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Milestone for journey of medicine through oral route: A brief review

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Abstract
Oral route is the first choice for the administration of drug since it is both convenient and economical. Among the various drug delivery system, the oral route has attracted the most attention due to its unique advantages, including sustained and controllable delivery, ease of administration, and feasibility for solid formulation, patient compliance and an intensified immune response in vaccines. Around 60% of established small-molecule drug product available commercially are administered via oral route. Oral drug absorption is a process influenced by the physiochemical and biopharmaceutical properties of the drug and its inter-relationship with the gastrointestinal tract. Drug administered by oral route move through the various parts of the digestive tract: oral cavity pharynx, esophagus, small intestine, large intestine and unabsorbed compounds leave the body through anal sphincter (anus). Primary factors such as drug solubility, dissolution and Permeability across intestinal barrier are the key parameter controlling drug absorption whereas the secondary factors such as gastric emptying, intestinal motility and GI transit time plays a major role in influencing drug absorption.

Keywords: Oral route, solid dosage form, GI tract, drug absorption

Introduction
In the Oral route the drug (tablet/capsule/pills etc.) travel throughout the GI tract (9 meters length with varying diameter) which is considered to be the tube starting from the mouth and the esophagus, where it has only a transport role. Digestion then begins in the stomach and continues in the small intestine to the colon. Absorption essentially takes place in the small intestine. The tablet goes through various physiological as well as physiochemical transition in the whole journey and lastly excreted as metabolite or unchanged drug. Although some drugs are specially targeted to gastrointestinal sites of action, such as bismuth subsalicylate for heart burn and ezetimibe for the reduction of cholesterol absorption, most of the pharmaceutical active ingredient exert their therapeutic effect outside the gastrointestinal tract. Therefore, they must be absorbed from the GI system to gain access to the systemic circulation and reach their site of action. The absorption of drugs administered by the oral route is determined physiological state of the GI tract, which is in turn affected by diet, hormones, autonomic nervous system, pathological states and other drugs. Whereas, the physiochemical properties of the drug will also be determinant for its absorption kinetics.

The five anatomical areas of GI Tract that influence the tablet journey:
1. Oral cavity & Pharynx
2. Esophagus
3. Stomach
4. Small intestine
5. Large intestine or Colon

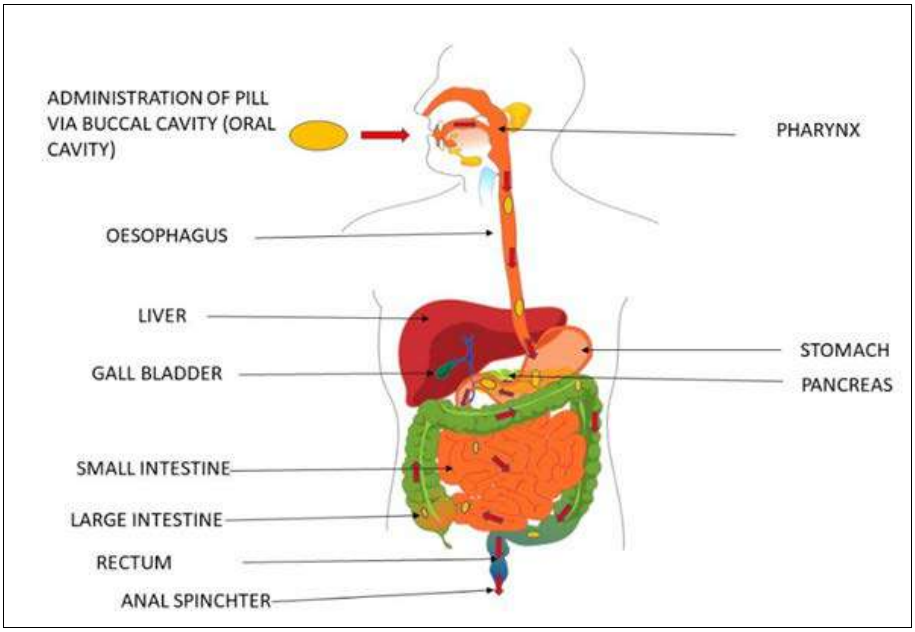

Fig 1: Journey of tablet throughout the body

1. Oral cavity and Pharynx

The tablet is administered into the oral cavity (or buccal cavity) at this point it comes in contact with the oral mucosa. Saliva is the main oral secretion, it has a PH close to 7 and is secreted in around 500-1500 ml/day, at a rate between 0 to 6 ml/min[1]. Its main components include ptyalin or salivary amylase and mucin, a glycoprotein that interact with the drugs. In the oral mucosal cavity, delivery of the drugs can be categorized broadly into three class:

1. Sublingual route
2. Buccal route
3. Local or Conventional route

1.1. Sublingual route

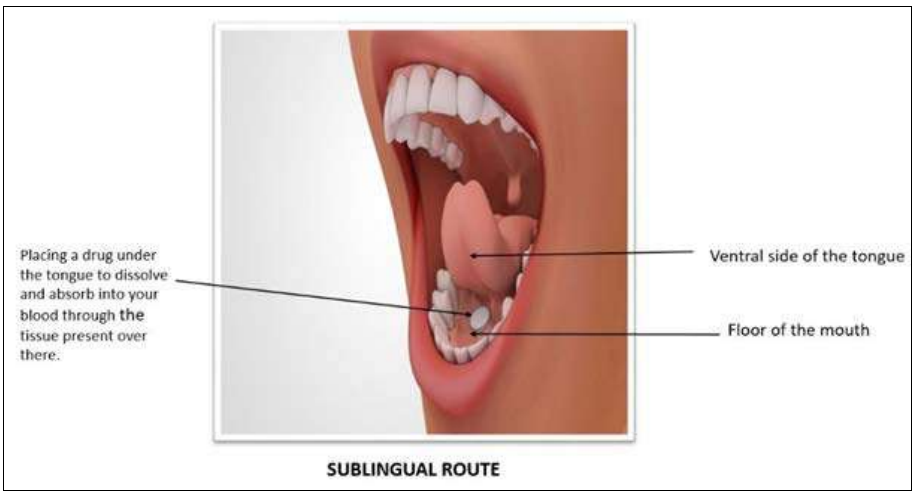

Fig 2: Administration drug via sublingual route

In sublingual route, drugs are taken as smaller tablet which are held under the tongue. Sublingual route of systemic drug delivery offers instant onset of therapeutic action. The absorption of the drug via sublingual routes is 3 to 10 times greater than oral route. Sublingual gland is the smallest vital salivary gland. Sublingual glands are present in the floor of oral cavity i.e., underneath the tongue. These glands produce mucin and help production of saliva, for necessary breakdown of drug. The drug is rapidly absorbed into the reticulated vein that is present underneath the oral mucosa, and transported it through the facial veins, internal jugular vein, brachiocephalic vein and then unload in to systemic circulation. The dose of sublingual drug is around 0-10 mg. The absorption potential of buccal mucosa is affected by the lipid solubility and therefore, the permeability of the solution (osmosis), the ionization (pH) and the molecular weight of the substances. The mean pH of the saliva is 6, this pH favors the absorption of drugs which remain in unionized form. If the pka is greater than 2 for an acid and less than 10 for a base then the absorption of the drugs through the oral mucosa occurs. Examples of some drugs administered through sublingual route include antianginal like nitrites and nitrates, antihypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol etc [2].

