UPI Journal of Pharmaceutical Medical, and Health Sciences
Content Available at www.uniquepubinternational.com ISSN: 2581-4532

Open Access **Review Article**

RECENT ADVANCES IN ORAL DELIVERY OF BIOLOGICS

Dudekula Nagoor*, Shaik Adavi Saida, Vejandla Vamsi and Chandu Babu Rao
Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur -522017.Andhra Pradesh, India.

DOI: https://doi.org/10.37022/jpmhs.v7i1.104

Article History
Received: 15-02-2024
Revised:08-03-2024
Accepted: 30-03-2024

***Corresponding Author**
Dudekula Nagoor

Keywords: Absorption enhancement, Biologics, Microneedle capsule, Nanomedicine, Oral delivery of biologics, Ultrasound.

Abstract

For the majority of patients, taking medications orally is the most beneficial method. The majority of doctors choose it because it is the most straightforward, practical, patient-complies, and non-invasive approach. Given the different gastrointestinal barriers, metabolic diseases, inflammatory illnesses, and ageing, oral biologic administration is not as helpful as other routes because to the harsh environment of the gastrointestinal tract. Various pharmaceutical technologies, such as cyclodextrins, micelles, nano carriers, and lipid-based carriers, have been investigated as drug delivery systems to improve oral medication absorption. Because it is usually the simplest and most comfortable method, patients tend to choose oral medicine administration. Because of all of its advantages—which include non-invasiveness, patient compliance, and ease of drug administration—it is usually the best option for doctors. Therapeutic efficacy and the short- and long-term biological consequences are significantly influenced by the routes of drug administration and the corresponding physicochemical properties of a given route. In the meanwhile, there are certain difficulties with oral delivery, which have dominated the field's recent research efforts. The most popular method for delivering drugs locally and systemically is oral administration.mechanisms, ideas, and elements.

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% (1). Oral administration is preferred over injections due to convenience (2). 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 hypoglycaemic episodes and weight gain problems (3,4). 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% (5,6), 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 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

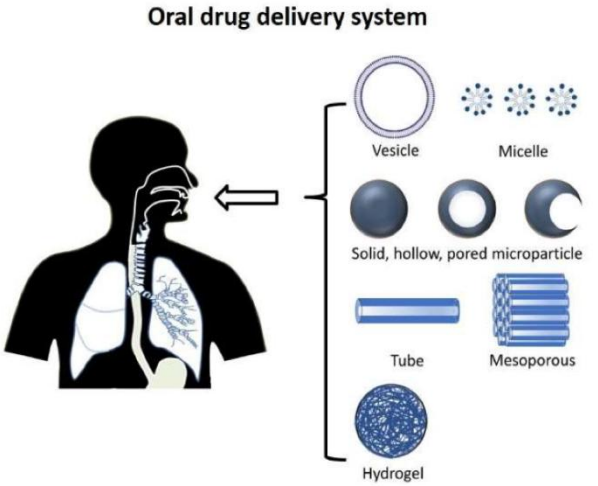
the sensitivity in gastrointestinal environment. Although oral administration is taking place for almost a century and is considered as most convenient and preferable method of drug administration. Ingestion provides the benefit when it is compared with administration by injection, for example, the physiology 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 (7,8).

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.

The proliferation of biological therapeutics has intensified research efforts into non-invasive delivery approaches, with oral delivery in particular attracting significant attention. The field has evolved from chemical absorption enhancers with the ability to increase epithelial membrane fluidity, such as surfactants, those that open epithelial tight junctions (TJs) (9) and mucoadhesive polymers for prolonging drug residence in the intestinal mucosa (10). The application of such absorption enhancers as means to promote oral delivery of biologics has been reviewed elsewhere (11) and therefore will only be briefly discussed here. Similarly, recent commercial activity and 3 progresses of technologies based on these more conventional approaches of absorption enhancement has also been subject to recent reviews. More modern approaches explored for enabling oral delivery of biologics utilise nanotechnology as means to deliver biotherapeutic payloads across the intestinal mucosal barrier. Another recently-emerging activity in the area is related to devices, such as those utilising ultrasound or microneedles. This article will initially discuss the properties of key physiological barriers to biologics delivery, including the less well-characterised barrier of the basement membrane (BM), and subsequently focus on emerging technologies for promoting oral absorption of biotherapeutic

