Oral drug delivery: Gastrointestinal tract adaptations, barriers and strategies for delivery enhancement - a review

§.1.2 Omeh Romanus Chijioke, 1Ugwueze Mercy Ebere, 4Offiah Raymond Ogbonna, 2Mbah Chukwuemeka Christian, 3Momoh Audu Mumuni, 2Onyishi Ikechukwu Virgilus, 2Onunkwo Godswill Chukwuemeka, 2Onyechi Jacob Okechukwu

1Department of Pharmaceutics and Pharmaceutical Technology, Enugu State University of Science and Technology, Enugu, Enugu State, Nigeria
2Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria Nsukka, Enugu State, Nigeria
3Drug Delivery Unit, Department of Pharmaceutics, University of Nigeria Nsukka, Enugu State, Nigeria
4Department of Pharmacology and Therapeutics, College of Medicine, Enugu State University of Science and Technology, Enugu State. Nigeria

§Corresponding author: Omeh Romanus Chijioke., Email address: romanus.omeh@esut.edu.ng

Abstract

The mouth is a vital route of drug administration with over 84 % of all medicines reportedly administered through it. The gastrointestinal system is equally imbued with a lot of adaptive features that make the oral route even more conducive for systemic drug delivery. The usefulness of the oral route is, however challenged by the existence of numerous absorption barriers which limit the effective absorption and delivery of drugs to their target sites in the body systems. Understanding these adaptive attributes, systemic barriers, and available strategies for overcoming such barriers will not only be helpful in drug development and design but also useful to the formulation scientists desirous of optimizing drug delivery. The objective of this work was to review the gastrointestinal route of drug administration with respect to some biochemical and physio-anatomic features that impede or enhance drug absorption and to highlight current strategies that have been deployed to achieve optimum per oral drug delivery. The current review reveals the emerging roles of nanocarriers in oral drug delivery. Polymeric nanocarriers enhance the solubility, targeting and safety profiles of many important pharmacological agents. Novel systems that offer protection against gastro enzymes and as such, promote oral administration of biologicals are being widely investigated. Mechanical, magnetic, and acoustic energy – induced membrane perturbation are other delivery options receiving research attentions. It may be concluded that, with the avalanche of research efforts in the area, the oral route will maintain its prominence among other routes of drug administration.

Keywords: Oral delivery, absorption, barriers, particle technology, first pass metabolism

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INTRODUCTION

Numerous literatures show that the oral route is the most frequently used route of drug administration and is generally preferred by patients, clinicians, health practitioners and even pharmaceutical manufacturers (Alqahtani et al., 2021; Liu et al., 2017). The route is reported to be, by far, the most popular of all other routes with over 84 % of all medicines estimated at a value of $35 billion and a growth rate of 10 % reportedly administered through it (Prasad et al., 2017). The preference for this route is attributed to the fact that it predominantly mimics the natural feeding process. It is simple, convenient, amenable to patient’s self-administration and enjoys flexible dosing schedule. Oral drug ingestion is also a non-invasive procedure associated with no pain and/or discomfort (Shreya et al., 2018; Homayun et al., 2019). More so, most dosage forms for oral administration are very simple to handle and do not need sterilization to maintain stability. Considered from safety perspective, overdose or poisoning by orally administered drugs may be controlled by simple induction of vomiting or immediate ingestion of an antidote.

Generally, the gastrointestinal system is naturally endowed with a lot of anatomic and physiologic features that enhance the passage, release, and absorption of drugs within the system. However, drugs administered orally encounter a lot of delivery barriers which limit their absorption, membrane permeation and systemic bioavailability. Some of the drugs are subject to hepatic first pass effect, first pass metabolism, food, and efflux system effects as well as influence of pathological conditions that may exist in the gastrointestinal tract. Other limitations of the oral route of drug administration include inappropriateness for use in vomiting and unconscious patients, frequent incidence of nausea, vomiting and other stomach disturbances and, challenge of pill burden especially in chronic and/or syndromic diseases as well as poor patient dosing compliance in cases of self-administered drugs. Some drugs do also induce local irritation within the GIT (Rubbens et al., 2018). Poor aqueous solubility of many drugs is also a major challenge to their oral administration. About 40 - 70% of new drug entities (NDE) and about 90% of those at developmental stages are known to exhibit poor aqueous solubility, (Kumar, 2016).

