

A REVIEW ON ORAL DRUG DELIVERY SYSTEM AND ITS EVALUATION
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ABSTRACT

Oral drug delivery is the most preferred administration route due to noninvasive, high patient compliance, convenient to handle, and does not require any specific sterile conditions. However, some of the drugs administered orally face several physical, biological, and biochemical barriers which lower the therapeutic efficacy of the drugs before getting absorbed into the systemic circulation. Oral medication is the most common form of drug administration because of advantages such as convenience of drug administration via the oral route, patient preference, cost-effectiveness, and ease of large-scale manufacturing of oral dosage forms. Around 60% of established small-molecule drug products available commercially are administered via the oral route. Current estimates indicate that oral formulations represent about 90% of the global market share of all pharmaceutical formulations intended for human use. The delivery systems are mainly based on natural or synthetic materials containing properties relating to absorption enhancer, pH-responsive, stimulation of the living cells. Bioinspired and biomimetic systems are biocompatible, biodegradable, nontoxic, selective, and specific, thus considered as excellent oral drug delivery tools. These systems are copied or modified from natural sources and utilized for oral drug delivery applications. They are very much capable of protecting the drug or therapeutics from GI acidic and enzymatic degradation and release adequately in the targeted site, enhance the drug delivery and ultimately produces the desired pharmacological action.

KEYWORDS: Oral drug delivery, bioinspired, biomimetic, biocompatible, oral route, patient preference, pharmacological action.

INTRODUCTION

Orally disintegrating tablets are the dosage forms that get disintegrated when they come in contact with the saliva present in the oral cavity. The saliva penetrates the tablets and disrupts its structural integrity which results in the release of the drug from the dosage form. The rapid disintegration of the tablets in the oral cavity may be rendered by the use of super disintegrants, such as croscopolidone, croscarmellose and sodium starch glycolate, thus making the dosage form favorable for the pediatric population, geriatric population, bedridden patients and patients with dysphagia. According to the United States Food and Drug Administration, an Oral Disintegrating Tablet is defined as "A solid dosage form which contains a medicinal substance or an active ingredient which rapidly disintegrates when placed upon the tongue, usually within matter of seconds. The names such as rapid dissolving, mouth dissolving and fast melt tablets has also been given to the orally disintegrating tablets. The orally disintegrating tablets disperse and

disintegrate when they come in contact with the saliva present in the oral cavity that omits the use of liquid to take the tablet, to swallow the whole dosage form or to chew the tablet.^[1-3]

Factors affecting the sublingual absorption

Thickness of oral epithelium: As the thickness of sublingual epithelium is 100-200 μm which is less as compared to buccal thickness. So the absorption of drugs is faster due to the thinner epithelium and also the immersion of drug in smaller volume of saliva.

Lipophilicity of drug: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

pH and pKa of the saliva: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remain unionized. Also, the absorption of the drugs

through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.

Oil to water partition coefficient: Compounds with favorable oil to- water partition coefficients are readily absorbed through the oral mucosa. An oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Solubility in salivary secretion

In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e. biphasic solubility of the drug is necessary for absorption. Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.^[4-6]

Advantages

- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- Low dosage gives high efficacy as hepatic first-pass metabolism is avoided and also reduces the risk of side effects.
- Due to rapidity in action, these sublingual dosage forms are widely used in emergency conditions e. g. asthma.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages

- Sublingual medication cannot be used when a patient is uncooperative.
- The sublingual administration of drugs interferes with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- The patient should not smoke while taking sublingual medication because smoking causes vasoconstriction of the vessels.
- This will decrease the absorption of the medication.
- The distinct feature in the formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapidly disintegrating tablet their by enhancing the dissolution of active ingredient.