1. Physiological barriers to oral delivery of biologics

The components of the gastrointestinal tract (GIT) that present barriers limiting the systemic bioavailability of biologics following oral delivery include acid, proteolytic enzymes in the gut lumen and at the brush border membrane, the mucus layer, the bacterial gut flora and the epithelium. The GIT mucosa is therefore organised to act as a selective barrier and minimise the entry of macromolecules and particulate matter from the external environment into the body. Although a restriction on the penetration of toxic materials and harmful pathogens is imposed, the mucosal surface is not completely impenetrable. The absorption of macromolecules and particulate matter is facilitated by a variety of mechanisms (12), the understanding of which is important if biological transport mechanisms are to be exploited for



Multiple physiological barriers in the GI tract (GI)are 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.

2. Mucus layer

The intestine is protected by a mucus layer, which ranges from 10 to 100-200 μm thick (jejunum to colon) (13) 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 organisation 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 (14).

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. Advantages of Oral Delivery Systems One component of the patient treatment experience is the way in which therapy is administered. 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 medications. Ingestion as opposed to injection also can offer additional benefits in the form of physiological mimicry. For instance, oral consumption of insulin can mimic the physiology closer to the physiology of endogenous insulin secreted by the pancreas (15). Furthermore, oral consumption can minimize any needle-related complications and costs associated with administration. 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. Drugs administered orally (e.g., tablets, capsules, syrup, solutions, suspensions, powder emulsion, etc]

3. Advancement in the field of oral biologics

Despite ongoing research in the oral delivery of biologics, the current reality of clinical application has remained stagnant regarding the therapeutic administration of biologic medications (16,17). However, the spread of biologics on the pharmaceutical market has intensified the research activity on the possibility of clinical application. In combination with advances in technology, research into oral delivery of biologics is increasingly producing more clinically relevant drug-delivery technologies, with the potential to make oral administration of biologics a viable option. Some viable design options such as the prodrug design can improve the oral bioavailability of drugs by enhancing their water solubility and gastrointestinal permeability and overcoming first-pass metabolism.

4. 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 (18).

5. 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 gelatis 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) (19). 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. 3. Make the mucosal barrier more permeable: 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 (20).

6. 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 absorptions

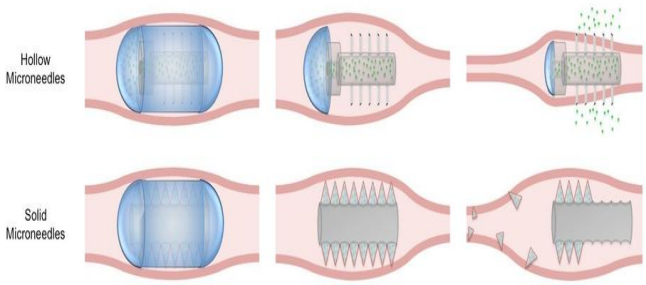
7. Basement membrane:

Basement membranes (BMs) are thin, specialised 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 heparan 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 [18]. Alongside collagen, laminin which strongly associates to cell surface, provides additional organised structural support to BMs. BMs play an essential role in controlling a variety of epithelial phenomena, including cell attachment, growth, migration and differentiation. BMs also serve a filter function due to a selective passage of molecules across this barrier. Prior work by Vllasaliu et al. reported that airway epithelium-synthesised BM significantly hindered the diffusion of macromolecules in a molecular size-dependent manner. Specifically, diffusion across BM (obtained via decellularisation of BM-synthesising airway epithelial cells) was hindered for FD4 (1.3-fold), Human Serum Albumin (HSA) (1.6-fold) and FITC-IgG (4.1-fold difference). 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 kDa, was impeded by BM, whilst the penetration of a 20kDa dextran was not affected. This 'molecular sieving' behaviour

