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A Review On Recent Advances In The Oral Delivery of Biologics

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ABSTRACT

The majority of patients find that the oral route of drug administration is the most convenient, easy to follow, non- invasive, and physician-preferred method. However, oral biologic administration is not as beneficial as other routes because of mucosal permeability and various gastrointestinal barriers that limit the systemic absorption of complex macromolecules after ingestion. 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. This article summarizes the main physiological barriers to oral delivery of biologics and discuss different research strategies to enable or improve oral delivery of biologics.

Keywords: Absorption enhancers; biologics; drug delivery; gastrointestinal barriers; insulin; micro needle pill.

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INTRODUCTION

Administration of biologics, such as peptides, therapeutic proteins and antibodies, is limited to injection (with a few exceptions). This is explained by the very poor bioavailability of most biotherapeutics following oral administration (in unformulated form) of less than 1%. Oral administration is preferred over injections due to convenience. The oral administration route offers additional advantages over invasive routes.

For example, oral insulin more closely mimics the physiology of endogenous insulin secreted by the pancreas, offering decreased levels of systemic insulin, hence less hypoglycemic episodes and weight gain problems. Furthermore, oral administration reduces needle-related complications and cost. With respect to the latter, it is difficult to calculate the cost-savings achieved with a switch from injection-based to oral therapy (as this depends on the individual therapeutics, patient numbers, dose, cost of oral delivery alternative, etc.).

However, the reduction in healthcare costs associated with the switch from injection to oral administration of vitamin B12, estimated to amount to 37-64% highlights that the potential reduction in healthcare costs can be significant. This is an important consideration taking into account the increasing availability and likely future routine use of biotherapeutics not only for life-threatening acute conditions but also chronic illnesses of an aging population.

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 complex molecules, the physical and chemical conditions of the Gastrointestinal (GI) environment. 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 biologics 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. The first and foremost advancement was to protect biologics from acidic and enzymatic degradation.

It occurred by having a collaboration of proteins and peptides with inhibitors, which helps to modify the chemical structure of the biologics and improve the stability of the fluids in the

gastrointestinal tract. This strategy of advancement has been made possible by an innovation process of cyclization approach. Another major advancement is the increased time of the biologic with the absorptive epithelium, this helps in the prevention of luminal loss from the biologic and is said to be consisting vital enhancement of absorption of the medicine in the gastrointestinal tract. The third advancement made for the betterment of oral biologic delivery is making the mucosal barrier highly permeable.

This strategy improves and enhances the oral bioavailability of the biologics due to the modification of the intestinal mucous barrier and epithelial barrier. It further helps in the diffusion of the bigger molecule of biologics. The fourth advancement in the field of oral delivery of biologic is, to increase the permeability of the delivery system of biologic.

It briefs that the oral delivery system of the biologic helps in better absorption of the medication within the body, hence, improving the efficacy and efficiency of the medicine leading to the reduction of diseases in the body. Biologics have also seen further advancements and success. Around 30% of the drugs approved by the US Food and Drug Administration were biologics the years 2015-2018. Today almost 60 peptides are being approved by the administration; this is twice the number previously being approved.

The table below shows the oral administration overview of the biologics. The growing success of biologics within days is expected to be dedicated to the safety and regulation of biologics. These advancements are successful and are proven to be making biologics the most promising drug among all the conventional medications.

Physiological barriers to oral delivery of biologics:

Overcoming the physiological barriers of the GI tract is one of the biggest challenges to attaining clinical oral administration of biologics. The GI tract is responsible for limiting the absorption of foreign materials from the environment, particularly harmful microorganisms or their byproducts. Another barrier to the uptake of biologics is the chemical barrier found within the GI environment.

Protein breakdown into individual amino acids, dipeptides, and tripeptides is known as proteolysis, which is pH induced is a significant chemical barrier. The intestinal epithelium is the biggest and most important barrier to the absorption of biologics. Although it is only one cell thick, the arrangement of its cells creates a nearly continuous cell membrane barrier that faces the lumen.

