



ORODISPERSIBLE PROTON PUMP INHIBITORS: A PALATABLE APPROACH TO GASTROINTESTINAL HEALTH

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ABSTRACT

Since ancient times, people have suffered from peptic ulcers. The account of this illness that is carved on the pillars of the Aesculapius temple in Epidaurus, dating to the fourth century B.C., may be the earliest known. PPIs inhibit the stomach H⁺/K⁺-ATPase, making them the most effective suppressors of gastric acid output. Pantoprazole is often taken in doses of 20–40 mg. These medications reduce basal and stimulated acid production by 80% to 95% at standard dosages. PPIs are frequently used to treat a variety of conditions, including heartburn, erosive esophagitis, ulcers of the stomach and duodenum, GERD, upper gastrointestinal bleeding in critically ill patients, and Zollinger-Ellison syndrome. They are also used in conjunction with antibiotics to treat stomach infections caused by *H. pylori*. When typical PPI pills are administered, there has been evidence of a prolonged lag time due to their enteric coating and fluctuations in plasma drug levels, which can lead to a decrease in blood drug concentration. ODTs can therefore serve as a dosage form that has the added benefits of improved patient compliance and prompt relief, negating all the shortcomings and issues associated with traditional enteric coated formulation.

KEYWORDS: Oral dispersible tablets, Orodispersible technologies, Solid dosage form, Sublimation.

INTRODUCTION

The majority of all administration routes are oral. Oral administration is advised for drug administration due to patient compliance and dosage design flexibility, even if other routes of administration are also utilized. The convenience of use, patient administration, precise dosage, low cost of production, and generally longer product shelf life account for the oral methods of administration's popularity. Tablets, capsules, and liquids are employed as drug carriers in a number of current drug delivery strategies. Solid formulation is less expensive to create than parental formulation and is not necessary for sterile conditions. Oral drug delivery system: This type of device delivers medication specifically to the gastrointestinal tract (GI tract). Oro-dispersible pills are a solid dose form that include excipients and active medicinal components. They typically dissolve quickly in three minutes. ODT delay normally lasts anything from a few seconds to over three minutes. Orally dispersible pills improve patient compliance and make it easier for patients who are unable to swallow tablets. such as patients in pediatrics, psychiatry, and geriatrics. Tablets are a type of solid unit

dosage form that include excipients and active pharmaceutical ingredients, or API. Active pharmaceutical ingredients, or APIs, are substances with biological effects. APIs are frequently referred to as drugs. Excipient is used to enhance the bulk, flow, and other properties of tablets. Tablets are the most popular dosage form, with 65% of medicines being dispensed in tablet form. This is due to the convenience of production, patient compliance, and ease of administration of tablets.^[1-3]

Advantages of Oral dispersible tablets^[5-6]

1. Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
2. Rapid drug therapy interventions.
3. Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down.
4. Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and

busy people, who do not always have access to water.

5. Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
6. Good solubility in water and saliva.
7. Free from bitter taste.
8. Dose lower than 20mg.
9. Small to lower molecular weight.
10. Partially non ionized to oral cavity.
11. Ability to permeate oral mucosal tissues.
12. Ability to diffuse and partition into the epithelial of upper part of Gut.

Disadvantages of Oral dispersible tablets^[6-7]

1. Due to their hygroscopic character they must be stored in a dry place.
2. Their mechanical integrity is quite low.
3. Special packaging is required owing to its unstable nature.
4. Dose uniformity is very hard to maintain in these kinds of tablets.

Proton-Pump Inhibitors (PPI'S)

According to the Biopharmaceutical Classification System (BCS), drug substances are classified as follows: Class I - High Permeability, High Solubility.

Class II - High Permeability, Low Solubility.

Class III - Low Permeability, High Solubility.

Class IV - Low Permeability, Low Solubility.

Class I drugs are likely to exhibit few bioavailability problems.

Class II drugs are prone to dissolution rate– limited absorption.

Class III drugs are likely to exhibit permeation rate–limited absorption.

Class IV drugs may present serious obstacles to oral bioavailability and some may be best formulated in a solubilized form such as a liquid filled or semisolid-filled capsule. Proton pump inhibitors (PPI), substituted benzimidazoles, which inhibit the final common step in gastric acid secretion.