Oral Drug Delivery Biological Barriers

The absorption of drugs can be limited by their poor chemical and biological stability, as well as by

physiological barriers, including pH, efflux transporters, and metabolic enzymes. Further, some drugs can cause local irritation and nausea. Thus, the elaboration of oral drug delivery systems necessitates a thorough understanding of the physicochemical properties, GI permeability, biological barriers, pharmacokinetics, and pharmacodynamics of drugs.^[7-9]

Biological Barriers

Most orally administered medications are primarily absorbed by the duodenum and jejunum in the upper parts of the GI tract. The drug absorption ability of the stomach is less than that of the intestine because of the smaller surface area and thicker mucus layer. The epithelial lining of the intestines is one of the major barriers to drug absorption in the GI tract. Epithelial cells are arranged in a single-column layer, and the building blocks, which are intercalated with enterocytes and joined by zonula occludens or tight junctions, are present at their apical surface. The tight junctions are mainly accountable for the passage of hydrophilic molecules via paracellular route. The epithelium on the apical surface projects with the lamina propria to form villi that contain microvilli. About 3,000–7,000 microvilli per cell in the small intestine provide a large surface area for drug interaction and absorption. Absorption of drugs from the lumen of the GI tract requires their passage through multiple layers including gastric juice, pericellular matrix, and mucous rich layer, to reach the epithelium, mucosa, and blood or lymph capillary walls. Therefore, bioadhesive drug delivery systems often exhibit improved performance compared to matrix tablets. Bioadhesive microspheres can diffuse into the mucous gel layer because of the small size of the nanocarriers and show a prolonged gastric residence time. The GI transit time is also important for developing an oral dosage form. In humans, the transit time of drug dosage forms through the small intestine is constant with a universally accepted value of 3 h and is independent of the physical characteristics of the dosage forms, such as density and size, as well as of food. However, the gastric transit time is known to vary and so does the drug bioavailability. This variability might eventually lead to unpredictable levels of drug plasma and can severely limit the clinical efficacy. Gastrointestinal movements are of two types: propulsive and mixing; they are mainly affected by the fed or fasted state as well as the sleep cycle. The peristalsis motilities primarily determine the passage rate and thus, the residence time of a drug after oral administration.^[10-15]

The passage rate is higher in the upper parts of the intestinal tract and declines toward the ileum. A drug capsule requires 3–4 h to pass through the entire small intestine. However, the transit time is considerably greater in the large intestine and depends on the volume of fiber in the intake. The residence time in the intestine also imitates the absorption of drugs that are poorly soluble or that dissolve slowly in the intestinal fluids, as well as of the pharmaceutical formulations that sustain

the release of the drug. Furthermore, the transit or residence time is essential for small drug molecules that are absorbed by transport carriers, as these drugs are favorably absorbed in the location with the highest carrier density. For instance, vitamin B2 is absorbed mostly in the proximal small intestine via sodium-dependent, carrier-mediated transport. Hence, influences that effect intestinal motility can impact the bioavailability of vitamin B2. Thus, the extent of drug absorption after oral administration is directly affected by the GI residence time. Food can influence the absorption of drugs: it can decrease, increase, delay, or accelerate drug absorption. Food affects the GI functions such as gastric emptying, intestinal transit time, bile acid secretion, stomach pH change, and liver blood flow increase. Further, it can alter the physiochemical characteristics of drugs, such as solubility, intestinal permeability, size, and dissolution profile. In general, hydrophobic drugs or drugs with solubility that is pH-dependent are mainly manipulated by the co-administered food. It is known that, high-fat meals increase the concentrations of the pancreozymin (cholecystokinin), which stimulates gallbladder secretion of bile within the GI tract. This leads to the formation of solubilizing micellar carriers, which can assist in the solubilization of drugs and their absorption from the lumen of the GI tract.

Certain fruit juices are known to either affect the transport and metabolism of drugs or enhance the extent of drug absorption. The effects of grapefruit juice have been extensively studied, although studies on other juices, including orange, tangerine, lime, and apple, have been performed. From the perception of drug metabolism, the inhibition of cytochrome P450 3A4 (CYP3A4) enzyme has been associated with the drug transport and metabolism inhibition effect of these juices. The oral administration, the dissolution of a drug starts when it comes in contact with the GI fluids, followed by the penetration of the aqueous medium into the dosage form, which generally contributes in the disintegration of the solid dosage into fine particles. The next step includes the mixing of the drug molecule into the dissolution medium. Drug molecules in solution can cross the mucosal membrane of the GI tract via several mechanisms that include passive diffusion or active drug transport. Passive diffusion involves two distinguished routes: the paracellular route, in which drugs diffuse through the small pores at the tight junctions between the mucosal enterocytes; the transcellular route, which involves lipophilic drug diffusion across the cell membrane phospholipid of intestinal enterocytes. Active drug transport is facilitated by cell membrane transporters and is divided into active influx of drug and efflux pump.