Additionally, the layer of mucus above the epithelium, which varies in thickness depending on the area of the gut, may function as a barrier to prevent the diffusion of biologics to the

epithelium beneath. Basement membranes can prevent macromolecules from penetrating the region below the epithelium, hence restricting systemic absorption. They are present as thin, specialized sheets of extracellular matrix between the epithelium and connective tissue.

These elements greatly influence why less than 1% of biopharmaceuticals bioavailable are oral. Drugs low chemical and biological stability, as well as physiological barriers like efflux transporters, pH, and metabolic enzymes, can further affect how well they are absorbed. The human anatomy's biological barriers have an impact on how quickly biologics taken orally are absorbed. The duodenum and jejunum, which are located in the upper GI tract, are primarily responsible for absorbing the majority of orally delivered drugs. Due to its smaller surface area and thicker mucus layer than the intestine, the stomach has a lower capacity for drug absorption.

One of the main GI tract barriers to drug absorption is the intestinal epithelial epithelium. The single-column layer of epithelial cells is primarily responsible for allowing hydrophilic molecules to flow through.

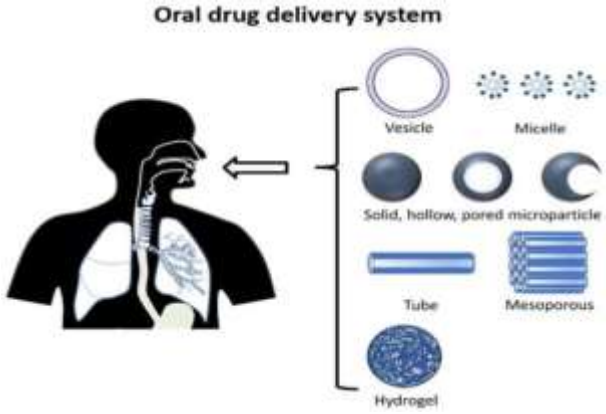

Figure 1: Oral delivery system

A small intestine cell's 3,000–7,000 microvilli offer a lot of surface area for drug interaction and absorption, but they also operate as an enzymatic barrier because the brush border is highly concentrated in digesting enzymes.

Drugs must pass through a number of layers in order to be absorbed from the GI tract lumen and reach the epithelium, mucosa, and blood or lymph capillary walls, including gastric juice, pericellular matrix, and mucous-rich layer. The pH of the GI fluid is another aspect that affects drug absorption; as a result, drugs with poor stability under acidic pH need to be protected in the stomach.

The bioavailability of oral biologics can also be impacted by the GI tract's active movement and contraction. The transit rate and thus, the residence time of a drug following oral administration are principally determined by the peristalsis motilities. Drugs may travel the mucous membranes

of GI organs such as the mouth, esophagus, stomach, duodenum, jejunum, ileum, and colon as they move along the GI tract. They are removed in the faeces and are not fully absorbed by the intestine if they are unable to pass the membranes by the time they reach the colon.

Food can decrease, increase or otherwise affect how quickly drugs are absorbed. Food has an impact on GI processes like gastric emptying, bile acid secretion, intestinal transit time, pH changes in the stomach, and increased blood flow to the liver.

Additionally, it can change a drug's solubility, size, intestinal permeability, and dissolution profile, among other physicochemical properties. In general, the food taken at the time of administration can have an impact on hydrophobic drugs or drugs whose solubility is pH dependent. Drug metabolism can affect their oral bioavailability in addition to their solubility and permeability.

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:

The intestine is protected by a mucus layer, which ranges from 10 to 100-200μm thick (jejunum

to colon) forming a single layer in the small intestine and a double layer in the colon, with the inner mucus layer firmly attached to the epithelium. Mucus is a thick substance composed of water, proteins and lipids with the main structural component being mucin.

Mucin is a highly glycosylated protein with oligosaccharide side chains including sulphate residues that give an overall negative charge. Mucin has extensive intermolecular interactions forming a mesh-like structure (average pore size 5 500 nm) and is responsible for the viscoelastic nature of mucus. These characteristics allow mucus to act as a natural barrier against certain material diffusing to the underlying epithelium.

