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Nayak Zeel Rupesh
B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India

Narkhede Kantilal B
B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India

Narkhede Sachin B
B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India

Corresponding Author:
Nayak Zeel Rupesh
B.N.B Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India

A review article on sublingual tablet of lansoprazole

Nayak Zeel Rupesh, Narkhede Kantilal B and Narkhede Sachin B

Abstract
Solid dispersion technology using mixed solvency Introduced in oral product facilitate the tablet of active drug. Lansoprazole is PPI (Proton Pump Inhibitors) used to treat of anti-ulcer. Sublingual based oral drug delivery system to avoid first pass metabolism, less side effects.

Keywords: Mixed solvency, PPIs, drug delivery, anti-ulcer, lansoprazole

Introduction

Introduction to disease

- Ulcers are sores that are slow to heal or keep returning. They can take many forms and can appear both on the inside and the outside of your body. They can be found on places of your body you can see, such as a leg ulcer found on the skin, or in places you can not see, such as a peptic ulcer in the lining of your stomach or upper intestine [1].
- Ulcers are most common on the skin of the lower extremities in the gastrointestinal tract. An ulcer that appears on the skin are often visible as an inflamed tissue with an area of reddened skin. A skin ulcer is often visible in the event to heat or cold, irritation, or a problem with blood circulation. They can also be caused due to a lack of mobility or which causes prolonged pressure on the tissues.
- Stress in the blood circulation is transformed to a skin ulcer, commonly called as bedsores or decubitus ulcers. Ulcers often become infected or pus forms [2].

Sign and symptoms include [3]

- Pain in the stomach
- Decreasing weight
- nausea
- vomiting
- bloating
- burping
- acid reflux
- heartburn
- anemia

Causes

- Helicobacter pylori bacterial infection
- Zollinger- Ellison syndrome
- Nonsterodial anti-inflammatory drug
- Excess stress
- Low levels nelatonin

Types of ulcers

- Peptic Ulcer
- Aphthous Ulcer
- Esophageal Ulcer

- Peptic ulcer are a broad term which include ulcer of digestive tract in the stomach and the duodenum and believe that one develop this type of ulcer due to stress and spicy food. The causative agent is infection caused by the bacteria H. pylori and reaction to certain medicines like non-steroidal anti-inflammatory drug (NSAIDs) [4].

- Aphthous ulcer that develop in the inner lining of mouth are referred to as mouth ulcer. Mouth ulcer common and usually due to trauma such as from ill fitting dentures and fractured teeth or filling. Aphthous minor is amongst the most common from the oral ulcerative diseases and affects an estimated 15-20% of population worldwide [5].
- Esophageal ulcer is lesions that occur in the esophagus and this are the most commonly form at the end of the food pipe and can be felt as a pain right below the breastbone. Esophageal ulcer are associated with acid reflux or GERD, prolonged use of drug like NSAIDs or smoking [6].