1.2. Buccal route

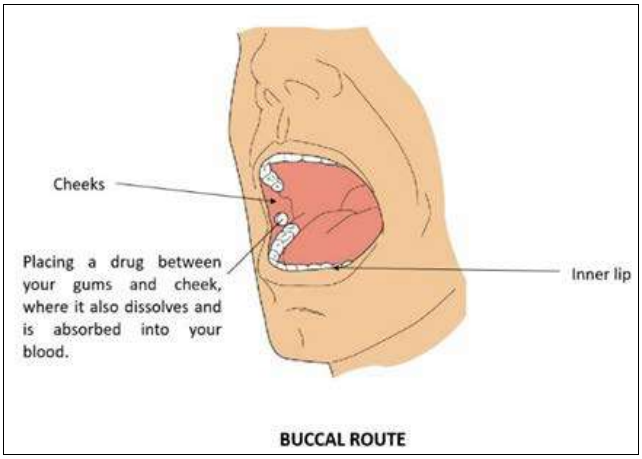

Fig 3: Administration drug via buccal route

In buccal route, the administration of drug is through the mucosal membranes at lining of the cheeks (buccal mucosa) to the systemic circulation. The drug is absorbed through saliva (pH 6), then circulate to internal jugular vein, superior vena cava, heart and lastly to entire body. Buccal tablets are small, flat and oval shaped dosage form varying in size 1-3 cm^2. Dose consisting of 25mg or less and having maximal duration of buccal delivery around 4 to 6 hrs. For delivery of drug via buccal route, the tablets which are inserted into the buccal pouch may dissolve or erode, therefore they must be formulated and compressed with sufficient pressure only to give a hard tablet. They soften (via saliva), adhere to the mucosa, and are retained in position until dissolution and/or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and the gum. Examples of some drugs administered through buccal cavity includes nitroglycerin Bio adhesive tablets for the treatment of angina pectoris, sumatriptan succinate buccal adhesive tablet which is effective in the acute treatment of migraine and cluster headache, etc. The oral cavity is followed by pharynx, which is part of both respiratory and digestive system.

1.3. Local route

In local route, there is no significance role of tablet over here as the main absorption will be done through the further parts of GI Tract such as stomach and small intestine. The tablet will only get moisten due to presence of saliva and tablet will swallowed down the esophagus for further adsorption, distribution, metabolism and excretion. It is mainly used for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease. They relatively consist of large dose about 500 mg and more and having hard consistency which react with stomach and small intestinal to break and get circulate into systemic circulation. Example of some local route administrative tablet are metformin for diabetes type 2, paracetamol is the most commonly used analgesic and antipyretic, etc.

These all three oral mucosa sites differ greatly from one another in terms of anatomy, permeability to an applied drug and their ability to retain a delivery system for a desired length of time.

2. Esophagus

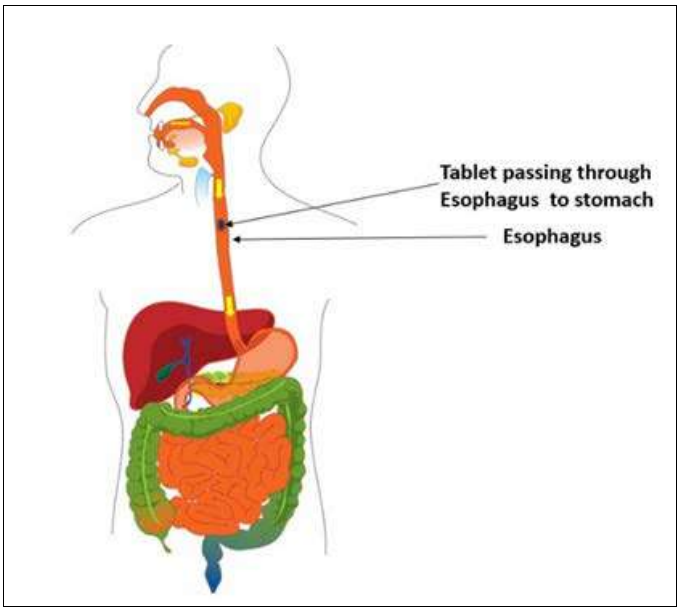

Fig 4: Tablet passing through esophagus

Now the tablet travels to esophagus. The Link between the oral cavity to the stomach is esophagus. The esophagus is composed of a thick muscular layer approximately 250 mm long and 20 mm in diameter. The pH of the esophageal lumen is usually between 5 and 6. Tablet moved down the esophagus by the act of swallowing. After swallowing, a single peristaltic wave of contraction, its amplitude linked to the size of the tablet being swallowed, passes down the length of the esophagus at the rate of 20-60 mm/sec, speeding up as it progresses. In the upright position, the transit of tablet through the esophagus is assisted by gravity. The esophageal transit of dosage forms is extremely rapid, usually of the order of 10-14 seconds. Very little (or none) drug dissolution occurs in the esophagus due to the mucous nature of its secretions, that possess a lubricating function to facilitate swallowing [7].