8. Surfactants:

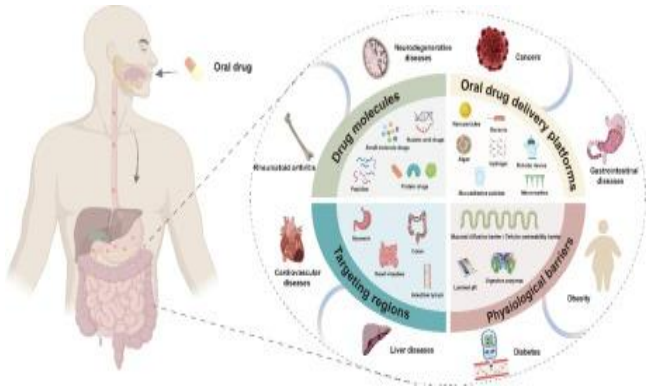
Surfactants are the materials that can absorb onto interference of a system that contain both a hydrophilic and hydrophobic component. It also alters the interfacial free energy and tension that results in intestinal epithelial plasma membrane fluidization also having a transient opening of epithelial 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] 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 similitude (Novo Nordisk) was recently reported to have. A large dose of SNAC contains in vitamin B12 tablets is already in the market.

enhancers of the epithelial barrier can be modified as the surfactants and other materials that open epithelial tight junctions.



9. Technical challenge:

In addition to biological barriers, oral delivery systems face technical difficulties as well, in terms of deciding whether to induce new properties addressing biological barriers or to scale up existing systems for commercial purposes. In this section, most common oral delivery devices, sustained delivery strategies, solvent-free microencapsulation techniques, co-delivery systems and the challenges associated with the scaling-up of systems are anlysied. Nanomedicine-based strategies for oral delivery of biologics



Nanomedicine-based systems for oral delivery of biologics potentially offer a number of advantages, including protection of the biotherapeutic payload in the acid- and enzyme-rich environment of the GIT, targeted delivery and potentially improved penetration across the intestinal mucosa. Furthermore, the drug-loaded system can be targeted to various receptors on the surface of intestinal epithelial cells, enabling a more selective delivery of the therapeutic compared to absorption-enhancer approaches that non-selectively increase epithelial permeability. However, developing nanosystems for oral delivery of biologics is associated with a number of challenges, including, therapeutic loading and delivery capacity

modification of nanosystems in the highly complex GIT environment (discussed below), poor penetration of nanomaterials across the intestinal mucosa and finally, uncertainties associated with the safety of the nanodelivery approach.

Polymeric NPs in particular have attracted considerable attention for oral delivery of biologics. These have been reviewed extensivel elsewhere. Here, we will focus on systems designed to permeate the intestinal mucosa via the biological transport process of transcytosis, followed by discussion of NP diffusion across the complex biological environments of mucus and the BM. We will also briefly discuss NP transformation via biocorona formation in the complex environment of the GIT

10. Devices for oral delivery of biologics:

The demand for non-invasive delivery of biologics, which so far have not been met by chemical absorption enhancer approaches, has recently intensified the focus on devices for drug delivery. This has been facilitated by modern advances in electronics and materials. Oral drug delivery devices resemble more conventional oral solid dosage forms., but carry small electronic and/or mechanical elements. According to Markets and Markets TM, 'smart pills' market is expected to reach.

11. Intestinal patch systems:

Intestinal patch-based devices are potentially attractive for oral delivery of biologics considering their ability to prevent drug degradation in the GIT and promote intestinal absorption by forming a local drug depot adhered to the intestinal wall. These systems can be designed to provide unidirectional, controlled drug release while preventing luminal drug loss. Such patch-based devices are being developed for oral delivery of several biologics including insulin, exenatide calcitonin, interferon-α, erythropoietin and human granulocyte colony-stimulating factor.