Mucus plays a key role in providing protection against invasion by foreign agents. In addition, the lubricating properties of mucus facilitate the passage of food through the digestive tract. However, in terms of drug delivery, the organization of mucus gel as linear, glycosylated mucin fibres entwined within a dense network can result in particle entrapment and restriction of their movement from the intestinal lumen to the underlying epithelium.

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Basement membrane:

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

Alongside collagen, laminin which strongly associates to cell surface, provides additional organized structural support to BMs. BMs play an essential role in controlling a variety of epithelial phenomena, including cell attachment, growth, migration and differentiation.

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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 has essential role in controlling a variety of epithelial phenomena, including cell attachment, growth, migration and differentiation.

In a study by Alfano et al. the penetration of relatively small macromolecule through the BM region of non-keratinized oral mucosal epithelium, namely inulin of molecular weight 5 Kad, was impeded by BM, whilst the penetration of a 20kDa dextran was not affected.

Advantages of oral delivery system:

- The manner in which therapy is delivered is one aspect of the patient treatment experience, compared to other parenteral routes like intravenous (iv), intramuscular (I'm), and subcutaneous (Sc) injections, as well as an inhalation for asthma treatments, patients are typically more compliance with oral formulations.
- Additional advantages of oral delivery over intravenous administration include: For example, oral insulin delivery more nearly resembles the physiology of pancreatic endogenous insulin secretion, which results in lower levels of systemic insulin and reduces the risk of weight gain problems and hypoglycemic episodes.
- Insulin used orally also lowers the cost and complications associated with using needles.
- Drugs taken orally can be targeted at certain GI tracts for treatment of pathological conditions, such as infections, inflammations, and malignancies of the stomach and colon.
- Orally administered drugs (such as tablets, capsules, solutions, syrup, suspensions, emulsions and powders, etc.) are ingested after being placed in the mouth.
- Due to its many advantages, including ease of administration, patient compliance, and cost-effectiveness, oral drug delivery offers a useful alternative for treating a variety of deadly diseases.
- Current estimates indicate that oral formulations make up roughly 90% of the overall global market for pharmaceuticals intended for human use.
- Approximately 84% of the top-selling drugs, which are currently worth $35 billion, are pharmaceuticals intended for oral administration.
- Drugs that are taken orally are typically the most practical for frequent and extended use.
- In non-sterile conditions, patients can administer their own drugs, which might increase patient compliance.

- 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.
- About 90% is the current estimation which indicates the global market share in oral pharmaceutical formulations intended for the human source.

Strategies for improving oral delivery of biologics:

Protect the biologic from acid and enzymatic degradation

A method that can increase the bioavailability of biologic medications is minimizing acid degradation. Delivery within enteric-coated systems, which are widely used in clinical practice, can accomplish this. Concomitant administration of protein and peptide medications alongside protease inhibitors can shield biotherapeutics from the proteolytic enzymes found in the gut environment. It is feasible to alter the chemical compositions of certain biologics, specifically peptides, to enhance their stability in gastrointestinal fluids.

Certain biologics exhibit greater inherent physicochemical stability against enzymatic breakdown in the gastrointestinal tract (GIT) and may have the potential for oral administration. Examples encompass antibody fragments generated from sharks and llamas, with particular focus on the latter for their potential use as oral delivery anti-tumour necrosis factor-alpha biologics in the treatment of inflammatory bowel disease (IBD). It is vital to emphasize that safeguarding the biologic medicine against acid and enzymatic degradation is a crucial necessity. Therefore, any approaches aimed at enhancing the oral administration of biologics, as described below, must also fulfill this criterion'

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 are 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.

The advantage of this strategy covers controlled or sustained oral administration as well can reduce fluctuations in systemic drug concentration as well as increase patient compliance by lowering the dose of drugs administered to patients who needs the number of dosages.

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

Given the length of the intestines and the fact that the medication is currently in close proximity to the absorptive epithelium and has a high concentration, the goal of this method is to prevent luminal loss of the drug. Typically, mucoadhesive materials are polymers that can interact with mucus through ionic and non-ionic interactions; this can help prolong absorption by extending the time that the medication spends at the absorption site.