A lot of strategies have been explored by both researchers and drug manufacturers to improve the absorption and bioavailability of orally administered drugs. Most often documented strategies involve solubility enhancement, modified release systems and other novel drug delivery approaches (Boyd et al., 2019). Strategies currently employed to enhance drug solubility include particle size reduction, pH adjustment, complexation, emulsification, lipid dispersion pegylation, solid dispersion among others. These approaches have led to significant improvement in the gastrointestinal solubility, absorption, and systemic bioavailability of many hitherto poorly water-soluble drugs.

Gastrointestinal tract adaptations for systemic absorption and delivery of orally ingested drugs.

The gastrointestinal tract is naturally structured to facilitate its major functions of transportation, digestion and absorption of food, drugs and other relevant materials introduced into it. The specific activities that take place and the bioactive chemicals recruited upon introduction of a material into the GIT depend partly on the nature, state, and chemical composition of the material. A lot of physiologic and anatomic characteristics of the GIT adequately adapt it to these functions. The following GIT features have been identified as useful adaptations that support gastrointestinal drug absorption and permeation:

The length and convoluted structure of the gastrointestinal tract

The gastrointestinal tract is about 9 meters in length with the small intestine constituting 6 meters of the total length, (Hua, 2020). The small intestine is particularly windy in packing a feature that allows the long structure to be accommodated in a relatively small portion of the abdomen. The length and convoluted packing of the intestine ensure delayed transit time, longer retention time and more intimate contact between the ingested drugs and the digestive enzymes and absorptive surfaces of the GIT. The implication of these features is that enough surface area and absorption time are available for maximum drug permeation (Brunton et al., 2018). This is even more so with the small intestine which is the major digestive and absorptive portion of the GIT constituting two thirds (2/3) of the entire length of the GIT.
Peristaltic movement of the GIT.

The peristaltic movement of the GIT not only facilitates physical disintegration of the dosage forms and movement of the drugs and their digestive products along the GIT but also provide the agitation required for needed emulsification of some stomach contents.

Presence of large absorptive cells.

Availability of numerous absorptive cells in form of the villi along the intestinal luminal surfaces facilitates absorption of drugs from the gastrointestinal solutions (Brunton et al., 2018).

Presence of digestive enzymes and other bioactive chemicals

The GIT has a lot of digestive chemicals, enzymes and gastric fluids, all which aid in the breakdown, digestion, dissolution, and absorption of drugs. These chemicals are released preferentially according to the nature of the formulation (lipid, carbohydrate or protein based). Presence of endogenous emulsifiers like bile salts facilitates formation of emulsions which is necessary for the solubilization of poorly water-soluble drugs.

Presence of membrane transport molecules

A lot of membrane transport molecules are present within the GIT membranes where they perform the trans-membrane transportation of some natural molecules like glucose, amino acids, neurotransmitters, and some natural ions. Such transporter molecules are also capable of binding to some drug molecules and facilitating their trans-membrane movement. In this regard, Trepat et al., (2007) listed L-dopa, gabapentin, 5-fluorouracil, and baclofen as examples of drugs transported by attaching to amino acid transporters, and beta-lactams transported by molecules designed to transport naturally occurring oligopeptides. The effect of membrane transporters may however be inhibitory in some cases as shall be discussed later.

Gastrointestinal tract drug absorption barriers

Orally administered drugs encounter a lot of barriers against their absorption and free passage into the systemic circulation and ultimately to their sites of action. These barriers may arise from: (i) the peculiar physiologic and anatomic features of the gastrointestinal tract (ii) the physicochemical properties of the drug molecules and (iii) the design of the pharmaceutical dosage forms. Drugs molecules must overcome these barriers to gain access to the circulatory system. Some of these barriers are described below:

Gastrointestinal membrane mucus barrier

The gastrointestinal membrane mucus is made of water, mucin, and high molecular weight glycoproteins. It is present on the GIT surfaces in the form of entangled network of tissues. Boegh and Nielsen (2015) noted that this network is hydrophilic in nature and so creates stearic and interactive barrier against the absorption of hydrophobic drug molecule. The mucus which is continuously secreted by the goblet cells of the GIT also constitutes dynamic barriers to the absorption of both hydrophilic and hydrophobic drugs due to its continuous shedding and clearance because of cell turnover from the mucosal surfaces (Homayun et al., 2019).

