:

By reducing acid degradation it can enhance the bioavailability of biologic medicines. With enteric-coated systems the delivery be achieved which are well-established and, also, it will not be discussed in this article.

In the intestinal environment by the co-administration of protein and peptide drugs with protease inhibitors can help in the protection of biotherapeutics from the proteolytic enzymes. In order to improve the stability in the GI fluids, particularly peptides, the chemical structures of some biologics is possible to modify. For example, via the ‘cyclisation’ this approach could be achieved.

For oral delivery it may show the potential in some of the biologics which have higher intrinsic physicochemical stability against enzymatic degradation in the GIT. Some examples include llama and shark for the treatment of IBD is derived antibody fragments, with the latter being investigated as oral delivery anti-tumor necrosis factor-alpha biologics. To improve oral delivery of biologics an important requirement that must be noted is the protection of the biologic drug from acid and enzymatic degradation.

2. Increase the contact time of the biologic with the absorptive epithelium:

To the absorptive epithelium present at high concentrations the aim of this strategy is to prevent the luminal loss of the medicine, which is important considering the length of the intestines.

To prolong the medicine's residence time at the absorption site, leading to enhanced absorption 'Mucoadhesive' materials are typically polymers capable of interacting with mucus via ionic and non-ionic interactions. Synthetic mucoadhesive polymers include poly(acrylic acid) polymers , poly(ethylene oxide), poly(vinyl alcohol) ,poly(ethylene glycol), poly(vinyl pyrrolidone) and cellulose derivates while natural mucoadhesive polymers include xanthan gum, pectin, sodium alginate, gelatin, , guar gum and chitosan. For oral delivery of biologics many of these materials have been investigated with varied success.

To improve oral delivery of the therapeutic which was based on mucoadhesive polymers, mucoadhesive 'transdermal patch-like' system has the ability such as carbopol 934, polypeptide, sodium carboxymethylcellulose, salmon calcitonin (sCT) 21, and pectin was delivered enclosed in gastro-resistant hard gelatin capsules. For oral delivery of exenatide and insulin Gupta et al have investigated having similar mucoadhesive patches. In the rat jejunum surgical placement of these systems results in a 42% decrease in blood glucose, while the no such effect showed in insulin solution-treated group (control). There is an increase in the relative bioavailability of insulin and exenatide dramatically when compared with intestinal injections (13-fold and 80-fold, respectively).

In vitro and in vivo for enabling oral delivery of biologics mucoadhesive systems have demonstrated potential, particularly with larger biologics (e.g. monoclonal antibodies) have faced challenges in the strategy which includes limited efficacy. Improvement in the bioavailability at the absorptive surface simply prolonging the residence time of the biotherapeutic may not be sufficient to achieve clinically relevant.

the intestinal epithelium is traverse with the limited ability of hydrophilic drugs of molecular weight orders having the magnitude above 500Da. Affect of the intestinal mucus turnover action of these systems is currently unclear. Diseases those are associated with mucus defects (e.g. IBD) there may be potential issues with application of such systems.

3. Make the mucosal barrier more permeable:

For improving the oral bioavailability of biologics these are the most commonly researched strategies. Modification can be done for both the intestinal mucus barrier and the epithelial barrier.

By using the mucus barrier which are mucolytic agents (mucusbreaking) can improve the diffusion of large molecule biologics such as N-acetylcysteine. The epithelium is the rate-limiting barrier which gives the advantage to manipulate. Several chemical absorption enhancers of the epithelial barrier can be modified as the surfactants and other materials that open epithelial tight junctions.

Surfactants:

Surfactants are the materials that can absorb onto interference of a system that contain both a hydrophilic and hydrophobic component. It also alter the interfacial free energy and tension that results in intestinal epithelial plasma membrane fluidization also having a transient opening of epithelial tight junctions hence facilitating permeation of macromolecules.