The transcellular route is the main pathway of absorption for the smallest drug molecules. Overall, the absorption via the transcellular route is basically due to diffusion down a concentration gradient, and the rate of absorption

is primarily determined by the rate of drug transport across the intestinal membrane, which is dictated by the physico-chemical properties of a drug. However, in the paracellular pathway, nonionized lipophilic drugs with molecular weight of more than 300 g/mol are absorbed via the transcellular pathway. In paracellular transport, drug molecules are absorbed by diffusion and convective volume flow through aqueous intercellular spaces. In common, drugs that are absorbed via this route are small hydrophilic molecules with molecular weight less than 200 g/mol. Moreover, since the junctional complex of the intestinal epithelium has an overall negative charge, cationic molecules pass through more freely. Nevertheless, absorption via this pathway is mostly low as the tight junctions between cells with a pore diameter of 4–8 Å limit free *trans*-epithelial passage of most drug molecules across the intestinal membrane. Unlike passive diffusion of drug, carrier-mediated transport requires the interaction of drug molecules with a protein carrier, usually in the apical membrane of the enterocyte cells. Several transporters belonging to the adenosine triphosphate (ATP) binding cassette transporters (ABC transporters) superfamily and solute carrier (SLC) transporters are expressed in the apical and basolateral membranes of the GI tract for the influx or efflux of endogenous substances and xenobiotics. The absorption via this pathway is an energy-consuming process requiring ATP hydrolysis and can occur against a concentration gradient, that is, from a region of lower drug concentration to that of higher concentration. For instance, ABC transporters superfamily utilizes ATP to initiate the transport and are called primary active transporters.

Physicochemical Barriers

The absorption of drugs in the GI tract require their release from the dosage form; the released drug dose need to be in a solution form or should have the ability to dissolve in the GI fluid. Further, the dissolved drug must be permeable through the intestinal membrane. In the BCS, the solubility criteria are based on the highest dose strength that can dissolve in a glass of water (250 ml; volume) or less of aqueous media over a pH range of 2–7.5. Class 1 BDDCS drugs, which have high solubility and are considerably metabolized, are not expected to display significant transporter drug interactions. Thus, high-fat meals should have no significant effect on the extent of the bioavailability of such drugs. However, high-fat meals delay stomach emptying and reduce absorption and thus increase the T_{max} . Class 2 BDDCS drugs, which are poorly soluble and highly metabolized, might be subjected to significant transporter effects, mainly efflux transporter effects, due to their insolubility. Therefore, high-fat diets might increase their bioavailability owing to the inhibition of efflux pump such as P-gp transporters in the intestine. Dosage form changes that significantly increase the solubility of BDDCS class 2 drugs might decrease or eliminate the effect of high-fat meals and mostly minimize other drug transporter interactions. Class 3 BDDCS drugs are

known to be more vulnerable to the effect of uptake transporters owing to their low permeability. Fatty diets can reduce the bioavailability of these drugs owing to the inhibition of intestinal uptake transporters. For class 4 BDDCS drugs, predicting the effect of a high-fat meal on drug absorption is difficult, as a combination of interactions of both class 2 and 3 compounds is possible.^[16-19]