12. Ultrasound:

Localised, low-frequency ultrasound has been shown to significantly improve the delivery of biologics. Schoellhammer at al. examined the use of one-minute ultrasound treatments in porcine GI tissue ex vivo and in vivo . Low-frequency ultrasound was reported to increase the absorption of model small molecular weight therapeutics 2–10-fold, as tested utilising ex vivo tissue. Ultrasound application resulted in penetration of 3- and 70-kD dextran throughout the colonic tissue ex vivo, while such permeation was not apparent with either dextran.

The same group also tested ultrasound in vivo, inserted rectally via a model device in Yorkshire pigs, alongside instillation of insulin enema.

A clear hypoglycaemic effect was achieved following co administration of insulin enema in the colon with ultrasound , while no effect on blood-glucose was apparent in the absence of ultrasound. the safety of this approach following chronic administration should be evaluated comprehensively. Furthermore, while it is aimed that ultrasound-mediated tissue permeabilization is in the future achieved by ingestible electronic devices, hence enabling oral administration, the cost of this technology and its suitability for repeated and long-term administration is currently unclear.

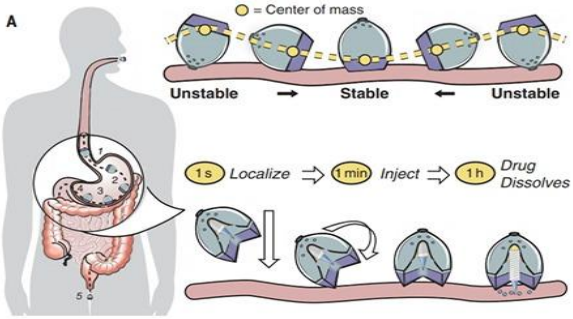
13. Expert opinion:

Oral delivery of biologics remains elusive despite research activity in the field for nearly a century. Approaches to improve oral bioavailability of biologics based on chemical absorption enhancers in general have not produced technologies that have successfully translated into the clinic and changed patients' lives. This highlights the scale of the challenge in promoting the stability and absorption of intact therapeutic biomolecules across the complex and multiple-barrier nature of the GIT. This has meant that, for example, while many compounds have been shown to be effective permeation enhancers in intestinal epithelial models in vitro, they have failed (or are unlikely) to demonstrate sufficient effect on bioavailability in vivo if used alone. However, these technologies fail to address additional issues, including luminal drug and absorption enhancer dilution and narrow permeability enhancement versus toxicity window, so are therefore only pursued for relatively small peptides and proteins. Furthermore, nanomedicine faces yet unaddressed challenges of translation in man, safety, scalability, cost and regulatory approval. The area of oral delivery via 'smart' devices that for example may use ultrasound or microneedles is in its infancy and concept stage but has nevertheless significantly attracted the attention of the Biopharma industry. This points to signs of future growth in research activity in this area, also likely to be fuelled by advances in electronics, robotics and materials. It is highly likely that in the future we will see delivery strategies and technologies that combine devices with chemical or 'nano'-based absorption enhancer strategies With rapid innovation in associated technologies, the future development of clinically used devices for oral delivery of biologics looks promising.

14. 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 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.



15. 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. A drug payload is injected towards the tissue wall by the direction of the injection with the self-orienting millimetre 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.