Chitosan, gelatine, pectin, guar gum, sodium alginate, and xanthan gum are examples of natural mucoadhesive polymers. While cellulose derivate, poly acrylic acid, polyethylene glycol, polyethylene oxide, polyvinyl pyrrolidone, and polyvinyl alcohol are examples of synthetic mucoadhesive polymers, with varied success, many of these materials have been looked into for oral biologic drug delivery.

Salmon calcitonin (sect), a therapeutic polypeptide, can be delivered orally more effectively via a mucoadhesive "transdermal patch-like" system. It was supplied in gastro-resistant hard gelatine capsules and was based on mucoadhesive polymers (pectin, sodium carboxymethylcellulose, and Carbopol 934). In vivo, the method significantly improved intestinal sect absorption; similar mucoadhesive patches for oral delivery of exenatide and insulin have been studied by Gupta et al.

Blood glucose decreased by 42% when these systems were surgically implanted in the rat jejunum, but not in the insulin solution-treated group (the control). Compared to intestinal injections, the relative bioavailability of insulin and exenatide significantly increased (13-fold and 80-fold, respectively). Although mucoadhesive systems have shown promise for oral biologic administration in vitro and in vivo, this approach may face challenges such as low efficacy, especially with larger biologics (e.g. monoclonal antibodies).

It might not be enough to simply increase the biotherapeutic's residence duration at the absorptive surface to achieve bioavailability in a clinically significant way. Given the restricted ability of hydrophilic drugs with molecular weight orders of magnitude exceeding 500 Da to get through the intestinal epithelium, this is understandable.

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 (mucus breaking) can improve the diffusion of large molecule biologics such as N-acetyl cysteine. 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:

These substances possess both a water-attracting and water-repelling component, allowing them to adhere to the boundaries of a system and modify the energy and tension at these boundaries. This leads to the fluidization of the plasma membrane of the intestinal epithelium, as well as the temporary opening of tight junctions in the epithelium, so enabling the passage of large molecules.

The primary contenders being employed in the advancement of oral peptide formulations are surfactants derived from medium-chain fatty acids (such as sodium caprate, sodium caprylate, and N-[8-(2-hydroxybenzoyl) amino] caprylate [SNAC]), bile salts, and acylcarnitine's.

Current clinical trials are evaluating technologies like as the 'gastro-intestinal permeating technology' and the 'eigen' technology, both developed by Novo Nordisk, which make use of these materials. A recent report indicated that a formulation of SNAC was used to orally administer semifluid; a long-acting GLP-1 analogue developed by Novo Nordisk, for the treatment of type 2 diabetes mellitus. This formulation successfully completed the first phase IIIa trial.

The trial, consisting of 703 participants, successfully met its main goal by showing significant enhancements in HbA1c levels for three different dosages of orally administered semifluid (3mg, 7mg, and 14mg) as compared to a placebo. Furthermore, high-dose SNAC-containing vitamin B12 tablets are currently available in the market.

The efficacy of Macassa (Chiasma) capsules is currently being evaluated in three worldwide phase III trials, showing promising prospects. Chiasma, an Israeli biopharmaceutical business, created the 'transient permeability enhancer' (TPE) technology that is currently employed in the Macassa capsule formulations.

These capsules are used for the maintenance therapy of adult patients with acromegaly. The active ingredient in this formulation is the peptide octreotide, which is an analogue of

somatostatin. The utilization of TPE technology can increase the oral bioavailability of octreotide due to the synergistic effect of pharmaceutical excipients. This combination forms an emulsion of hydrophilic particles in a hydrophobic matrix.

Octreotide, along with sodium caprylate and other additives, is dissolved in the hydrophilic component. The surfactants used in this formulation induce the transient widening of tight junctions, enabling the medication, which is shielded from digestive enzymes, to penetrate the intestinal epithelial membrane and enter the circulation.