Metabolic and Biochemical Barriers

Intestinal metabolism is normally triggered by digestive enzymes secreted by the pancreas, such as lipases; amylase; and peptidases, including chymotrypsin and trypsin, as well as those that are originated from the intestinal flora of the colon found mainly within the lower part of the GI tract. In addition, the first-pass metabolism, which includes intracellular and brush-border metabolism, occurs on the enterocyte surface by enzymes present within the membrane of the brush border. Brush-border metabolism occurs mainly in the small intestine. Isomaltase, alkaline phosphatase, sucrose, and other peptidases contribute to the brush border metabolism. Intracellular metabolism occurs in the enterocytes and mainly involves phase-I metabolizing enzymes, including cytochrome P450 enzymes such as CYP3A4; several phase-II conjugating enzymes associated with reactions such as sulfation and glucuronidation; and other enzymes such as esterases. In addition to the intestinal epithelium, hepatic first-pass metabolism represents the major metabolic barrier. Membrane transporters can be categorized into two types: uptake and efflux transporters; they facilitate the transport of drugs and endogenous compounds out or into the cells. Thus, membrane transporters are important determinants for oral drug absorption, disposition, and bioavailability. The main uptake transporters that enable xenobiotic transport of drugs into the cells belong to the solute carrier (SLC) superfamily, whereas the efflux transporters belong to the ABC superfamily. In the liver and intestine, efflux transporters, including bile salt export pump (BSEP), Pgp, MRP1-6, and BCRP, are highly expressed.

Drugs for sublingual administration

Medically, sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion, the elderly and invalids the nutritional benefit is independent of gastro-intestinal influences.^[20-25]

Structure of the Human oral mucosa

The oral cavity is lined with mucous membranes with a

total surface area of 100 cm². The teeth, keratinized epithelium, and non-keratinized epithelium occupy about 20%, 50%, and 30% of this surface area, respectively. The oral mucosa can be distinguished according to five major regions in the oral cavity:

1. The floor of the mouth (sublingual region)
2. The buccal mucosa (Lining of the cheeks)
3. The gum (gingiva)
4. The palatal mucosa
5. The inner side of the lips.

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μ m, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue and the gingiva measure at about 100-200 μ m. The composition of the epithelium varies depending on the site in the oral cavity. The mucosa of the gingiva and hard palate are keratinized epithelium similar to the epidermis contain neutral lipids like ceramides and acylceramides which are relatively impermeable to water. The mucosa of the soft palate, the sublingual, and the buccal regions, are non-keratinized epitheliums containing only small amounts of ceramides which are relatively more permeable. The oral mucosa in general is somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosa.

In general, the permeability's of the oral mucosa decrease in the order of sublingual greater than buccal and buccal greater than palatal. In general it appears that the patterns of epithelial differentiation in the oral mucosa vary to produce a surface layer that sufficiently meets the demands placed upon that particular tissue. Furthermore, in dealing with drug delivery, the amount of a certain drug absorbed through the oral mucosa is determined by many factors, including the pKa of the base, the rate of partition of the unionized form of the drug, the lipid-water partition coefficient of that particular drug, and lastly, on the p^H of the solution.

Ulcer

An ulcer is basically an inflamed break in the skin or the mucus membrane lining the alimentary tract. Ulceration occurs when there is a disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance. Ulcers are crater-like sores (generally 1/4 inch to 3/4 inch in diameter, but sometimes 1 to 2 inches in diameter) which form in the lining of the stomach (called gastric ulcers), just below the stomach at the beginning of the small intestine in the duodenum (called duodenal ulcers) or less commonly in the esophagus (called esophageal ulcers). In general, ulcers in the stomach and duodenum are referred to as peptic ulcers. An ulcer is the result of an imbalance between aggressive and defensive factors. On one hand, too much acid and pepsin can damage the stomach lining and cause ulcers. On the other hand (and more commonly), the damage comes first from some other causes, making the stomach lining susceptible to even an ordinary level of gastric acid. Hence, ulcers are sores on the lining of the digestive tract. The digestive tract consists of the esophagus, stomach, duodenum (the first part of the intestines) and intestines.^[26-29]

An ulcer may arise at various locations

1. Stomach (called gastric ulcer)
2. Duodenum (called duodenal ulcer)
3. Esophagus (called Esophageal ulcer)
4. Meckel's Diverticulum (called Meckel's Diverticulum ulcer).