3. Stomach

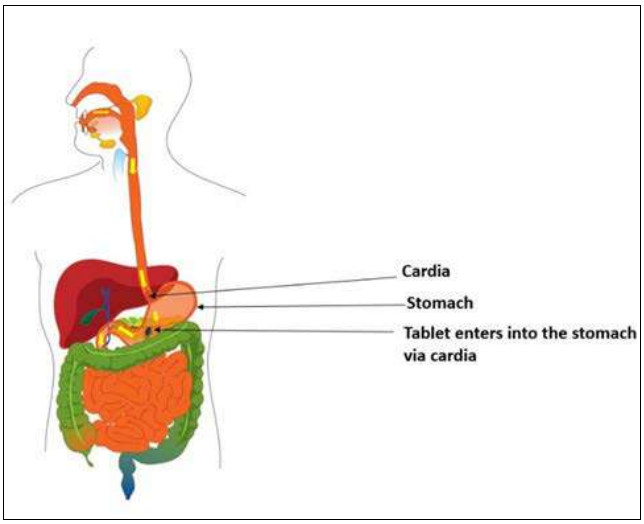

Fig 5: Tablet enters into the stomach

The next part of the gastrointestinal tract to be encountered by the tablet is the stomach. The stomach is the most dilated part of the gastrointestinal tract and is situated between the lower end of the esophagus and the small intestine. Its opening to the duodenum is controlled by the pyloric sphincter. The stomach can be divided into our anatomical regions: the fundus, the body, the antrum and the pylorus. The stomach has a capacity of approximately 1.5 L, although under fasting conditions it usually contains no more than 50 mL of fluid, which are mostly gastric secretions [7].

These include

- Hydrochloric acid secreted by the parietal cells, which maintains the pH of the stomach between 1 to 3.5 in the fasted state.
- The hormone gastrin, which itself is a potent stimulator of gastric acid production and pepsinogen and is released by the G -cells in the stomach. The release of gastrin is stimulated by peptides, amino acids and distension of the stomach and causes increased gastric motility.
- Pepsins, which are secreted by the chief cells in the form of its precursor pepsinogen. Pepsins are peptidases which break down proteins to peptides at low pH above pH 5, pepsin is denatured.
- Mucus, which is secreted by the surface mucosal cells and lines the gastric mucosa. In the stomach, the mucus protects the gastric mucosa rom auto digestion by the pepsin-acid combination.

Few drugs are absorbed in the stomach. Theoretically the low pH of the gastric fluid should render all but the most acidic drugs into a lipid-soluble nonpolar form, which would favor absorption. However, this is usually not the case for two main reasons.

a) The stomach lining is coated with a thick protective mucus which makes diffusion difficult.
b) The stomach has a fairly small surface area when compared to the small bowel.

The consequences of this are that the stomach participates minimally in drug absorption, and any situation which involves drugs sitting in the stomach for a long time will result in poor drug bioavailability.

Thus, gastric emptying rate is one of the main determinants of oral drug bioavailability and gastrointestinal drug absorption. If the stomach does not empty, practically nothing is going to get absorbed. Even drugs which are undissociated in gastric acid and fully dissociated in the small bowel are still predominantly absorbed in the small bowel because of its comparatively massive surface area. [7]

Drug absorption with respect to empty stomach and full stomach

A drug should be taken on empty stomach (without food) because: Food may delay or reduce the absorption of a drug and hence reducing effectiveness, such as Flucloxacillin, rifampicin. To reduce side effects by reducing absorption of a drug, such as efavirenz.

A drug should be taken on full stomach (with food) because: Food reduces gastrointestinal side effects, such as allopurinol, NSAIDS. To reduce the risk of hypoglycemic episodes, such as sulfonylureas. To increase the extent of absorption of a drug such as itraconazole, griseofulvin.

Drug absorption with respect to its acidic and basic nature

Most of drugs are weak acids or weak bases and exist in solution as an equilibrium between the ionized and unionized forms. One of the main factors influencing lipid solubility of a drug, apart from chemical structure, is its state of ionization. Ionized drug is not lipid soluble and only unionized drug can cross cell membranes. Increased accumulation of the drug occurs on that side of the membrane where pH favors a greater ionization of the drug and this is called the pH partition hypothesis. [5]

The pH of gastric fluid varies between 1.5 and 6.0, while the intestinal fluid is considerably more alkaline. Fluid is considerably more alkaline. The fraction of a drug unionized at the absorption site is controlled by two factors:

1. The pH of the medium
2. The pKa of the drug

The pKa of a drug is a characteristic of that drug and is defined as the pH at which 50% of the drug is unionized. PH of the medium affects degree of ionization of drugs.

Weak acidic drugs are best absorbed in stomach because stomach consist of acidic medium and drug exists in nonionized form that is lipid soluble and easily absorbed.

For example, aspirin is an acidic drug which are better absorbed in stomach (acidic medium).

Weak basic drugs are best absorbed in small intestine because small intestine consist of basic medium and nonionized form that is lipid soluble and easily absorbed. For example, diazepam is a basic drug which are better absorb in the small intestine (basic medium).