Epithelial cells barriers

The inner surface of the GIT is lined with many columnar shaped cells known as epithelium. The epithelia are the main absorptive cells of the intestine. The epithelial cells responsible for gastrointestinal food and drug absorptions are
the enterocytes which are heavily distributed at the apical region of the intestinal villi, (Engman, 2013). In humans, the epithelial layer is thought to be continuous in the stomach and duodenum but may not be so in the rest of the small and large intestines. (Marianne, 2015). Each epithelial cell is firmly joined to the next cell thereby creating a joint known as “tight junction” between adjacent cells.

Following the diffusion of drug molecule through the mucus membrane barrier, it encounters the epithelium as another barrier, (Laffleur; Bernkop-Schnürch, 2013). Drug passage through the epithelial cells may occur through two distinct routes namely, paracellular, and transcellular routes. While the paracellular transport refers to the passage of drugs through the tight junctions (between cells), transcellular route involves transportation through the cell membranes, (Muheem et al. 2016). Aulton (2002) noted that the tight junction constitutes a natural barrier to par cellular absorption of large molecular size drugs. Similarly, the absorptive apical cell membrane of the columnar cell appears to behave, with respect to nutrient and drug, like lipoidal membrane penetrated periodically by sub microscopical aqueous-filled channels or pores. The predominantly lipoidal membranes act as absorption barriers to aqueous drug molecules while the aqueous pores allow only molecules of selected molecular sizes to pass through. The membrane, therefore, acts as passage sieve to both hydrophilic and lipophilic compounds. Luo et al. (2021), postulated that the transcellular transport is mostly restricted to molecules that comply with Lipinski’s rule of five and which are lipophilic in nature. On the other hand, the tight junctions (paracellular transport route) allow the passage of hydrophilic molecules of molecular weight not more than 1000g/mol. The paracellular route (tight junction), therefore, constitutes an absorption barrier to hydrophobic/lipophilic and large molecular weight drugs while the lipoidal cell membrane act as absorption barriers to hydrophilic drug molecules.

**Efflux system barriers**

Efflux systems refer to a group of transporter gene proteins that are found in the cell membranes of many tissues and organs especially the intestine, liver, kidney, and the lungs, (Srivalli & Lakshmi, 2012. They inhibit the natural process of drug transport across the cell membranes. These gene proteins belong to the class known as adenosine triphosphate (ATP) binding cassette (ABC) super family with family members such as, the permeability glycoprotein (P-gp) also known as ABCB1; bile salt export pump (BSEP) or ABCB11; the multidrug resistance proteins (MRP1-6) or ABCC 1-6 and the breast cancer resistance proteins (BCRP) or ABCG 2. (Kuar et al., 2015). Members of this super family utilize adenosine triphosphate (ATP) to generate energy enabling them to pump substrate drugs back against their concentration gradients (from the enterocyte membrane back to the intestinal lumen (Shugarts & Benet, 2009). Their action limits the quantity of drugs that eventually enter the circulatory and/or the lymphatic system.

**Unstirred water layer barrier**

The unstirred water layer (UWL) refers to an aqueous diffusion layer just adjacent to the intestinal membrane. This layer exerts some resistance against passive permeation of molecules into the epithelial membranes and drug diffusion across the mucous membrane (Wilson & Dietschy (1972). An experimental investigation on absorption across the unstirred water layer and brush boarder of the rat jejunum concluded that the uptake of polar bile was limited solely by membrane permeation while the mucosal uptake of less polar bile was significantly limited by the unstirred water layer. The report also claimed that the permeation retarding effect of the UWL was more pronounced for micellar solutions than for free monomers (Thomson, 1980).