16. Methods for Improving Oral Delivery of Biologics:

Increase the Permeability of the Biologic Drug Another method to improve the oral bioavailability of biologics is via a chemical modification to alter the molecule to impart its epithelial-permeating properties. It is also possible to increase the ability of the biotherapeutic to cross the intestinal epithelium by attaching it to another molecule that is capable of doing so. The "transport-enabling molecule" can be attached through chemical attachment or via biotechnology-mediated fusion technologies. Examples of transport-enabling molecules include other peptides or proteins that utilize biological transport processes to traffic across the epithelium. Biologic carriers can be based on biodegradable polymeric nanoparticles, which have numerous advantages. For example, some nanoparticles offer protection of the therapeutic drug from acid and enzymes present in the GI tract. Selective drug delivery can be achieved by targeting specific receptors located on the surface of intestinal epithelial cells. However, similar to large molecule biologics, nanoparticle carriers are typically poorly absorbed across the intestinal mucosa Permeability across biological membranes is a key factor in the absorption and distribution of drugs. Poor permeability can arise due to a number of structural features, as well as membrane-based efflux mechanisms. Membrane permeability tends to restrict the transfer and distribution of drugs once they are delivered to the tissue. While these compounds are pharmacologically effective, poor absorption due to low permeability becomes the rate-limiting step in achieving adequate bioavailability. Several approaches have been explored and utilized for improving the permeability profiles of these compound rolonging the gastric residence time of dosage forms is particularly beneficial for drugs that are predominantly absorbed in the stomach or upper GI tract, or for drugs that suffer from solubility issues in the intestinal fluid. This promotes the slow release of drugs in the stomach, which subsequently extends the time available for drug dissolution and absorption in the stomach and/or small intestine The benefit of this approach also includes sustained or controlled release drug delivery, which can reduce fluctuations in systemic drug concentrations as well as increase patient compliance to medications by minimizing the number of doses required. The ability to successfully predict the pharmacokinetic properties plays a crucial role in the selection of candidate drugs and significantly reduces the number of potential failures in drug development

17. Microjet systems:

Another recently described device technology for mucosal delivery of biologics relies on the generation of high-pressure liquid jet with sufficient velocity to penetrate the mucosa. The so called 'MucoJet' is a self-administered, two-compartment plastic device. A proof-of-concept study demonstrated its potential for vaccine delivery to the buccal mucosa Detailed description and mechanism of action of the MucoJet system has been described previously , but it is essentially a cylindrical plastic device (designed to be compatible with industry-scale thermoplastic fabrication methods) with an exterior compartment which is a water chamber and an interior compartment hosting separated propellant and vaccine reservoirs, a movable piston and a sealed delivery nozzle. Upon administration, water contact with the chemical propellant in the propellant reservoir triggers chemical generation of CO2, increasing the pressure in the propellant chamber. This forces the piston toward the vaccine reservoir, breaking the nozzle membrane and ejecting a high-pressure liquid jet of vaccine. MucoJet produced a significant (eightfold) increase in the delivery of ovalbumin across the buccal tissue over three hours compared to dropwise application. In vivo experiments on New Zealand white rabbits showed that vaccination with

MucoJet dramatically enhanced the immunogenicity of buccally administered antigens, as tested by blood and tissue (buccal, lymph node and Peyer's patch) specific antibody titres, relative to control groups, which received equivalent dosages of ovalbumin via a dropper at the buccal site. Specifically, antibody titres of IgG and IgA were three orders of magnitude higher in the MucoJet group compared to buccal administration of free ovalbumin.

18. Article highlights:

• The absence of clinically-used technologies for oral delivery of biologics despite long research activity in the field highlights the scale of the challenge of overcoming the physiological barriers of the gastrointestinal tract for successful delivery.

• Many chemical absorption enhancer strategies for oral biologics delivery are limited to in vitro success.

• Some physiological barriers, such as the basement membrane, require further evaluation, particularly if nanomedicine approaches are utilised to improve delivery.

• Nanomedicine shows potential for oral biologics delivery but is associated with yet to be addressed issues of safety, delivery capacity and regulatory approval

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

Author contributions

All authors are contributed equally.