Peptic Ulcer

Peptic ulcer is a mucosal erosions equal to or greater than 0.5 cm of an area of the gastrointestinal tract that is usually turned acidic and thus extremely painful. It is a sore in the lining of stomach or duodenum. A peptic ulcer in the stomach is called a gastric ulcer. One that is in the duodenum is called a duodenal ulcer. Peptic ulcers happen when the acids that help you digest food damage the walls of the stomach or duodenum. The most common cause is infection with a bacterium called *Helicobacter pylori*. Another cause is the long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. Stress and spicy foods do not cause ulcers, but can make them worse. As many as 70-90% of ulcers are associated with *Helicobacter pylori*, a spiral-shaped bacterium that lives in the acidic environment of the stomach. However, only 40% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin and other NSAIDs. Four times as many peptic ulcers arise in the duodenum the first part of the small intestine, just after the stomach as in the stomach itself. About 4% of gastric ulcers are caused by a malignant tumor, so multiple biopsies are needed to exclude cancer. Duodenal ulcers are generally benign.

Modified Johnson Classification of peptic ulcers

Type I: Ulcer along the lesser curve of stomach

Type II: Two ulcers present - one gastric, one duodenal

Type III: Prepyloric ulcer

Type IV: Proximal gastro esophageal ulcer

Type V: Anywhere along gastric body, NSAID induced.

Causes: two main classical causes of peptic ulcer diseases

(A) Acute peptic ulcer (B) Chronic peptic ulcer

A. Acute peptic ulcer/ stress ulcers: are multiple, small mucosal erosions, seen most commonly in the stomach but occasionally involving the duodenum. These ulcers occur following causes:

1. Psychological factors- stress, anxiety, fatigue.
2. Physiological factors —shock, severe trauma, septicemias, extensive burns.
3. Local irritants (e.g.; alcohol, smoking, coffee, spicy food).
4. Genetic factors, tobacco, blood group, diet, bile reflux, gastritis.
5. Drug intake (aspirin, ibuprofen).

B. Chronic peptic ulcers (gastric and duodenal ulcers)

Two major causes of chronic peptic ulcer disease. (1). *Helicobacter pylori*, (2). Long term use of non-steroidal anti-inflammatory drugs (NSAIDs). e.g: aspirin, ibuprofen, steroids, indomethacin, butazolidine. A major causative factor (60% of gastric and up to 90% of duodenal ulcers) is chronic inflammation due to *Helicobacter pylori* that colonizes the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis), resulting in a defect in the regulation of gastrin production by that part of the stomach, and gastrin secretion can either be increased, or as in most cases decreased, resulting in hypo- or achlorhydria. Gastrin stimulates the production of gastric acid by parietal cells. In *Helicobacter pylori* colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation. Studies in the varying occurrence of ulcers in third world countries despite high *Helicobacter pylori* colonization rates suggest dietary factors play a role in the pathogenesis of the disease. Another major cause is the use of NSAIDs. The gastric mucosa protects itself from gastric acid with a layer of mucus, the secretion of which is stimulated by certain prostaglandins. NSAIDs block the function of Cyclooxygenase-1 which is essential for the production of these prostaglandins. Cyclooxygenase-2 selective anti-inflammatory (such as Celecoxib or the since withdrawn Rofecoxib) preferentially inhibit Cox-2, which is less essential in the gastric mucosa, and roughly halve the risk of NSAID related gastric ulceration. The incidence of duodenal ulcers has dropped significantly during the last 30 years, while the incidence of gastric ulcers has shown a small increase, mainly caused by the widespread use of NSAIDs. The drop in incidence is considered to be a cohort-phenomenon independent of the progress in treatment of the disease.