**Gastrointestinal fluid pH absorption barrier**

The pH of the intraluminal fluid varies widely along the length of the GIT, generally lying between 1.0 – 3.0 within the stomach, about 6 in the duodenum, between 6 – 7.4 in the small intestine and between 7.5 and 8.0 within the ileum and rectal regions. (Evans et al., 1998). These variations in pH values influence the ionization statues of dissolved drugs ((Brunton et al., 2018). The ionization levels equally determine the population of the charged and uncharged species of ingested drug molecules at any given region of the GIT. This, in turn, influences the membrane permeation of drugs. For a drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. (Kalepu & Nekkant, 2015). This implies that dissolution medium that facilitates ionization of a drug will cause poor membrane permeation and poor absorption of the drug through the adjacent biological membranes. Most drugs are either weakly acidic (polar) like aspirin and phenobarbitone or weakly basic. Weakly acidic drugs exist in unionized (neutral)
state in the gastric fluid (with acidic pH) and hence exhibit good absorption in the stomach while weakly basic drugs ionize in the same region and exhibit poor absorption there. Since drugs are absorbed in their unionized forms, the absorption of weakly acidic drugs in the gastric segment of the GIT is enhanced while absorption of weakly basic drugs is impeded by the prevailing low pH environment. To the contrary, weakly acidic drugs undergo significant ionization in the high pH (basic) intestinal fluid and as such exhibit poor absorption as against weakly basic drugs that remain unionized in the intestinal fluid. (Kalepu & Nekkant, 2015). The pH condition of a specific GIT region may, therefore, constitute absorption barrier for some drugs. The pH environment of various sections of the GIT may also pose serious challenge to the stability of the administered drug such that a greater portion of both the intact and ionized drug is not absorbed. The acidic condition of the gastric fluid can cause denaturation and/or degradation of drugs while bile salts of the small intestine can destabilize biological products (Khonsary et al., 2017 & Luo et al., 2021)

**First pass metabolism barrier.**

First pass metabolism refers to the metabolism or biotransformation of orally administered drugs that take place before the drug gets into the systemic circulation. The main sites of such pre-systemic metabolism are the intestine and the liver. First pass metabolism reduces the quantity of free active molecules that get into the systemic circulation. (Engman 2003). Bioavailability is described as the fraction of orally administered drug that reaches the systemic circulation in intact form. The relationship between bioavailability and first pass metabolisms has been expressed by Thorn, (2012) as;

\[ F = f_{abs} (1-E_G)(1-E_H). \]

where,

F represents drug’s total bioavailability, \( f_{abs} \) is the total quantity of drug absorbed by the intestinal enterocyt, \( E_G \) represents gastric extraction or quantity of drug metabolized in the intestine and \( E_H \) is the quantity metabolized in the liver before entering the circulatory system. Any change in \( (1-E_G) \) or \( (1-E_H) \) affects the bioavailability (F). Liver enzymes involved in hepatic first metabolism are, the cytochrome P450 (CYP450) and the uridine diphosphate glucuronosyltransferase (UGT) families of enzymes. Some drugs that are substrates of various permeability glycoprotein (Pg-p) enzymes are shown in Table 1. (Brown, 2010).

| CYP 450 enzymes | Substrate drugs                                                                 |
|-----------------|-------------------------------------------------------------------------------|
| CYP1A2          | Amitriptyline, Imipramine, Theophyline                                         |
| CYP2B6          | Cyclophosphamide, Methadone                                                   |
| CYP2C9          | Warfarin, Tolbutamide, NSAIDS                                                  |
| CYP2C19         | Omeprazole, S-mephentoin, Propranolol                                          |
| CYP2D6          | Antidepressants, B-blockers                                                    |
| CYP2E1          | Acetominophen, ethanol, halothane                                               |
| CYP3A45 and 6   | Ketoconazole, Atovastatin, Lovastatin, Azithromycin, Clarithromycin, Benzodiazepines, Calcium channel blockers, Protease inhibitors. |

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**Gastric emptying rate**

The rate at which the stomach empties its digestive product to the intestine through the pyloric sphincter may facilitate or constitute absorption barrier to orally administered drugs. The small intestine is the major absorption site of the GIT. Fast emptying of digestive product containing a drug will deliver such drug faster to the absorption sites of the small intestine thereby fast-tracking absorption. The reverse is true for slow emptying rate. Prescott (1974) reported that, for drugs that are rapidly absorbed, gastric emptying time is the absorption rate limiting step He also noted that, on the contrary, slow gastric emptying rate has the potential of retaining drugs longer in the stomach, slowing drug absorption and subjecting it to possible gastric enzyme and acid degradation. The impact of gastric emptying rate on absorption therefore depends partly on the nature of the drug.

**Pathological conditions and surgery**

Many pathological conditions occurring locally within the GIT or elsewhere in the body can alter the physiologial functions of the organ in a way that can disrupt its normal drug absorbing activities. For instance, pain can alter gastrointestinal blood perfusion, motility, enzyme secretion and membrane permeability in a way that reduces its capacity for drug absorption. (Konturek et al. 2015, as cited in Hua, S. (2020). Britton and Young (2014) noted that acute gastrointestinal infections can cause temporal impairment in the microbiome (dysbiosis) and alter the normal fluid secretion and other functions within the bowel. This can also cause altered bowel motility in a manner that affects drug transit (Grover et al. 2008); Albenberg and Wu, (2014). Many other disease conditions including some non-GIT diseases like Parkinsonism, fibrosis, HIV infection and diabetes can alter the gastrointestinal physiology and functions (Hatton et al., 2019).