The key action mechanism of the PPI's is inhibition of H⁺/K⁺- adenosine triphosphate (also known as acid pump or proton pump), an enzyme presents in the gastric parietal cells. This effect on the final step of the gastric acid formation thereby reducing gastric acid output both during basal conditions and simulated acid secretion, irrespective of stimulus.

Reflux esophagitis, duodenal ulcer, gastric ulcer, NSAID associated gastric and duodenal ulcers or erosions, acid related dyspepsia, Gastroesophageal reflux disease. Stress-related or drug-induced erosive gastritis, esophageal refluxes are the various ailments where treatment with esomeprazole proves to be appropriate. Group of proton pump inhibitors includes derivatives of benzimidazoles, like omeprazole, lansoprazole, pantoprazole, rabeprazole, etc.^[8]

EVALUATION

The powder mixture's bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose were all assessed. The tablets were evaluated for thickness, hardness, friability, weight variation test, drug content and In-Vitro release rate studies.^[13,14]

1. General Appearance: The overall "elegance" and general appearance of a tablet, along with its size, shape, color, taste, texture, physical faults, and consistency and legibility of any identifying markings, are crucial factors in determining consumer acceptance.

2. Size and Shape: Dimensions can be used to describe, track, and regulate the tablet's size and shape.

3. Tablet thickness: A straightforward method can be used to measure tablet thickness. Using a Vernier Caliper^[15], the thickness of five tablets is measured.

4. Weight variation: To look for weight variation, 20 pills were chosen at random from the lot and each one was weighed separately. Specification for weight variation as per I.P.^[16]

Table 1: Weight variation specification as per I.P.^[17,18]

Average Weight of Tablet	%Deviation
80 mg or less	±10
80 mg to 250 mg	±7.5
250 mg or more	±5

5. Hardness: Tablet hardness testers (Monsanto hardness testers) are used to determine fracture strength, which is defined as the force needed to break a tablet by radial compression. The unit of measurement is kg/cm².

6. Friability: A Roche Friabilator is used to test the friability of a sample consisting of six tablets. In a plastic chamber that rotates at 25 rpm and drops the tablets six inches every revolution, this apparatus subjects the tablets to the combined effects of stress and abrasion. For four minutes, six pre-weight tablets are rotated at 25 rpm. Following the removal of fines, the tablets are weighed again using 60 mesh screens, and the proportion of weight loss is computed as 20. %. Friability is equal to (weight loss / starting weight) x 100.

7. Wetting time: Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. **8. Disintegration Time:** The test was conducted on six tablets using the apparatus specified in I.P.-1996. Distilled water at 37°C ± 2°C was used as a disintegration media, and the time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. For this purpose, a tablet is placed on a piece of tissue paper

folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water. The time for complete wetting is measured 15. 28. Modified Disintegration Test: The normal disintegration test protocol for these dosage forms has a number of drawbacks and is insufficient for measuring extremely short disintegration times. The FDT disintegration time.^[21]

9. In-Vitro Dispersion Time Test: To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined.^[18]

10. Dissolution test: The process used to develop ODT dissolution techniques is nearly the same as that used to develop traditional tablet dissolve techniques. One useful starting point for conducting scouting runs for a bioequivalent ODT is the dissolution parameters for medications specified in a pharmacopoeia monograph. Other media, like buffer (pH 4.5 and 6.8) and 0.1 M HCl, should be assessed for ODT in a manner similar to that of regular tablets. It has been proposed that the USP 2 paddle device, which typically uses a paddle speed of 50 rpm, is the most practical and widely utilized option for orally disintegrating pills.^[22]

11. In vivo clinical studies: In vivo studies show the actual action of ODT in the oral-esophageal tract, their pharmacokinetic and therapeutic efficacy, and acceptability. The investigation using gamma scintigraphy showed that the dissolution and buccal clearance of fast disintegrating dosage form is rapid. The esophageal transit time and stomach emptying time are comparable to those of traditional dosage forms i.e. tablets, capsules, or liquid forms.^[23-24]

12. Disintegration in oral cavity: The time required for complete disintegration of tablets in mouth is obtained from six healthy volunteers, who have given tablets from optimum formulation.^[25]

13. Accelerated stability study: As directed by the ICH guideline for expedited studies, the oral disintegrating tablets are packaged appropriately and kept under the following conditions for the designated amount of time.