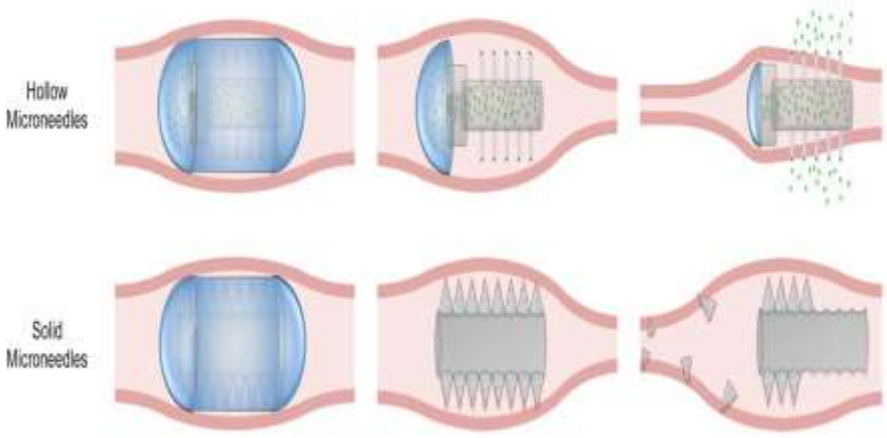

Figure 2: Therapeutic use concept of hollow and solid micro needle pills in the gastrointestinal tract

Tight junction opening permeation enhancers:

Many materials capable of opening epithelial tight junctions, including surfactants, have been identified over decades of research in this area. Epithelial tight junction-opening is a potent tally useful approach to increase the permeability of the intestinal epithelium as the medicine can avoid entering the epithelial cells and be present in an enzyme-rich cytoplasmic environment during its absorption process.

The process involves widening the space between adjacent epithelial cells (the paracellular space), which is normally too small to accommodate biologics. However, tight junction-opening must be reversible so that the physiological role of the epithelial tissue is maintained as a tight barrier. Although many materials have shown capability to reversibly open epithelial tight junctions, chitosan are probably the most extensively researched compounds.

These are derived from the natural polymer, chitin, which is found in cell walls of fungi and the exoskeletons of arthropods, such as crustaceans and insects. Various forms of chitosan have been investigated; however, as with other permeation enhancers, the long-term effects of repeatedly opening intestinal epithelial tight junctions are unknown and require further study.

It must be noted that drug delivery approaches that employ chemicals to modify the mucosal barrier namely absorption enhancers, such as surfactants and tight junction-opening agents rely on concentration-dependent effects on barrier permeability.

Therefore, clinical implications of this method may relate to latent variability in absorption as a result of fasted and fed state, as well as the volume of water used for swallowing solid dosage forms. In addition, the long-term effects of repeated alteration of GIT permit ability currently remain unclear and require careful evaluation.

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 advantage 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).

Overcome the mucosal barrier using smart ingestible devices:

Furthermore, ingestible 'smart' devices not only shield therapeutic substances from the adverse conditions of the gastrointestinal tract (GIT), but also improve the absorption of biologics in the

intestines using various methods such as ultrasound and microneedles.

Rani Therapeutics, a business based in the United States, is currently developing the microneedle oral delivery technology. According to the company, the ongoing preclinical research has yielded promising outcomes.

The technology utilizes a specially engineered capsule that remains intact within the stomach. Once it reaches the small intestine, the capsule administers the drug by injecting it into the wall of the intestine.

The absence of pain receptors in the intestinal mucosa makes this method painless. Furthermore, it has demonstrated remarkable insulin bioavailability, which is comparable to or even superior than subcutaneous injections.

This method offers the benefit of delivering not only low-to-medium molecular weight biologics but also bigger biologics, including antibodies. The capsules are originally covered with a pH-responsive coating to facilitate swallowing. Once the tablet has reached the intended place in the gastrointestinal tract (GIT), the coating disintegrates, thereby releasing the microneedles.

In systems including hollow microneedles, the drug reservoir undergoes compression by peristalsis, resulting in the release of the drug through the needles. In systems employing solid microneedles, the medicine is incorporated into the microneedles themselves.