Similarly surgical partial resections on both stomach or intestine or even colons performed in the treatment of diseases like peptic ulcer disease, malignancies, inflammatory bowel disease and other GIT pathologies can affect drug absorption ostensibly due to reduction in absorption surface areas and other pathological changes, (Titus et al. 2013; Hua et al., 2015; Hatton et al., 2018; Kyietya, 1999 and Thompson et al. 1998).

Effinger et al. (2018) have reviewed the impact of some gastrointestinal disease states including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease on oral drug absorption and the implications for formulation design. They concluded that drug absorption via the oral route is adversely affected by these disease conditions.

**Food effects and drug – drug interaction**

The effect of food on drug absorption has been widely reported showing that the influence of food is related to both drug formulation and the type of food. These effects present as decreased gastric emptying time, change in intestinal pH, change in intestinal fluid viscosity, increase in secretion of digestive enzymes and emulsifying endogenous bile (Kostewicz et al. 2002. These changes affect drug absorption in various ways. The beagle dog pentagastrin model has become the standard approach for studying the effect of food on drug absorption (Zhang et al. 2018). This model can establish and extrapolate the effect of food on drug absorption from pharmaceutical formulations (Zane et al. 2014). For instance, presence of fatty food enhances the absorption of BCS class II drugs (Chatterjee et al. 2016) whereas the absorption of some oral penicillins is inhibited by the presence of antacids.

In like manner, drugs can affect the absorption and bioavailability of other drugs by altering the physiological state of the GIT, forming complexes with other drugs or by outright competitive antagonism. Laxatives can cause a reduction in the absorption of co administered drugs by reducing the GIT retention times of such drugs. Many antacids are also known to reduce the absorption of the tetracyclines by forming insoluble complexes just as proton pump inhibitors can affect release of drugs from formulations that depend on specific GIT pH for drug release (Brunton et al., 2018; Lahner et al. 2009). Some potent antibiotics can destroy the GIT flora and result in poor absorption of some other drugs (Sartor, 2010, as cited in Hua, S. (2020).

**Age related drug absorption barriers**

Many physiological and anatomic functions of the GIT like intestinal motility, gastric acid secretion, length of the GIT, gastric emptying time, enzyme secretion and microbial flora are affected by age. In children and the elderly, these functions are often sub optimal and as such drug absorption, bioavailability and metabolism are negatively affected, (van den Anker, 2018). Reduced gastrointestinal motility and/or slow gastric emptying time have implication in delayed delivery of drugs to absorptive sites in the GIT. Similarly, age related alteration in the intestinal flora which aid drug metabolism may undermine absorption in the children, the elderly and other underdeveloped persons. Jones, (2020) specifically noted that "infants with congenital atretic bowel or surgically
removed bowel or who have jejunal feeding tubes may have specific absorptive defects depending on the length of bowel lost or bypassed and the location of the lost segment. Advancing age is associated with alteration in many physiological functions including gastrointestinal performances. Gastric pH and gastric emptying time have been reported to be significantly altered in the elderly, (Russell et al., 1993; Russell et al., 1994; Vertzoni et al., 2020b). Apart from these two parameters, variation in gastrointestinal absorption is very likely due to multimorbidity and polypharmacy which are common among the geriatrics (Mojaverian et al., 1988; Moore et al., 1983; Stillhart et al., 2020).

Strategies for improving gastrointestinal absorption of orally administered drugs

Most of the strategies deployed to enhance gastrointestinal absorption of drugs target, (i) increase in the GIT fluid solubility of poorly water-soluble drugs, (ii) promotion of drug membrane permeability and (iii) creating drug forms, carriers and devices that are capable of overcoming drug absorption and delivery challenges. Dissolution in the GIT fluid is a prerequisite for drug absorption through the GIT membrane, distribution in the circulating blood (which is aqueous in nature) and eventual accumulation of the drug at the site of pharmacological action (Dhillon et al., 2014). The lymphatic system plays comparatively lesser roles in this regard. For the purposes of pharmaceutical formulation, a drug is said to be highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over pH range of 1 to 7.5 (Savjani et al., 2012). Drugs which fall into the British Pharmacopoeial grouping of sparingly soluble, slightly soluble, very slightly soluble, and practically insoluble may, for the purposes of formulation design, be generally described as poorly water-soluble drugs (PWSD). The most widely reported techniques for increasing drug aqueous solubility include use of particle size technologies, use of lipid-based systems, co-solvents and surfactant systems, salt formation and use of delivery carriers like liposomes, niosomes, cyclodextrins, micelles and other similar nanodevices. Some other techniques involving molecular structural manipulations like co-crystal habit modification, polymorphism and amorphous solid dispersion have also been employed. These various strategies employed for improving drug solubility, absorption and systemic bioavailability are discussed below.