Pathophysiology of ulcer

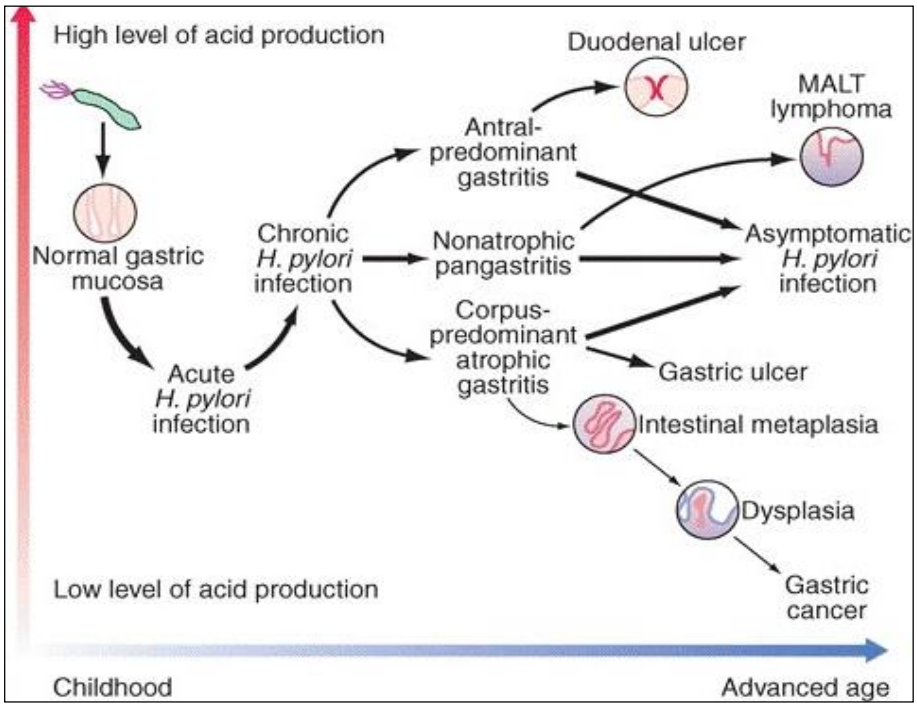


Fig 1-1: Pathophysiology of ulcer

- Under normal conditions of a physiologic balance exists between gastric acid secretion and gastric and duodenal mucosal defense systems or mucosal injury occurs when the balanced between aggressive and protective factors is disrupted.
- Peptic ulcers are defined as defects in the gastric or duodenal mucosa and submucosa, which extend through the muscularis mucosa, the epithelial cells of the stomach and duodenum secrete mucus under the influence of cholinergic stimulation and in response to irritation of the epithelial lining.
- The foveolar cells produce mucus and bicarbonate and which form a gel layer impermeable to aggressive factors such as acid and pepsin.
- This layer is most important, as it prevent the stomach from digesting itself or in the event of injury, additional mechanisms help to prevent acid and pepsin from entering the epithelial cells.
- Aggressive factors include H. pylori infection, NSAIDs, alcohol, bile salts, acid, or pepsin. The mechanism includes mucous, bicarbonate, prostaglandins [7].

Why to treat ulcer? [8]

- The goals of treatment are reducing the amount of acid in the stomach, strengthening the protective linings that come in direct contact with gastric acids and if your ulcer is caused by bacterial infection treating the H. pylori infection with medication.
- It is one of the top ten reasons for a visit to primary care physicians.
- About 4.72 % - 11.22 %/ of Indian population suffers from at least one ulcer diseases.
- affecting ulcer,
  - Burning sensation
  - Extreme sensitive
  - Pain to touch
  - Loss of appetite
  - Brain trauma
  - Stress

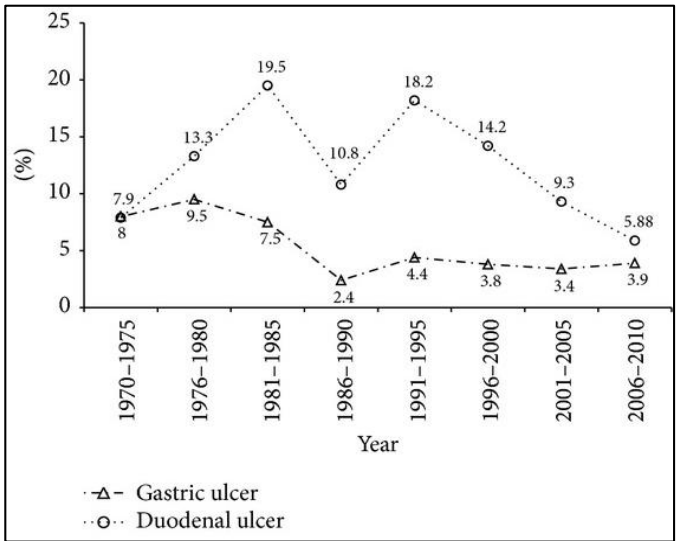


Fig 1-2: Prevalence of ulcer

Fig 1-3: Symptoms of ulcer

Diagnosis of Ulcer [9]

- Radiological
- Urea breath test
- Endoscopic
- Stool monoclonal antigen test

Available treatments [10]

- Treatment is depend on the underlying cause of your ulcer and if tests show that you have an *H. pylori* infection.
- Doctor will prescribe a combination of medication. You will have to take the medicines for up to two weeks.
- The medicine include antibiotics to help kill infections and proton pump inhibitors (PPIs) to help reduce stomach acid.
- Minor side effects like diarrhea and upset stomach from antibiotic regimens, If these side effects cause significant discomfort or do not get better over time,
- Determines that you don't have an H. *pylori* infection, they may recommend a prescription or over-the-counter PPI for up to eight weeks to reduce stomach acid and help your ulcer heal.
- Acid blockers like ranitidine or famotidine also reduce stomach acid and ulcer pain.
- These medicine are available as a prescription and also over the counter in lower doses.