Signs and symptoms

- Abdominal pain, classically epigastric strongly correlated to mealtimes. In case of duodenal ulcers the pain appears about three hours after taking a meals.
- Bloating and abdominal fullness.
- Water brash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus although this is more associated with gastroesophageal reflux disease).
- Nausea, and copious vomiting, loss of appetite and loss of weight.
- Pain 2-3 hours after eating, heart burn, hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe/continuing vomiting, melena (tarry, foul-smelling feces due to oxidized iron from hemoglobin).
- Indigestion (dyspepsia), belching, Pain is often aggravated by an empty stomach for example: night time pain is common. Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis. This is extremely painful and requires immediate surgery.
- A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAID (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, most glucocorticoids (e.g. Dexamethasone and Prednisolone). The timing of the symptoms in relation to the meal may differentiate between gastric and duodenal ulcers: A gastric ulcer would give epigastric pain during the meal, as gastric acid production is increased as food enters the stomach. Symptoms of duodenal ulcers would initially be relieved by a meal, as the pyloric sphincter close to concentrate the stomach contents; therefore acid is not reaching the duodenum. Duodenal ulcer pain would manifest mostly 2–3 hours after the meal, when the stomach begins to release digested food and acid into the duodenum.

Drugs Used to Treat Peptic Ulcer Disease

Although the pathogenesis of peptic ulcer disease is not fully understood, several major causative factors are recognized: non-steroidal anti-inflammatory drug (NSAID) use, infection with gram-negative *Helicobacter pylori*, increased hydrochloric acid secretion, and inadequate mucosal defense against gastric acid.

Treatment approaches include

- Eradicating the *H. pylori* infection
- Reducing secretion of gastric acid with the use of proton pump inhibitors (PPIs)
- Providing agents that protect the gastric mucosa from damage, such as misoprostol and sucralfate
- Neutralization of gastric acid.

1. Reduction of gastric acid secretion

- H₂-histamines receptor blockers: Cimetidine, Ranitidine, Famotidine, Roxatidine.
- Proton pump inhibitors: Omeprazole, Lansoprazole, Rabeprazole, Esomeprazole.
- Anticholinergics: Pirenzepine, Propantheline, Oxyphenonium.
- Prostaglandin analogue: Misoprostol.
- Anti-muscarinic agents: Hyoscyamine, Mepenzolate, Pirenzepine

2. Neutralization of gastric acid (antacids)

- Systemic antacids: Sodium bicarbonate, Sodium citrate.
 - Non-systemic antacids: Magnesium hydroxide, Calcium carbonate, Magnesium trisilicate, Aluminum hydroxide gel.
3. Mucosal protective agents: Sucralfate, Colloidal bismuth subcitrate.
 4. Anti-*Helicobacter pylori* drug/ant-microbial agents: Amoxicillin, Tinidazole, Tetracycline, Metronidazole, Bismuth compound.

Proton pump inhibitors

Proton pump inhibitors (or "PPI"s) are a group of drugs whose main action is pronounced and long-lasting reduction of gastric acid production. They are the most potent inhibitors of acid secretion available today. The group followed and has largely superseded another group of pharmaceuticals with similar effects, but different mode- of action, called H₂-receptor antagonists. These drugs are among the most widely- selling drugs in the world as a result of their outstanding efficacy and safety. Structurally, the vast majority of these drugs are benzimidazole derivatives; however, promising new research indicates that imidazopyridine derivatives may be a more effective means of treatment, high dose or long-term use of PPIs carries a possible increased risk of bone fractures.

Regulation of gastric acid secretion

Gastric acid secretion by parietal cells of the gastric mucosa is controlled by acetylcholine, histamine, prostaglandins E₂ and I₂ and gastrin (Figure no: 06). The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of H⁺/K⁺ ATPase (adenosine triphosphatase) proton pump that secretes hydrochloric acid (HCL) into the lumen of the stomach. In contrast, receptor binding of prostaglandin E₂ and I₂ diminishes gastric acid production. [Histamine binding causes activation of adenylylcyclase, whereas binding of prostaglandin E₂ and I₂ inhibits this enzyme. Gastrin and acetylcholine act by inducing an increase in intracellular calcium levels. Effects of acetylcholine, histamine, and prostaglandin I₂ and E₂ and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

Examples of proton pump inhibitors: Clinically used proton pump inhibitors

- Omeprazole
- Lansoprazole
- Esomeprazole
- Rabiprazole
- Rabeprazole

Clinical uses

These drug are utilized in the treatment of many condition such as Dyspepsia, Peptic ulcer disease, Zollinger-Ellison Syndrome, Gastro-oesophageal reflux disease (GERD), Barrett's oesophagus, Prevention of stress gastritis, Gastronomes and other conditions that cause hyper secretion of acid, Laryngopharyngeal reflux disease .