Use of particle technologies

In Pharmaceutics, the term ‘particle technologies’ is used to describe various techniques for size and morphology manipulations employed to modify the physicochemical, micromeritic and biopharmaceutical characteristics of drug particles. Common particle technologies involve particle size reduction (micronization, and nanosization), engineered particle size control using cryogenic spray technique and crystal growth habit modification.

Micronization and nanosization

Micronization is the process of reducing coarse drug particles to an ultrafine powder with mean particle size in the range of 2 – 5 µm and only a very little fraction of the particles lying below 1µm size (Khadka et al., 2014). Like other particle reduction processes, micronization results in increase in the particle surface area – to - volume ratio and subsequent increase in the dissolution rate. Particle size reduction equally reduces particle thickness and solvent diffusion part length thereby increasing rate of drug passage from the particle to the dissolution media in accordance with the Noye- Withney dissolution theory, (Smita et al., 2015).

It has, however been argued that a decrease in particle size has relatively little effect on the solubility of a drug substance since as such reduction does not alter the solid-state properties of the particles (Khadka et al., 2014). However, Williams et al (2013) in their work concluded that particle size reduction indeed increases kinetic solubility of poorly soluble drugs by increasing the solute – solvent interaction surface areas. Nanosizing involves the reduction of particles to nanoscale sizes which fall within the range of 1-100 nanometers (Kalepu & Nekkant, 2015). Apart from physical size reduction, nano properties can also be conferred on a drug material by embedding or conjugating the drug to a nanocarrier (Dhiman. 2006). Nanosizing dramatically confers on drug substances many pharmacokinetic characteristics that are clearly distinct from those of their bulk or macro counterparts. In addition to having larger surface areas nanomaterials acquire other attributes like, enhanced electrical, optical, thermal, and other physicochemical characteristics which can be exploited in designing products with enhanced solubility, absorption, and bioavailability. Wanigasekara & Witharana. 2016).

Crystal habit modification (co-crystal and polymorphism)

Crystal engineering also known as crystal habit modification can lead to co-crystalization or polymorphism. The deliberate objective of crystal habit modification is to design and control the molecular packing within a crystal structure with the intention of generating a new solid crystal that

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exhibit some desired characteristics such as altered shapes and sizes, increased surface area, new crystal packing arrangement, increased solubility, and other similar features (Joshi, 2020). If a crystal engineering process leads to the formation of one or more crystalline solids that differ only in the molecular arrangement the process is known as polymorphism and the products are called polymorphs. Co-crystals, on the other hand result from a molecular complex formed between a drug molecule and a crystal former leading to change in the original lattice arrangement (Williams et al., 2013). Either of these modifications can create new molecular entity with enhanced pharmacokinetic properties. Bucovec et al. (2016) investigated the effect of crystal habit on the dissolution behaviour of simvastatin crystals and its relationship to crystallization solvent properties. The researchers reported that different crystal morphology types of simvastatin resulting from crystal isolation using different solvents exhibited different dissolution rates in the same dissolution medium. They associated this difference with differences in sizes, shapes, and wettability of different crystal lattice structures. They reported a significant increase in the dissolution rate of the re-crystallized drug sample in a buffer medium.

**Salt formation and pH adjustment technique.**

Salt Formation and pH adjustment are both forms of chemical modification that can improve the aqueous solubility and gastrointestinal absorption of poorly water-soluble drugs. The ionized forms of drugs are generally more soluble in polar solvents like water than their neutral base forms. This has been explained to be because the affinity of ionized species for water is more than that of the unionized species. (Williams, et al., 2013). Any chemical modification (pH adjustment or salt formation) that results in increased molecular ionization will likely enhance the aqueous solubility of the drug of interest. Most drugs are either ionizable weak acids or weak bases in which ionization is a major factor for solubilization. The extent of solubilization may also be dependent on the pH of the solution and the pKa (ionization constant) of the drug molecules. Weakly acidic drugs are more soluble at pH ≥ pKa (Kalepu, et al., 2015). For solid dosage forms, salt formation play the same role since the salt forms undergo easier ionization in aqueous media than the pure base.