Available dosage forms [12-13]

Table 1-1: Dosage form of anti-ulcer class drugs

Antiulcer Drugs	
Brand Name (Generic Name)	**Possible Common Side Effects Include:**
Axid (nizatidine)	Diarrhea, headache, nausea and vomiting
Carafate (sucralfate)	Constipation, insomnia, hives, upset stomach
Cytotec (misoprostol)	Cramps, diarrhea, nausea,headache, menstrual disorders
Pepcid (famotidine)	Constipation or diarrhea, dizziness, fatigue,
Prilosec (omeprazole)	headache, diarrhea,abdominal pain
Tagamet (cimetidine)	breast development in men, depression and dis orientation
Zantac (ranitidine hydrochloride)	Constipation, diarrhea, joint pain

Introduction to sublingual dosage form [12-16]

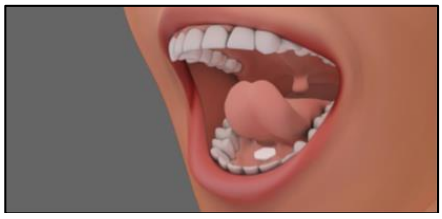


Fig 1-4: Sublingual Route

- Sublingual administration of the drug means placement of drug under tongue. Drug reaches directly into the bloodstream through the ventral surface of the tongue and floor of the mouth [12].

Sublingual mucosa

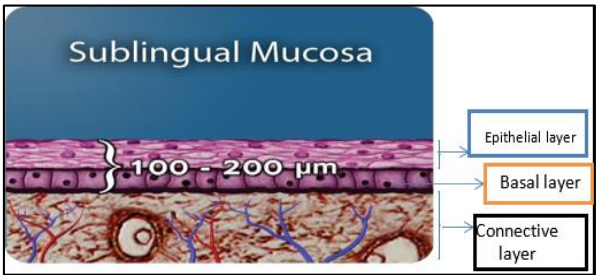


Fig 1-5: Sublingual Mucosa

- The sublingual mucosa is divided into two layers [13], There are
  1. Epithelium layer
  2. Connective tissue layer
- The epithelium is stratified non-keratinized type of squamous epithelium and it is relatively thin as compared to the buccal epithelium.
- Epithelium ends with basement membrane known as basal lamina or which connects the epithelium to the connective tissue and is 1 to 2 micrometre thick.
- Connective tissue layer which is about 150-500 micrometre thick and consists of the lamina propria and submucosa region.
- The lamina propria consists of,
  - Collagen fibrils
  - Blood vssels
  - Never fibers
- The submucosa is relatively dense connective tissue that contains a few salivary glands.

Blood supply to sublingual [14]

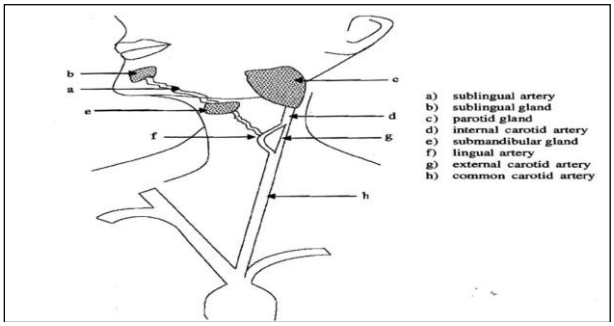


Fig 1-6: Blood Supply to Sublingual

- The sublingual artery supplies blood to the salivary glands, branches into surrounding muscles as well as other mucous membranes of the mouth, tongue, and gums.
- Sublingual artery stems from the lingual artery. Which constitutes the primary blood supply to the tongue and the floor of mouth region.
- Lingual artery branches from the external carotid artery.
- The blood vessels in this region branch off into smaller blood vessels that join with adjoining vessels to form an extensive network of blood supply.
- Because of this network – more perfusion than skin.

Advantages of sublingual dosage form [15]

- Due to high vascularization rapid absorption.
- Fast dissolution or disintegration in the oral cavity without need of water and chewing.
- Oral mucosa is more permeable than skin.
- It is rapid onset of action compared to the oral route.
- If any irritation and discomfort occurs and then it can be removed.
- The liver is bypassed- so the advantage for highly liver metabolized drug.
- The drug is protected from degradation due to pH and digestive enzymes of the middle GIT.
- Improved patient compliance due to the elimination of associated pain with injections.
- Reduces dosage and side effects - as hepatic first-pass metabolism is avoided.
- Due to fast action. These route sublingual dosage forms are widely used in emergency conditions.