The main candidates that are currently being used in the development of oral peptide formulations are based on medium-chain fatty acid (e.g. sodium caprate and N-[8-(2-hydroxybenxoyl) amino] caprylate [SNAC], sodium caprylate), bile salts and acyl carnitine. The 'gastro-intestinal permeating technology' (Novo-Nordisk) and the 'eligen' technology (Novo-

Nordisk Technologies) are currently undergoing clinical trials that utilizes these materials. The successful completion of the first phase III trial is the long-acting GLP-1 analogue SNAC formulation for the oral delivery,) type 2 diabetes mellitus and semaglutide (Novo Nordisk) was recently reported to have. A large dose of SNAC contains in vitamin B12 tablets is already in the market.

With the promising potential in three global phases III Mycapssa (Chiasma) capsules are currently being investigated. For the maintenance therapy of adult patients with acromegaly Mycapssa capsule formulations currently used in developing the 'transient permeability enhancer' (TPE) technology which is a biopharmaceutical company based in Isreal.The active drug in this formulation is the peptide, octreotide — a somatostatin analogue. Combination of pharmaceutical excipients the TPE technology can enhance the oral bioavailability of octreotide. In a hydrophobic matrix the composition creates an oily suspension of hydrophilic particles. Sodium caprylate along with Octreotide and other excipients are solubilised in the hydrophilic component. To permeate the intestinal epithelial membrane and reach the bloodstream which is protected from the digestive enzymes the surfactants contained in this formulation trigger the temporary expansion of tight junctions and allows the drug.

Tight junction-opening permeation enhancers:

Over the decades of research in this area including surfactants many materials are capable of opening epithelial tight junctions. An enzyme-rich cytoplasmic environment during its absorption process it increases the permeability of the intestinal epithelium as the medicine and can avoid entering the epithelial cells which is a potentially useful approach in epithelial tight junction-opening.

For the maintenance of physiological role of the epithelium as a tight barrier the tight junction opening must be reversible, also the widening space between adjacent epithelial cells (the par cellular space), is normally too small to accommodate biologics. Chitosans are the most researched compounds which shoes the capability to reversibly open epithelial tight junctions. Chitins which are derived from the natural polymer are found in exoskeletons of arthropods, cell walls of fungi such as insects and crustaceans.

This method may relate to potential variability in absorption as the clinical implications results fasted and fed state, the volume of water used for swallowing solid dosage forms. Careful evaluation of repeated alteration of GIT permeability currently remains unclear for the long-term effects.

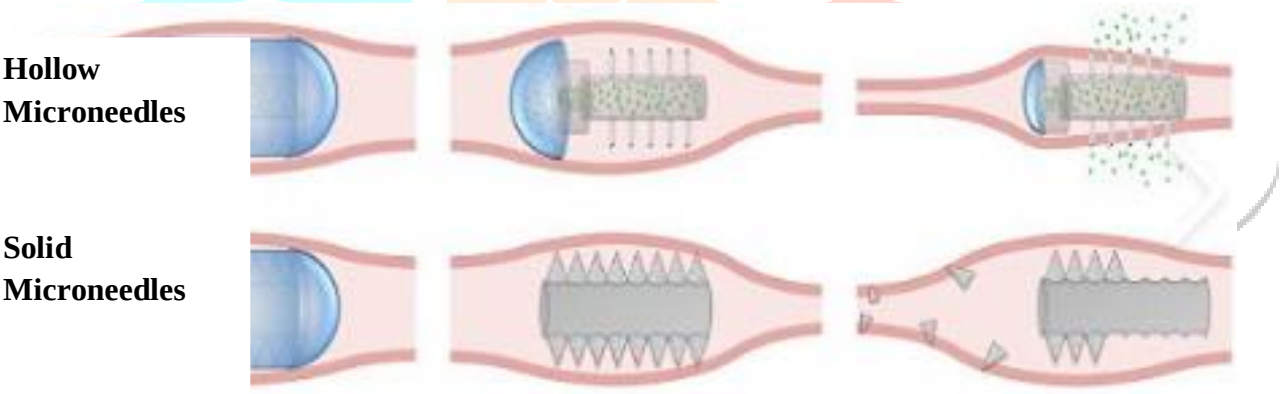
4. Make the biologic drug or drug delivery system more permeable:

To alter the molecule and to impart its epithelial-permeating properties it is possible via the chemical modification which depends on the nature of the biologics. By attaching it to another molecule which is capable to do so, there is a possibility to increase the ability of the biotherapeutic to cross the intestinal epithelium. The intestinal epithelium gets traverses with the 'transport-enabling' molecule by a specific receptor expressed in the intestinal epithelial cells. The attachment of the two entities can be done through biotechnology mediated fusion technologies or chemical attachment (conjugation).Example: peptides or proteins which utilize biological transport processes to traffic across the epithelium are some of the transport enabling molecules.