**Use of solid dispersion systems**

Solid dispersion describes a dosage formulation in which a drug in solid form is uniformly distributed (dispersed) in another solid material (dispersion matrix) with the intent of improving the solubility or other delivery features of the dispersed drug. Lipids are widely used as matrix materials. Uniform dispersions can be achieved using various techniques such as, mechanical blending, hot melt fusion, hot melt extrusion and solvent evaporation methods. Popular matrix materials include, polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), sodium lauryl sulphate (SLS), Plasdone-S630, Tween 80 and many other polymers (Savjani et al., 2012). Solid dispersion of diclofenac potassium in hydroxypropylmethyl cellulose (HPMC) has been successfully used not only to improve the aqueous solubility of the drug but also to sustain the release for up to 14 h. (Omeh, 2009). Studies have established different mechanisms by which solid dispersions enhance the aqueous dissolution of poorly water-soluble drugs to include reduction in effective particle size, improvement in particle surface wetting and elimination of the impact of lattice energy via stabilization of drugs in amorphous state (Williams, et al., 2013).

**Strategies for oral delivery of proteins, peptides and other biologics**

A plethora of strategies for safe delivery of organic therapeutics that are subject of gastrointestinal tract enzyme degradation have been developed and some are already patented or commercialized. Momoh et al., (2020) successfully formulated snail mucin-based microemulsion for oral delivery of insulin. The researchers reported an enhanced capsulation efficiency of 70 %, sustained drug release of over 12 h and blood glucose reduction over a period > 8 h in rat model. Another per oral protein delivery approach involves the use of protease enzyme inhibitors. Some tested inhibitors include aprotinin, soybean trypsin inhibitors, camostat mesilate and chromostatin (Muheem, et al., 2016) all which were used to inhibit the effect of protein degradative enzymes like the peptidases. Agarwal & Khan (2001) reported the use of chicken and duck ovomucoids as enzyme inhibitors to offer 100% protection against the degradative action of intestinal trypsin and a-chymotrypsin.

Many recent works have also reported the use of permeation enhancers to facilitate passage of proteins and other large molecular weight compounds though the epithelial membranes (Brayden & Mrsny, 2011). Permeation enhancers increase transcellular membrane transport by modifying the tight junctions of the epithelial cells and the paracellular transport by epithelial membrane perturbation, Zonula occludens toxin (ZOT) (Salama et al., 2006), chitosan (Prego et al., 2005), thiolate polymers (Bernkop-Schnurch,2005) and Pg-p. Surfactants have also been used to...
modify the integrity of the gastro absorption membranes for enhanced drug absorption, (Muheem et al., 2016)

Use of carrier systems

Although most popular for delivery of parenteral formulations, novel lipid, polymeric and other novel carrier systems such as liposomes, niosomes, microspheres, emulsion systems, nanoparticles and a host of others are being widely studied for oral delivery of medications. These carriers not only increase the gastrointestinal solubility and absorption of poorly water-soluble drugs but also protect the drugs from harsh gastrointestinal conditions perpetrated by various enzymes and biological chemicals. They also serve as effective devices for drug targeting, sustained release, and stimulus response devices. Successful formulation of breadfruit seed oil-based self-emulsifying drug delivery system for the enhancement of the bioavailability of two non-steroidal anti-inflammatory drugs - aceclofenac and ibuprofen has been reported with improvement in the solubility, drug release profiles and other pharmacokinetic parameters (Omeh, R, University of Nigeria, Nsukka, Nigeria. Ph.D. thesis). Versicular systems like liposomes, bilosomes, micelles and microcapsules have been used to embed sensitive drugs and biomolecules for targeting effects or protection against opsonisation, phagocytosis and gastroenzyme degrading effects. Gastro-mucoadhesive carriers have also been suggested to improve drug residence time and reduce clearance time thereby increasing drug absorption and bioavailability.