Disadvantages of sublingual dosage form

- Interfere with drinking, talking, eating.
- This site is not well suited for sustained release system.
- Limited surface area.
- Requires taste masking.
- A low dose of the drug is required.

Suitability of drug

- No bitter taste.
- Should possess small molecular weight
- Should have good stability in water and saliva.
- Remain partially non-ionized at the oral pH.
- A drug having first pass effect.

Evaluation of sublingual tablets

- Hardness
- Thickness
- Weight variation
- Friability
- Disintegration time
- Wetting time
- Water absorption ratio
- Drug content uniformity
- In-vitro drug release study

Method of preparation of sublingual tablets [16]

Table 1-3: Method of Preparation of Sublingual Tablets

Sr. No.	Method	Comment
1	Freeze drying	• Expensive or time-consuming produces tablets are poor mechanical strength. • Suitable for unstable and heat sensitive products.
2	Sublimation	• Prepared by addition of volatile salt substantial removal of volatile salt creates pores in tablets and which helps in achieving rapid disintegration.
3	Compression moulding	• Tablets manufactured by this method pose special challenges during handling or shipping and because of the poor mechanical strength or may require special packaging.
4	Direct compression	• Do not required water and heat during formulation. • Economic. • Fewer manufacturing steps or equipment. • No granulation step.

Types of sublingual dosage form [17-18]

- Fast disintegrating sublingual tablets
- Bioadhesive sublingual tablets
- Lipid matrix sublingual tablets
- Sublingual vitamin tablets
- Sublingual immunotherapy

Fast disintegrating sublingual tablets

- Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. Tablets that disintegrate or dissolve rapidly in the patient's mouth are convenient for young children, the elderly and patients with swallowing difficulties, and in situations where potable liquids are not available. For

these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity.

Bio adhesive sublingual tablets

- The new sublingual tablet concept presented is based on interactive mixtures consisting of a water-soluble carrier covered with fine drug particles and a bio-adhesive component. With this approach, it is possible to obtain rapid dissolution in combination with bio-adhesive retention of the drug in the oral cavity. The new sublingual tablet concept presented is based on interactive mixtures consisting of a water-soluble carrier covered with fine drug particles and a bio-adhesive component. With this approach, it is possible to obtain rapid dissolution in combination with bio-adhesive retention of the drug in the oral cavity.

Lipid matrix sublingual tablets

- Lipid Matrix Sublingual Tablet is formulated using advances in sublingual and liposomal technology to create a dosage form that offers a faster and more complete absorption than traditional oral routes of administration. The Lipid Matrix Sublingual Tablet is a bioavailable, quick, convenient, and consistent dosage form for many specialty nutraceuticals that are often taken orally.

Introduction to solubility enhancement [19-23]

Definition [19]

- In qualitative term- as the spontaneous interaction of two and more substances to form a homogeneous molecular dispersion.
- In quantitative term- as the concentration of the solute in a saturated solution at a certain temperature.
- A saturated solution is that in which the solute is in equilibrium with the solvent
- Drug solubility is expressed as,

Table 1-4: Expressions of Solubility

Expressions	Symbols	Definition
Normality	N	Gram equivalent weights of solute in 1 litre of solution
Molarity	M	Moles of solute in 1 litre of solution
Molality	M	Moles of solute in 1000 g of solvent

Table 1-5: Solubility Criteria

Descriptive Term	Part of Solvent Required Per Part of Solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>10000

Needs for solubility enhancement [20]

- Drug absorption is limited to Poor aqueous solubility or Poor membrane permeability of drug molecules.
- Before it permeates the membranes of GIT to reach systemic circulation it must first dissolve in gastric and intestinal fluids
- Hence two areas of pharmaceutical research that focus on improved the oral bioavailability of active agents.
- Including Enhancing solubility and Dissolution rate of poorly water soluble drugs.