It is possible for a drug to have two (or more) sites of ionization and thus to have two pKa values (amphoteric drugs). The pH partition hypothesis can best be explained by examining an n example such as warfarin, an acidic drug with a pKa of 4.8. At a pH of 4.8 it is 50% unionized. Thus, at pH 5.8, 91% of the drug is ionized and 9% unionized. Thus, absorption of warfarin is favored in an acidic medium (i.e. the stomach) where the large majority of the drug is in the unionized form. This shows that the fraction unionized only changes dramatically for those acids with pKa values between 2.5 and 7.5 (or bases with pKa values between 5 and 11). Those weak acids with pKa values greater than 7.5 are essentially unionized at all pH values. In practice, the pH partition hypothesis does not explain all aspects of absorption by passive diffusion. Some quaternary ammonium compounds which are always ionized are absorbed, albeit very slowly and erratically. Warfarin is absorbed from the alkaline contents of the small intestine, where it should be largely in the ionized form. There is, of course, an equilibrium between the ionized and unionized states and the discrepancies in warfarin absorption may be explained by the far greater surface area for absorption in the small intestine compared with the stomach [5].

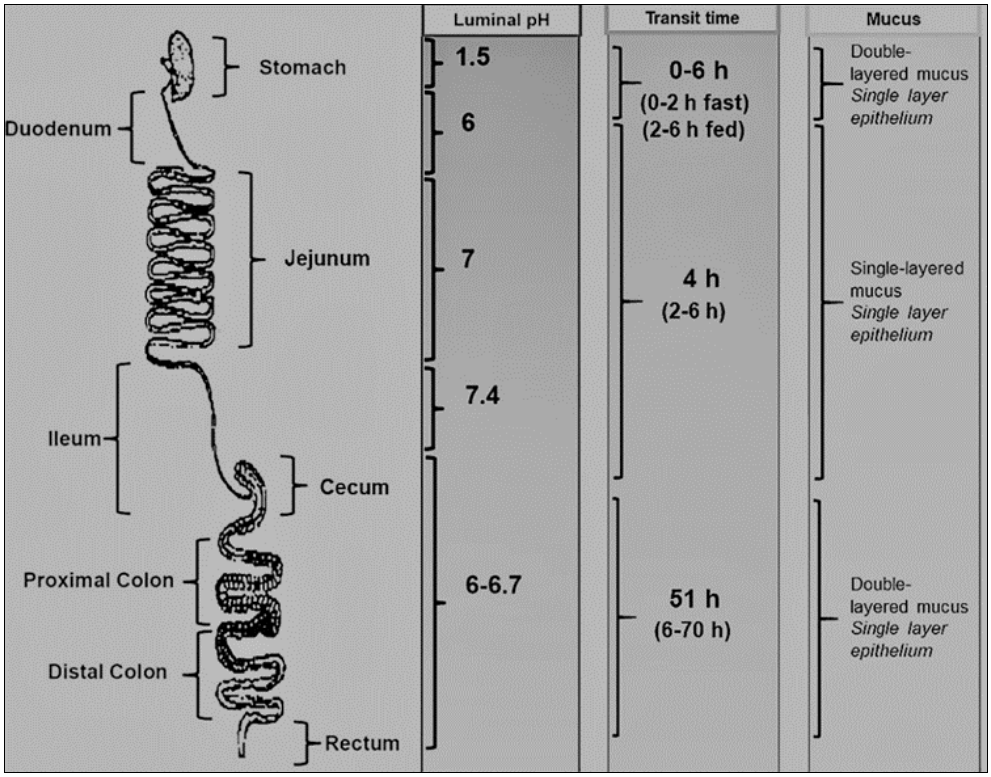

Fig 6: Luminal pH, transit time and Mucus in the GIT

4. Small intestine

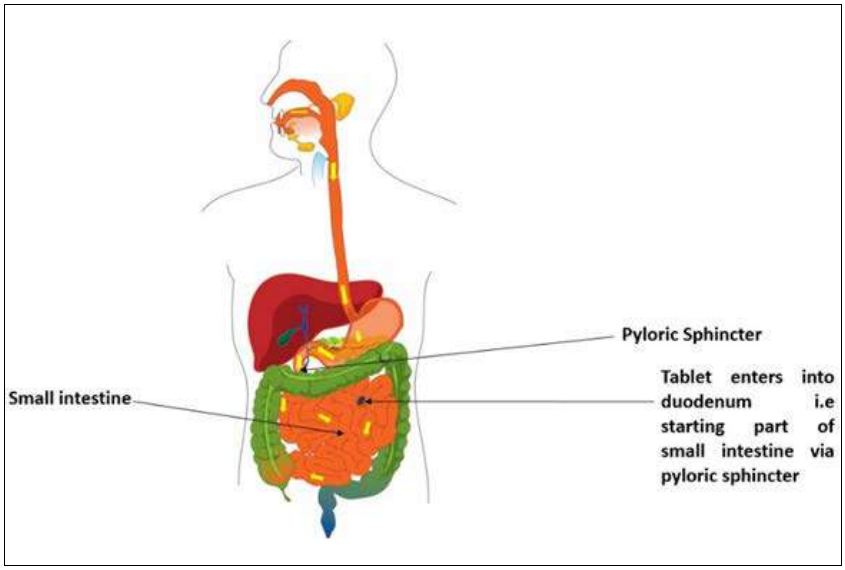

Fig 7: Tablet enters into the small intestine

Now the tablet with enters the small intestine. The small intestine is the longest (4–5 m) and most convoluted part of the gastrointestinal tract, extending from the pyloric sphincter of the stomach to the ileocecal junction where it joins the large intestine. It is approximately 25 to 30 mm in diameter. Its main functions are:

- Digestion – the process of enzymatic digestion, which began in the stomach, is completed in the small intestine.
- Absorption – the small intestine is the region where most nutrients and other materials are absorbed.

The small intestine is divided into the duodenum, which is 200–300 mm in length, the jejunum, which is approximately 2 m in length, and the ileum, which is approximately 3 m in length.

The wall of the small intestine has a rich network of both blood and lymphatic vessels. The gastrointestinal circulation is the largest systemic regional vasculature and nearly a third of the cardiac output flows through the gastrointestinal viscera. The blood vessels of the small intestine receive blood from the superior mesenteric artery via branched arterioles. The blood leaving the small intestine flows into the hepatic portal vein that carries it via the liver to the systemic circulation. Drugs that are metabolized by the liver are degraded before they reach the systemic circulation; this is termed hepatic pre-systemic clearance or first-pass metabolism. The wall of the small intestine also contains lacteals, which contain lymph and are part of the lymphatic system. The lymphatic system is important in the absorption of fats from the