Researchers have incorporated biotherapeutics into drug carrier systems which can traverse the intestinal barrier to alter the biologic and to improve its likelihood to cross the intestinal barrier. It has a countless advantages which are based on the biodegradable polymeric nanoparticles for biologic carriers. For example, by locating the surface of intestinal epithelial cells targeting of specific receptors can be achieved by the selective drug delivery. In GIT some of the nanoparticles provide the therapeutic drug from enzymes and acid present in it. Diffusion of the nanoparticles is poor in the intestinal mucus as they are not capable of crossing the intestinal epithelium. Specific materials are engineered on the surface of the nanoparticle based drug carriers for the oral delivery of biologics which acts as ligands for biological transport receptors expressed in intestinal epithelial cells. Several researches have been there for exploitation of the nanoparticles in the intestinal epithelial transport pathways of vitamin B12 and immunoglobulin G (IgG).

Figure 1

Therapeutic use concept of hollow and solid micro needle pills in the gastrointestinal tract: - The drug reservoir is compressed through peristalsis in a hollow micro needles releasing the drug through the needles. The drug is formulated into the micro needles in a solid micro needles. It leaves the needle to release the drug in a controlled manner by penetrating the tissue and break off from the pill.



Development in nanomedicine-based strategies have faced several challenges even there is potential advantages and promising results at the preclinical research stage:

The monoclonal antibodies with larger biologics may suffer from low therapeutic loading capacity for nanoparticle based carriers. A low transport capacity of the delivery capacity with biological pathways exploitation may also be an issue.

In the presence of highly complex intestinal biofluid their can be alteration in the GIT or extensive degradation of the complex nanoparticles. The ability to target biological receptors and to utilize these systems for epithelial transport is the adsorption or the attachment of materials as normal intestinal biofluid which includes proteins and peptides adsorbing on the surface of nanocarriers.

5. Overcome the mucosal barrier using 'smart' ingestible devices:

The ingestible 'smart' devices help in protecting the therapeutic from harsh environment of the GIT which enhance the intestinal absorption through micro needles and ultrasound. The encouraging results have been showed in the preclinical research of the micro needle delivery oral delivery technology which is being developed in the United States by Rani Therapeutics.

Once the capsule reaches to the small intestine the technology is designed in such a way that it remains intact in the stomach and injects medicine into the intestinal wall. This is better than subcutaneous injection as it is a painless process due the absence of pain receptors in the intestinal mucosa which shows the favorable insulin bioavailability. The delivery of low-to-medium molecular weight biologics as well as deliver of larger biologics such as antibodies is the advantage of this technology.

When the pill reaches to the desired location of GIT the coating gets dissolves as it is coated by a pH-responsive coating to aid ingestion, releasing the micro needles (shown in Fig 1).The release of drug in the case of hollow micro needles is through the needles from a drug reservoir which is compressed through peristalsis. In the case of solid micro needles the penetration of the tissue is from the drug which is formulated into micro needles and break off from the pill based on the needle formulation makes the release of the drug in a controlled manner.

Advancements in the Field of Oral Biologics:

The current reality of clinical application in the oral delivery of biologics has remained stagnant regarding the therapeutic administration of biologic medications. On the pharmaceutical market the spread of biologics has intensified in the research activity on the possibility on clinical application. To make potential of oral administration of biologics a viable option, research with the help of advance technology into oral delivery of biologics is increasingly producing more clinically relevant drug-delivery technologies. Prodrug design which is a viable option helps in improving the oral bioavailability of drugs by overcoming first-pass metabolism and by enhancing the water solubility and gastrointestinal permeability. For further research in biologics in a clinical application design models of pharmacokinetic principles can be utilized.