These microneedles pierce the tissue and detach from the pill, allowing the needle to gradually release the drug in a regulated manner, determined by the composition of the needle. Following the release of the medicine, the microneedles remain firmly embedded in the gastrointestinal tissue until they undergo biodegradation.

Potential for clinical translation of oral biologics delivery strategies:

Devices for oral delivery of biologics are showing significant potential, but research in this area is still in its infancy. While many of the drug delivery strategies discussed above have shown positive results and potential in vivo and in vitro, they are yet to be used in patients.

Unfortunately, with many of the delivery approaches discussed above, safety and efficacy are often mutually exclusive and, therefore, such strategies are unlikely to progress to the clinic. Furthermore, it is well known that small intestinal epithelial damage is caused by many of the permeation enhancers in current oral peptide clinical trials.

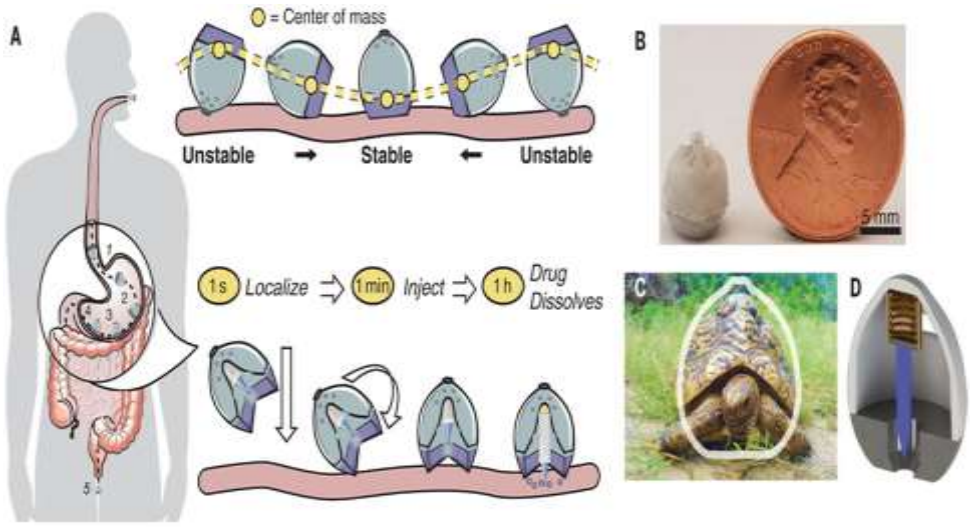

Figure 3: An ingestible self-orienting system for oral delivery macromolecules.

Although tissue damage is often temporary and repairable, it remains unknown if chronic repeat dosing of such absorption enhancers could overcome the body's repair mechanisms. A safer alternative could be one that relies on improving the intestinal absorption of biologics by exploiting biological trans port processes to achieve delivery without damaging the tissue; however, these are likely to be faced by limited capacity and may be best suited for more potent biologics.

Such devices need to clearly demonstrate safety on repeated administration in humans; it seems that efficacy is not an issue. Furthermore, the costs of these technologies are currently unclear, but are likely to be high in the short-to-medium term in which case, it will be critical to give careful consideration to the selection of the biologic, disease area and patient population for use of these drug delivery systems.

Future trends of oral drug delivery:

Oral delivery is the most common mode of administration for both adult and paediatric patients. However, advances in formulation strategies have raised issues with conventional oral formulations. One such advancement is the establishment of reliable in vitro- in vivo correlation models, which deserve consideration in the future because they predict better in vivo performance and can produce data that offers a cost-benefit analysis compared to existing formulations.

Another development is the acceleration of the transition from laboratory to commercial production scale formulations. A target patient population must be considered when designing new formulations. Adult drug formulation uses nanoparticle technologies to create better paediatric formulations.

The time it takes to bring a lead compound from drug discovery to clinical trials is anticipated to be shorter than it is now, and pharmaceutical researchers will face many challenges in their quest for better therapy in oral formulations.

In both adult and paediatric 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 adult's nanoparticle technologies are used for the development of better podiatric 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. Although oral delivery is considered to be the most promising administration route.

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