gastrointestinal tract. In the ileum there are areas of aggregated lymphoid tissue close to the epithelial surface which are known as Peyer's patches [7]. These cells play a key role in the immune response as they transport macromolecules and are involved in antigen uptake. The surface area of the small intestine is increased enormously, by about 600 times that of a simple cylinder, to approximately 200 m^2 in an adult, by several adaptations which make the small intestine such a good absorption site:

- Folds of Kerckring – these are submucosal folds which extend circularly most of the way around the intestine and are particularly well developed in the duodenum and jejunum. They are several millimeters in depth.
- Villi – these have been described as finger-like projections into the lumen (approximately 0.5–1.5 mm in length and 0.1 mm in diameter). They are well supplied with blood vessels. Each villus contains an arteriole, a venule and a blind-ending lymphatic vessel (lacteal).

  The luminal pH of the small intestine increases to between 6 and 7.5. Sources of secretions that produce these pH values in the small intestine are:
- Brunner's glands – these are located in the duodenum and are responsible or the secretion of bicarbonate, which neutralizes the acid emptied from the stomach.
- Intestinal cells – these are present throughout the small intestine and secrete mucus and enzymes. The enzymes, hydrolases and proteases, continue the digestive process.
- Pancreatic secretions – the pancreas is a large gland that secretes about 1–2 L of pancreatic juice per day into the small intestine via a duct. The components of pancreatic juice are sodium bicarbonate and enzymes. The enzymes consist of proteases, principally trypsin, chymotrypsin and carboxypeptidases, which are secreted as inactive precursors or zymogens and are converted to their active forms in the lumen by the enzyme enterokinase. Lipase and amylase are both secreted in their active forms. The bicarbonate component is largely regulated by the pH of chyme delivered into the small intestine from the stomach.
- Bile – bile is secreted by hepatocytes in the liver into bile canaliculi, concentrated in the gallbladder and hepatic biliary system by the removal of sodium ions, chloride and water, and delivered to the duodenum. Bile is a complex aqueous mixture of organic solutes (bile acids, phospholipids, particularly lecithin, cholesterol and bilirubin) and inorganic compounds (such as the plasma electrolytes sodium and potassium). Bile pigments, the most important of which is bilirubin, are excreted in the feces but the bile acids are re-absorbed by an active process in the terminal ileum. They are returned to the liver via the hepatic portal vein and, as they have a high hepatic clearance, are re-secreted in the bile. This process is known as enterohepatic recirculation. The main functions of the bile are promoting the efficient absorption of dietary fat, such as fatty acids and cholesterol, by aiding its emulsification and micellar solubilization, and the provision of excretory pathways or degradation products.