Use of physical methods

One of the latest novel approaches to gastrointestinal drug absorption enhancement involves techniques based on physical interactions and manipulations of the GIT membrane using magnetic, mechanical, and acoustic energies to improve drug permeability across the GI mucosa (Luo et al. 2021). Application of such energies to the cell membrane through some relatively complex procedures has been reported to be capable of disrupting the tight columnar epithelial packing (Trepata et al., 2007, as cited in Luo et al. 2021) thereby increasing both paracellular and transcellular transport of drugs (A.-L. 2019).

Gastroretentive approaches

Formulation of dosage forms in a way that delays their transit time through the stomach and other parts of the GIT has also been exploited for the enhancement of drug absorption and local effects. Floating formulations that exhibited three-fold floating time increase of albendazole tablets on gastrointestinal fluids have been successfully designed (Omeh, R. Enugu State University of Science and Technology, Nigeria – accepted manuscript). Sunogrot et al. (2017) equally sort to overcome the problem of rapid clearance of some model drugs from the stomach by incorporating some mucoadhesive components into some nanoparticulate formulations while Sharma et al. (2018) used high density systems to delay transit of iron nanoparticles-based formulation through the stomach. A few researchers have reported promising drug delivery results with regards to gastric retention and/or mucoadhesion in both invitro and in vivo experiments (Hua, 2020).

Use of nanoparticles for oral delivery of biological products

Nanoparticles have been successfully used in novel ways for both local and systemic delivery of drugs that otherwise were not possible because of the effects of gastrointestinal tract bioactive chemicals, poor GIT membrane permeability and effects of phagocytic enzymes. Many researchers have, however, reported improved absorption of drugs in the small intestine from nanoparticle loaded formulations and attributed this to the enhanced mucosal membrane permeation by the nano sized particles (Ahmad et al., 2018; Prajapati et al., 2018). Rapid uptake of nanoparticles by the microfold cells (M-cells) of the Peyer's patches in the small intestine has also been exploited for the delivery of biological products and oral vaccines. The M-cells act as both protective biological carriers and antigenic targeting moieties for therapeutic compounds (Yu et al., 2019; Managuli et al., 2018). Such systems have been found to be very strategic in oral delivery of vaccines. The M-cells may also promote preferential passive lymphatic targeting resulting in improved systemic delivery of some drugs.

Other oral drug delivery enhancement techniques

Other technologies that have shown potential for improving oral drug delivery include, among others, fast-dispersing tablets, three-dimensional Printing (3DP) and electrostatic coating technologies. These are aimed at modifying the physicochemical and pharmacokinetic properties of drugs to improve their systemic and local delivery. Fast dispersing tablets promote rapid disintegration of tablets and quick release of drugs for systemic absorption. Electrostatic coating which involves the spraying of dry charged powder on tablet surfaces provides superior surface protection for active ingredients against gastric acid and enzyme degradation (Yang et al., 2016).
The 3D printing technology is unique for combination therapies and patient specific treatment solutions (Tsintavi et al., 2020).

CONCLUSION

A lot of research activities had been and are still being undertaken to elucidate the physiological and anatomical features of the gastrointestinal tract that either enhance or impede effective oral systemic delivery of many pharmacologically active and clinically important drugs. Many reviewed reports show that these strategies range from formulation design, molecular modification, and gastrointestinal membrane perturbation, all which have shown great potentials for overcoming poor gastrointestinal absorption of many drugs. The future of oral drug delivery may be confronted with increasing poor drug solubility and suboptimal membrane permeation arising from the deployment of sophisticated drug discovery technologies like high throughput screening (HTS), combinatorial chemistry and others which are associated with synthesis of large molecular weight, structurally complex and non-polar hydrophilic new drug entities (Szymański et al., 2012; Guram et al., 2015) Nanotechnology, gastrointestinal membrane alterations and 3D technologies are likely to play significant roles as solutions to evolving per oral route drug delivery challenges.

Conflict of interest

Authors have no conflict of interest to declare in respect of this work.

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Authors’ contributions

ORC conceptualized, designed, and wrote the introductory part of the work. UME and ORC wrote the abstract and organized the work into sections and subsections, ORC and ORO wrote the section on gastrointestinal tract adaptations for drug absorption, MCC and MAM wrote the aspect on barriers to gastrointestinal tract drug absorption while ORC wrote the section on strategies for enhancing gastrointestinal tract drug absorption. MAM collated various contributions, compiled them into one document with necessary corrections. OVI proofread the materials, edited all aspects, and gave preliminary approval for submission, OGC and OJO did the final proof reading/corrections and gave final approval for submission of manuscript for publication.

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