Potential for clinical translation of oral biologics delivery strategies:

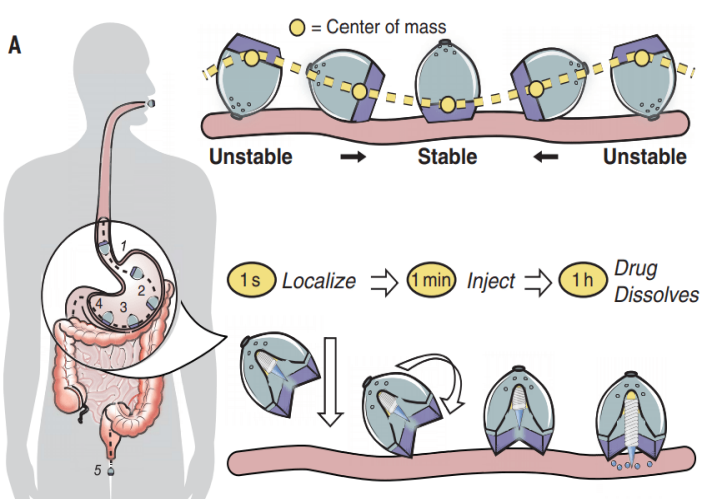
There is a start in the research of the devices for the oral delivery of biologics which shows a significant potential. The use in the patients is yet to be but it shows the positive results in vivo and in vitro. Safety and efficacy are excusive which cause in unlike progress in clinic studies. Moreover in the current clinical trials small intestine epithelial damage is caused due to the permeation enhancers. Despite the fact that tissue damage is repairable and temporary but could overcome the body repair system mechanism due to the chronic repeat dosing of such absorption enhancers.

Figure 2

(A) A drug payload is injected towards the tissue wall by the direction of the injection with the self-orienting millimeter-scale applicator (SOMA) that is localizes to the stomach lining. The rest of the device passes out of the body when the drug gets dissolves.

(B)

There is a comparison between a SOMA and the shape of a leopard tortoise (Stigmochelys pardalis). After reaching its preferred orientation the SOMA quickly orients and remains stable in the stomach environment.



To achieve delivery without damaging the tissue and by exploiting biological transport processes on improving the intestinal absorption of biologics a safer alternative could be that one although for more potent biologics it is likely to be faced by limited capacity. These devices should be demonstrated safely with repetition in the administration on humans as the efficacy is not an issue with it. Moreover the cost is unclear of these technologies but it can be likely in short to medium term. There should be a careful consideration in the use of this drug delivery system which must be there for the selection of the disease area, biologics and patient population.

Future Trends Oral Drug Delivery:

In both adult and pediatric patients the oral delivery is the most common routes of administration. With the advancement of formulation strategies the issues can be raised by the conventional oral formulation. There is the establishment of reliable in vitro-in vivo correlation models that still deserves more consideration in the future that predicts better in vivo performance and to generate data that offer cost-benefit over existing formulations. Formulations from laboratory to commercial production scale will help to accelerate the transition. For designing new formulations there must be a target population of patient. Formulation of drug for adults nanoparticle technologies are used for the development of better pediatric formulation. To bring a lead compound it is expected that the overall time for formulation development will be shorter than the currently existing one from the drug discovery to clinical trials. Moreover, to accomplish better therapy in the oral formulation numerous obstacles will have to face by the pharmaceutical researchers.

Conclusion:

There is no significant impact in the clinic studies up to date although the research in the oral delivery of biologics has significant progress towards the medical advancement. It is yet to be proven significant for the patients with the drug delivery strategies in possible pharmacokinetic scenarios. Although there is a lack of clinical translation success safety and efficacy that are mutually exclusive which reflects the high effective in the physiological barriers in the GIT to make oral delivery of biologics a clinical reality there should be an increased knowledge of physiological barriers with unmatched recent developments in materials which are propelling in this area.

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