In summary, drug absorption in the small intestine is influenced by the following major factors [3]:

1. Physicochemical properties of the drug (lipophilic drugs and small molecules are absorbed faster).
2. Resemblance of the drug to a physiological substrate for active transport proteins (so it might be actively transported).
3. Surface area of the small bowel.
4. Duration of intestinal transit.
5. Intestinal blood flow (though this is usually not a rate limiting step).

As the tablet enters the small intestine, weakly basic drug is mainly absorbed in the small intestine. This is because:

- The average pH is between 6-8.
- Drugs spend longer in the small intestine & small intestine has a larger surface area.

Drug absorption in the intestine can occur by three possible ways [4]:

- Passive diffusion of lipophilic drugs, though the membrane.
- Passive diffusion of hydrophilic drugs, through pores and gap junctions.
- Active transport of larger molecules by transport proteins.

Passive diffusion through the gut membrane

For majority of an orally administered drug, this is the main mechanism for absorption of drug. Lipophilic drugs are able to penetrate though cell membranes, whereas water-soluble drugs penetrate through paracellular spaces, moving across the barrier by a combination of concentration-driven diffusion and convective volume flow along with water.

Drug characteristics which favor good paracellular absorption in the intestine are:

- Small molecule (molecular weight < 250g/mol)
- Hydrophilic (ionized at intestinal pH of 5.5-7.0)
- Positively charged (the junctions between cells have a negative charge)

The problems with this manner of transport are:
- Paracellular junctions account for less than 0.01% of the total surface area.
- These junctions become less and less permeable as one progresses from jejunum to colon.

Therefore, transcellular transport (i.e., through the lipid membrane) is the most important form of drug absorption in the intestine.

Active transport from the gut lumen
The mechanism of drug absorption from the gut is passive transfer at a rate determined by the ionization and lipid solubility of the drug molecules. Generally, one can simplify things by assuming that most drugs will be transported actively if they resemble some "natural" substrate chemically. For example, they might appear to be an innocuous amino acid. Thus, drugs like methyldopa and levodopa sneak in through transporters which mistake them for dopa, and 5-fluorouracil is mistaken for uracil.

Intestinal transit time
There are two main types of intestinal movement – propulsive and mixing. The propulsive movements primarily determine the intestinal transit rate and hence the residence time of the drug or dosage form in the small intestine. As this is the main site of absorption in the gastrointestinal tract or most drugs, the small intestinal transit time (that is, the time of transit between the stomach and the caecum) is an important actor with respect to drug bioavailability. Small intestinal transit is normally considered to be between 3 to 4 hours although both faster and slower transit have been measured. In contrast to the stomach, the small intestine does not discriminate between solids and liquids, and hence between dosage forms, or between the fed and the fasted state [6].

Effect of splanchnic blood flow on drug absorption
For rapidly absorbed lipophilic drugs, intestinal blood flow may be the rate limiting step. Probably the only drugs absorbed fast enough for this to be an issue are ethanol or methanol. In contrast, in critical illness intestinal blood flow might be so poor that it will be the rate-limiting step for many or all drugs.