Mechanism of action

Proton pump inhibitor act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system(the H^+/K^+ ATPase, or more commonly just gastric proton pump) of the gastric parietal cell. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H^+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. Targeting the terminal-step in acid production, as well as the irreversible nature of the inhibition, result in a class of drugs that are significantly more effective than H_2 antagonists and reduce gastric acid secretion by up to 99%. The lack of the acid in the stomach will aid in the healing of duodenal ulcers, and reduces the pain from indigestion and heartburn, which can be exacerbated by stomach acid. However, lack of stomach acid may also contribute to Hypochlorhydria a lack of sufficient hydrochloric acid. Hydrochloric acid is required for absorption of nutrients, particularly calcium. The proton pump inhibitors are given in an inactive form. The inactive form is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) that have acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form.^[30-32]

Rabeprazole sodium

In the present study, Rabeprazole sodium is selected as a model drug for the formulation and evaluation of sublingual drug delivery system. Rabeprazole sodium is a proton pump inhibitor belongs to the class of anti-ulcerative agent effectively used in the treatment of peptic ulcer diseases. Rabeprazole sodium is the third proton pump inhibitor (PPI) to be launched for the treatment of peptic ulcer diseases. Like other drugs in this class. Rabeprazole sodium results in faster and more rapid ulcer healing, reduce gastric acid secretion and greater efficacy in gastro-oesophageal reflux disease, Zollinger-ellison syndrome. Rabeprazole sodium is freely soluble in water, phosphate buffer at p^H 6.8 and 7.4. Practically in-soluble in n-hexane, chloroform and it is bioavailability is 77%, biological half life is 1hour; short

duration of action.^[33-34]

Mechanism of Action

Rabeprazole is a highly proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+,K^+) -ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+,K^+) -ATPase results in a duration of anti-secretory effect that persists longer than 24 hours for all doses tested.

Several characteristics of Rabeprazole sodium pharmacologic profile distinguish it from other PPIs. These include

1. The specific sites of binding within the membrane bound proton pump.
2. Little or no potential to induce or inhibit cytochrome P-450 (CYP-450) enzymes that metabolize many other drugs.
3. Consistent bioavailability.
4. Short-duration of action.
5. Consistent pharmacokinetics in a wide variety of patient type.

The three PPIs currently available display almost identical efficacy in the treatment of a peptic ulcer diseases and when included as part of Helicobacter pylori eradication regimes. However, Rabeprazole sodium shows improvements in selectivity and pharmacokinetic properties compared with Omeprazole and Lansoprazole. The bioavailability of Rabeprazole is considerably higher than Omeprazole (It has an absolute bioavailability of 77%), It follows a linear pharmacokinetic after both, i.v. and oral administration. Almost 80% of an oral or intravenous dose is excreted as metabolites in urine and the remainder is found in feces. Significantly, Rabeprazole does not influence hepatic cytochrome P450 activity and does not therefore interact with co-administered drugs. The Rabeprazole sodium is available in both oral and intravenous formulations. It is effective across all age groups, although only indicated in adults (and adolescents in Europe). It has been approved for use in over 100 countries and has been used for over 13 years. Rabeprazole has an excellent safety profile and a low potential for drug-drug interactions. While still widely prescribed, Rabeprazole and the other branded proton pump inhibitors are under considerable market pressure from the less expensive but similarly effective generic and over-the-counter formulations of Omeprazole.

Evaluation of post-compression parameters

The Rabeprazole sodium tablets prepared were evaluated for the following parameters:

- Organoleptic properties
- Weight variation
- Hardness
- Thickness

- Friability
- Drug content
- Wetting time
- In-vitro Disintegration time
- In-vitro Dissolution Studies
- Stability studies

Colour, Odour, Taste, of tablets

Organoleptic properties such as colour, odour, taste, were evaluated for tablets from each batch were randomly selected and taste tested, colour visually compared and odour checked.