Table 1-6: BCS Classification

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Techniques for solubility enhancement [21-22]

Table 1-7: Solubility Enhancement Techniques

Physical modifications	Particle size reduction	▪ Supercritical fluid process ▪ Sonocrystalization ▪ Micronization ▪ Nanosuspension
	Modification of the crystal habit	▪ Polymorphs ▪ Pseudo polymorph
	Drug dispersion in carriers	▪ Eutectic mixtures ▪ Solid dispersions ▪ Solid solution
	Complexation	▪ Use of complexing agents
	Solubilization by surfactants	▪ Microemulsions
Chemical Modification	▪ Changing pH ▪ Salt formation	
Other methods	▪ Hydrotropy ▪ Nanotechnology ▪ Co solvency ▪ Co-crystallization ▪ Use of soluble prodrug ▪ Self-micro emulsifying drug delivery ▪ Mixed solvency ▪ Liquisolid	

Factors affecting solubility [23]

- Temperature
- Pressure
- Particle size
- Molecular size
- Polarity
- Polymorphs

Mixed solvency method [24-25]

- Apply Hydrotropy in titrimetric and spectrophotometric estimations of a large number of poorly water-soluble drugs precluding the use of organic solvents.
- Carried out solubility studies on salicylic acid.
- Solubility was carried in the solution containing,
- Hydrotropic agent (urea, sodium citrate)
- Co-solvent (Glycerine, propylene glycol, PEG 300, PEG 400)
- Water soluble solid (PEG 4000, PEG 6000)

Advantages of mixed solvency method

- It may reduce the individual concentration of solubilizer & so reduce their toxicity associated with their higher concentration.
- Provided synergistic solubility enhancement.
- It precludes the use of organic solvent & thus avoids the problem of residual solvent toxicity, pollution, cost etc**.**

Hydrotropy method [26]

- Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing solute.
- Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs**.**

Advantages of hydrotropy method

- In the hydrotropy method solvent character is independent of pH, has high selectivity and does not require emulsification.
- In this method simply mix the drug with the hydrotropes in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Liquisolid method [27-29]

- In liquisolid technique liquid may be transfer into free flowing, readily compressible and apparently dry powder by simple blending with selected carrier and coating material.
- The liquid portion which can be liquid drug, drug suspension or drug solution in a suitable non-volatile liquid vehicle can be converted into acceptably flowing and compressible powders by blending with selected powder excipients.
- The acceptable flowing and compressible powder form of liquid medication is liquisolid compact. The liquisolid is newer and promising approach because of simple manufacturing process, low production coast, and applicable for industry due to good flow and compact property of liquisolid formulation.
- When the drug dissolve in the liquid vehicle is incorporated into a carrier material which has a porous surface or closely matted fibers in its interior as cellulose and both absorption and adsorption take place.
- The coating material having high adsorption properties or large specific surface area gives the liquisolid system the desirable flow characteristics.

Advantages of liquisolid method

- Method improved the solubility or bioavailability of orally administered water insoluble and poorly soluble drugs.
- Method is applicable in large scale.
- Useful for the formulation of oily drugs or liquid drugs.
- By using different carrier or additives drug release can be modified like PVP, PEG 60000, HMPC and Eudragit etc.
- A number of poorly soluble drugs can formulated in to the system.
- Production cost is low compared to the preparation of soft gelatin capsules.
- This system is specific for the powdered liquid medications.

Cosolvency [30]

- The solubility of poorly soluble drugs in water can be increased by mixing with some water miscible solvent in which the drug is poorly soluble.
- This process is known as cosolvency and the solvent used in combination are called as cosolvent.
- Cosolvent system works by decreasing the interfacial tension between the aqueous solution and hydrophobic solute. It is also known as solvent blending.
- There is a constantly change in the solubility of drugs by addition of organic co-solvent into the water.
- The cosolvents are having hydrogen acceptor and donor groups with a small hydrocarbon region.
- The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently decreases the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Advantages of cosolvency

- Compared to other solubilisation approaches very high drug concentrations of poorly soluble compounds can dissolve.
- Co-Solvents can enhance the solubility of poorly soluble compounds several thousand times compare with the aqueous solubility of the drug alone.
- Weak electrolytes or nonpolar molecules have poor water solubility and it can improve by altering polarity of the solvent.
- It is Simple and fast method to formulate and produce.