Financial support

None

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Acknowledgements

None

References

1. Mahato RI, Narang AS, Thoma L, Miller DD. Emerging trends in oral delivery of peptide and protein drugs. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2003;20(2&3). https://pubmed.ncbi.nlm.nih.gov/14584523/
2. Eek D, Krohe M, Mazar I, Horsfield A, Pompilus F, Friebe R, Shields AL. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. Patient preference and adherence. 2016 Aug 24:1609-21. https://pubmed.ncbi.nlm.nih.gov/27601886/
3. Pridgen EM, Alexis F, Farokhzad OC. Polymeric nanoparticle drug delivery technologies for oral delivery applications. Expert opinion on drug delivery. 2015 Sep 2;12(9):1459-73. https://pubmed.ncbi.nlm.nih.gov/25813361/
4. Gedawy A, Martinez J, Al-Salami H, Dass CR. Oral insulin delivery: existing barriers and current counter-strategies. Journal of pharmacy and pharmacology. 2018 Feb;70(2):197-213. https://pubmed.ncbi.nlm.nih.gov/29193053/
5. Vidal-Alaball J, Butler CC, Potter CC. Comparing costs of intramuscular and oral vitamin B12 administration in primary care: a cost-minimization analysis. The European journal of general practice. 2006 Jan 1;12(4):169-73. https://pubmed.ncbi.nlm.nih.gov/17127603/
6. Anderberg EK, Nyström C, Artursson P. Epithelial transport of drugs in cell culture. VII: Effects of pharmaceutical surfactant excipients and bile acids on transepithelial permeability in monolayers of human intestinal epithelial (Caco-2) cells. Journal of pharmaceutical sciences. 1992 Sep 1;81(9):879-87.
7. Fix JA, Engle KA, Porter PA, Leppert PS, Selk SJ, Gardner CR, Alexander J. Acylcarnitines: drug absorption-enhancing agents in the gastrointestinal tract. American Journal of Physiology-Gastrointestinal and Liver Physiology. 1986 Sep 1;251(3):G332-40.
8. Vllasaliu D, Casettari L, Fowler R, Exposito-Harris R, Garnett M, Illum L, Stolnik S. Absorption-promoting effects of chitosan in airway and intestinal cell lines: a comparative study. International journal of pharmaceutics. 2012 Jul 1;430(1-2):151-60.
9. Vllasaliu D, Exposito-Harris R, Heras A, Casettari L, Garnett M, Illum L, Stolnik S. Tight junction modulation by chitosan nanoparticles: comparison with chitosan solution. International journal of pharmaceutics. 2010 Nov 15;400(1-2):183-93.
10. Krauland AH, Guggi D, Bernkop-Schnürch A. Oral insulin delivery: the potential of thiolated chitosan-insulin tablets on non-diabetic rats. Journal of Controlled Release. 2004 Mar 24;95(3):547-55.
11. Gupta V, Hwang BH, Lee J, Anselmo AC, Doshi N, Mitragotri S. Mucoadhesive intestinal devices for oral delivery of salmon calcitonin. Journal of controlled release. 2013 Dec 28;172(3):753-62.
12. Aungst BJ. Absorption enhancers: applications and advances. The AAPS journal. 2012 Mar;14(1):10-8.
13. Florence AT. The oral absorption of micro-and nanoparticulates: neither exceptional nor unusual. Pharmaceutical research. 1997 Mar;14:259-66.

14. Lundquist P, Artursson P. Oral absorption of peptides and nanoparticles across the human intestine: Opportunities, limitations and studies in human tissues. Advanced drug delivery reviews. 2016 Nov 15;106:256-76.
15. Dey B, Katakam P, Mitra A, Chandu BR. Comparative evaluation of hypoglycemic potentials of eucalyptus spp. leaf extracts and their encapsulations for controlled delivery. J Pharm Drug Deliv Res. 2014;3(2).
16. Mao M, Alavi MV, Labelle-Dumais C, Gould DB. Type IV collagens and basement membrane diseases: cell biology and pathogenic mechanisms. Current topics in membranes. 2015 Jan 1;76:61-116.
17. Buchiraju R, Nama S, Sakala B, Chandu BR, Kommu A, Chebrolu JK, Narasimhamurthy Y. Vesicular drug delivery system-an over view. Res J Pharm Biol Chem Sci. 2013 Jul;4(3):462-74.
18. Alfano MC, Chasens AI, Masi CW. Autoradiographic study of the penetration of radiolabelled dextrans and inulin through non-keratinized oral mucosain vitro. Journal of Periodontal Research. 1977 Oct;12(5):368-77.
19. Banerjee A, Mitragotri S. Intestinal patch systems for oral drug delivery. Current Opinion in Pharmacology. 2017 Oct 1;36:58-65.
20. Sosnik A, Augustine R. Challenges in oral drug delivery of antiretrovirals and the innovative strategies to overcome them. Advanced drug delivery reviews. 2016 Aug 1;103:105-20.