Weight variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The IP weight variation test is done by 20 tablets were selected randomly from each formulation after compression, weighed individually using a "Electronic weighing balance" and average weight was determined. The individual weights are compared with the average weight for the weight variation.

Table 1: Weight Variation Limit.

Sl. No.	Average weight of tablet (mg)	± Percentage deviation
1	80 mg or less	10
2	More than 80 mg but less than 250 mg	7.5
3	250 mg or more	5

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using "Monsanto hardness tester". The hardness was measured in terms of kg/cm². 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

20 tablets were weighed and the initial weight of these tablets was recorded and placed in "Roche friabilator" and rotated at the speed of 25 rpm for 100 revolutions. The tablets were removed from the friabilator dusted off the fines and again re-weighed and the weight was recorded. The percentage friability was calculated from the loss in weight as given in equation below. The weight loss should not more than 1%.

Percentage friability was calculated by using the formula

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using "Vernier Callipers". It was determined by checking the thickness of ten tablets of each formulation.

Drug content uniformity

The tablets were tested for their drug content uniformity. At randomly selected 5 tablets from each formulation were finely powdered and powder equivalent to 100 mg of Rabepazole sodium drug was weighed accurately and dissolved in 100ml of phosphate buffer solution at p^H 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 284nm. The concentration of the drug was computed from the standard curve of the Rabepazole sodium in phosphate buffer solution at p^H 6.8.

Wetting time

The wetting time of the tablets was measured using a very simple process. Five circular tissue papers of 10cm diameter were placed in a "Petridish" with a 10cm diameter. 10 ml of distilled water containing a water-soluble dye (Eosin), a water-soluble dye was placed in a Petridish of 10 cm diameter. Tablets were carefully placed in the centre of the Petridish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as mean value of three determinations.

In-vitro Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in "Electro lab USP disintegration test apparatus". It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing phosphate buffer p^H 6.8 as medium. The volume of medium was 900ml and temp was 37°C ± 0.2°C. The time taken for the complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

In-vitro Dissolution studies

Dissolution testing of sublingual tablets of Rabepazole sodium was carried out with "Paddle type-II USP dissolution test apparatus" at rpm 50 and temperature 37±0.5°C both dissolution media and water. At each specified intervals of time 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by UV spectroscopy method at wavelength of 284 nm. The % drug release was calculated using an equation

obtained from the calibration curve.

Stability Studies

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity.

Importance of stability studies

Stability studies are important for the following reasons.

1. This is an assurance given by the manufacturer that the patient would receive a uniform dose throughout the shelf life.
2. The drug control administration insists on manufacturers on conducting the stability studies, identity, strength, purity and quality of the drug for an extended period of time in the conditions of normal storage.
3. Stability testing prevents the possibility of marketing an unstable product. Both physical and chemical degradation of drug can result in unstable product.

Purpose of stability studies

Stability studies are done to understand how to design a product and its packaging such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used.

CONCLUSION

The oral delivery is considered to be the most promising administration route due to its specific advantages. The delivery material, design, size and polydispersity must be accurately controlled, due to their significant influence on treatment efficacy. Oral drug delivery carriers deal with various biological barriers (the lumen, mucus and tissue of the GI tract) to successfully deliver drugs³⁴. The main advantages of oral delivery systems, include sustained delivery, interaction with mucus and the capability for solid formulations that preserve pharmaceuticals are most attractive administration route for drugs. The oral drug delivery is one of the most common route of drug administration in both adult and pediatric patients. The use of nanocarriers that could improve drug solubility, permeability and bioavailability. Better understanding of the effects of common diet and inter-patient variation in drug absorption is required. The establishment of a reliable *in vitro-in vivo* correlation models to predict better *in vivo* performance and to generate data that offer cost benefit over existing formulations. The development of better pediatric formulations by using nanoparticle technologies that are currently used for developing various drug formulations for adult patients. The nanocarriers technology to develop oral formulations need to consider the use of safe and effective excipients. The novel drug delivery technologies changes, formulation development and excipient screening will continue to evolve consequently. It is expected that the overall time for formulation development will be shorter than the current existing one

to manufacture lead compound from drug discovery to clinical trials.

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