5. Colon

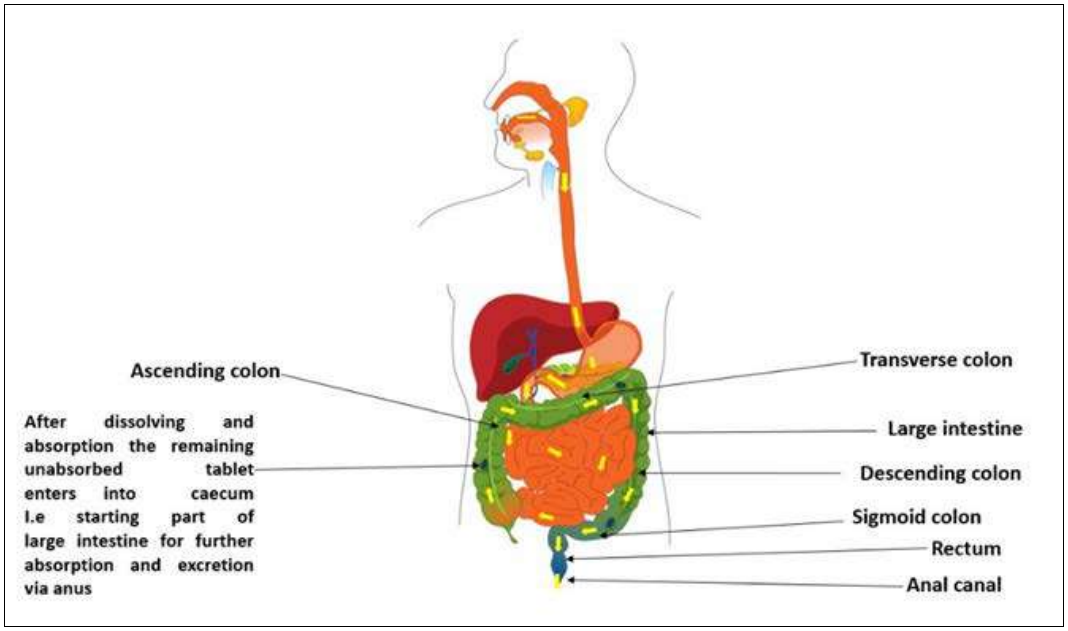

Fig 8: Remaining tablet enters into the large intestine (colon)

The tablet now passed to the colon i.e., part of large intestine for the excretion. Colon is the final major part of the gastrointestinal tract. It stretches from the ileocecal junction to the anus and makes up approximately the last 1.5 m to the 6 m of the gastrointestinal tract. It is composed of the caecum (~ 85 mm in length), the ascending colon (~ 200 mm), the hepatic flexure, the transverse colon (usually greater than 450 mm), the splenic flexure, the descending colon (~ 300 mm), the sigmoid colon (~ 400 mm) and the rectum. The ascending and descending colons are relatively fixed, as they are attached via the flexures and the caecum. The transverse and sigmoid colons are much more flexible. The colon, unlike the small intestine, has no specialized villi. However, the microvilli of the absorptive epithelial cells, the presence of crypts and the irregularly folded mucosae serve to increase the surface area of the colon by 10–15 times that of a simple cylinder. The surface area nevertheless remains approximately l/30th that of the small intestine. The main functions of the colon are:
- The absorption of sodium ions, chloride ions and water from the lumen in exchange or bicarbonate and potassium ions. Thus, the colon has a significant homeostatic role in the body.
- The storage and compaction of feces.

The colon is permanently colonized by an extensive number (about 10^{12} per gram of contents) and variety of bacteria. This large bacterial mass is capable of several metabolic reactions, including hydrolysis of fatty acid esters and the reduction of inactive conjugated drugs to their active form.

The bacteria rely upon undigested polysaccharides in the diet and the carbohydrate components of secretions such as mucus or their carbon and energy sources. They degrade the polysaccharides to produce short-chain fatty acids (acetic, propionic and butyric acids) [7], which lower the luminal pH, and the gases hydrogen, carbon dioxide and methane. Thus, the pH of the caecum is around 6–6.5. This increases to around 7–7.5 towards the distal parts of the colon.

Colonic drug absorption

The colon is a forgotten contributor to drug absorption, even though there is usually about $5m^2$ of surface area there (and so it should contribute to some extent)[5]. The major limitations on drug absorption from the colon are:

- Solid stool make diffusion difficult.
- Concentration is usually low, as most of the drug has already been absorbed.
- Gut bacteria are more numerous, and transit time is slower (i.e., bacterial metabolism is more prevalent).

Conclusion

In the conclusion, the tablet goes through various phases with respect to adsorption, distribution, metabolism and excretion and biopharmaceutical theory of acidic and basic nature of different gastrointestinal tract starting from the mouth to the anus. There are many physiological factors that influence the rate and extent of drug absorption; these are initially dependent on the route of administration. For the oral route, the physiological and environmental factors of the gastrointestinal tract, the gastrointestinal membrane and pre-systemic metabolism can influence the drug bioavailability.

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