Self-emulsifying or self-micro emulsifying systems [31-33]

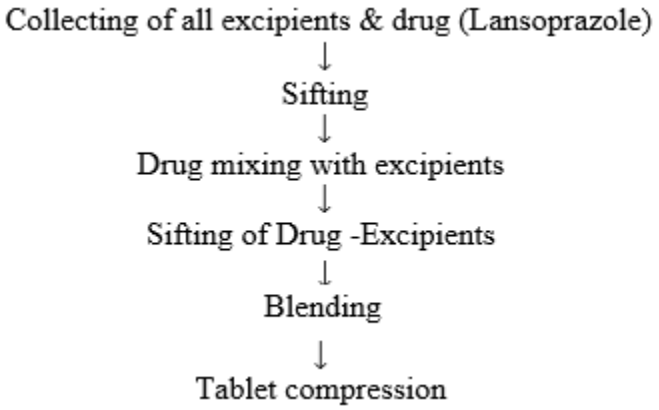
- Self-emulsifying and self-micro emulsifying systems use the concept of in situ formation of emulsion in the GIT.
- The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is called as the self-emulsifying drug delivery system (SEDDS).
- In the absence of external phase (water) and forms fine oil in water emulsions and micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT, is used for improved lipophilic drug dissolution and absorption.
- The easy of emulsification could be associated with the easy of water penetrating into the various liquids crystalline and gel phases formed on the surface of droplet.
- One of the advantages of SEDDS in relation to scale up or manufacture is that they form spontaneously upon mixing their components under mild agitation or they are thermodynamically stable.
- The drawbacks of this system include chemical instable of drugs and high surfactant concentrations.
- The large quantity of surfactant in selfemulsifying formulations (30-60%) irritation in GIT.
- Most selfemulsifying systems are limited to administration in lipid filled soft and hard shelled gelatin capsules due to the liquid nature of product.
- Interaction between the capsule shell and the emulsion should be considered so prevent the hygroscopic contents from dehydrating and migrating into the capsule shell.

Advantages of self-emulsifying or self-micro emulsifying systems

- Improvement in oral bioavailability permissive reduction in dose.
- Ease of manufacturing or scale up.
- High drug loading efficiency.
- Protection of drugs from the gut environment.

- More consistent and reproducible profile of drug absorption, b
- Load time profile.

Method



Results and discussion evaluation of tablets

All batches of prepared tablets were evaluated for various parameters like hardness, friability, thickness, weight variation, content uniformity, in-vitro dissolution studies.

Tablet hardness

The crushing strength (Kg/cm2) of prepared tablets was determined by using Monsanto hardness tester. The hardness tests was performed for each batches of prepared tablets in triplicate manner.

Friability

Friability test was done by Roche Friabilator. Twenty tablets were weight (Wo) and were subjected to combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at a distance of 6 inch with each revolution, operated for 100 revolutions. The tablets were dusted and reweighed (W) after completion of 100 revolutions. The percentage friability was calculated using following formula.

% Friability = W0 – W / W0 × 100

Friability test

Friability test is performed to evaluate the ability of the tablet to withstand wear and tear in packing, handling and transporting.

Thickness

Ten tablets from each batch of formulations were selected randomly and thickness of tablets was measured using vernier caliper. The average value of thickness was calculated.

Weight variation

For uniformity of weight, twenty tablets from each batch of formulation were selected at random and determined their individual weights by using electronic balance. Then, average weight and standard deviation of the tablets was calculated

Uniformity of drug content

Assay is done in distilled water to find out the amount of drug present in one tablet. For this test, 5 tablets were weighed and powdered in a glass mortar and 200 mg of the powder equivalent to 8 mg of drug was placed in a stoppered 100 mL volumetric flask and dissolved in 100 mL water. The resulting solution was filtered and absorbance was measured at λmax 220 nm using UV visible spectrophotometer. The concentration of Lansoprazole in milligram per milliliter was obtained from standard calibration plot of drug.

***In-vitro* drug release studies**

In-vitro release were determined using USP type II dissolution apparatus in 900 mL of phosphate buffer (pH 6.8) at constant temperature of 37° ± 0.5 °C at 50 rpm. Aliquots (5 mL) of the solutions were withdrawn from the dissolution apparatus at different time intervals and replaced with fresh dissolution medium to maintain the sink condition. These aliquots were filtered and the absorbance of these solutions were measured by using a double beam ultra-violet spectrophotometer at 220 nm against fresh phosphate buffer solution as blank. All the studies were conducted in triplicate and percent drug release was calculated by using the following formulae and the % drug release.

% Drug Release = K × Absorbance

Where K can be calculated by using the equation as follows

K = Std. conc. × vol. of dissolution media × dilution factor × 100 / std. abs. × dose × 1000

Conclusion

Around 70% People are suffering from Antiulcer Disease. To treate this Disease Lansoprazole is Effective Drug, It is Class –II drug. Sublingual Tablet of Lansoprazole Prove best choice.

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