(1) $40 \pm 10^\circ\text{C}$

(2) $50 \pm 10^\circ\text{C}$

(3) $37 \pm 10^\circ\text{C}$ and Relative Humidity = $75\% \pm 5\%$ The tablets are withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegration, and Dissolution etc.) and drug content. The data obtained is fitted into first order equation to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the self-life at 25°C .^[26]

Oral dispersible tablets Formulation development\ methods of preparation

One very important phase is the formulation of a

medication. When producing a product in large quantities, the formulator must exercise extreme caution because a poorly designed product will undoubtedly not exhibit its therapeutic effect as intended. There are various methods available for producing ODTs. Every methodology has advantages and disadvantages of its own; the sort of drug-excipient nature will determine which way is most appropriate to use.

- 1. Freeze drying:** For medications that are thermolabile, lyophilization technology is primarily utilized, because it uses a low temperature to dry the medication. Sublimation allows the medications' moisture to escape. The medication is preserved in a water-soluble matrix in this procedure, and it is dried by passing it through a freezing tunnel. Because of its porous nature, the finished product dissolves quickly, enhancing its bioavailability.^[9]
- 2. Moulding:** One of the best approaches for creating oral dispersible pills is this one. To ensure that the product dissolves fast, only chemicals that are soluble in water are chosen. Here, all of the solid components are dissolved in hydro alcoholic liquids before the dispersible tablets are compressed at a reduced pressure. The solvent is shelved using the air-drying process following compression. The final product has a high degree of porosity and excellent dissolving.^[10]
- 3. Spray drying:** This process is typically used when very fine, porous powders are required. This approach uses mannitol as a bulk-forming agent and gelatin as a supporting ingredient. Effervescent compounds can also be used to improve the features of dissolution and disintegration. Lastly, spray drying is used to create a porous powder from the processed material.^[11]
- 4. Sublimation:** Because of the limited porosity of the tablets, the rate of dissolving of compressed tablets can occasionally be delayed. The sublimation procedure involves combining the other adjuvant, the volatilizing agent, and the active medicinal ingredient to make a tablet. Sublimation tablets made using this method evaporate the volatile content after compression and often dissolve rapidly.^[12]
- 5. Mass extrusion:** This process involves softening the active blend of methanol and water-soluble polyethylene glycol in a solvent mixture. The resulting softened mass is then fed into an extruder or syringe to form a cylinder-shaped product, which is subsequently divided into smaller pieces to form tablets. The resulting product can also be coated to hide the flavor in the case of bitter medications.

Advancements in Oral dispersible tablets technologies

Zydis technology: The Zydis technology was one of the most important milestones in the history of dispersible tablets. It was discovered by R.P. Scherer. With the aid of lyophilization technique, the tablet is surrounded within a fast-dissolving carrier material.^[27,28] So that

when it reaches the oral cavity it should disintegrate quickly. Various kinds of adjuvants are used in these tablets to make the final product as much as stable. Due to freeze drying process the tablet is not prone to microbial contamination. These tablets generally are packed in blister packs to preserve from moisture in the environment. The examples of some marketed formulations are Grazax®ODT, Maxalt® MLT, Xilopar® 1.25, Zofran® Zydis, claritin®Reditabs® Pepcid®RPD etc

Orasolv technology: CIMA Labs devised this approach. To cover up the unpleasant taste of A.P.I., an effervescent disintegration agent is added in accordance with a flavor masking agent. The other tools utilized in the tablet making process are traditional in nature. Low compression force should be used while compressing the tablets to ensure a soft, quickly disintegrating final product. Furthermore, extreme caution must be taken when storing these nauseating dosage forms in order to maintain their stability over time. Six marketed formulations have already made use of this technology. This method allows the incorporation of more than two elements.^[27,29]

Durasolv technology: CIMA laboratories also developed this technology. This formulation's primary ingredients are the medication, lubricant, and fillers. Durasolv technology allows for the production of tablets using the same basic tools used to make regular tablets. It is also not necessary to use specific packaging for the storage of these products. Generally speaking, this method is appropriate for medications with comparatively little active component.^[30]

Wowtab technology: This technology is patented by Yamanouchi pharmaceutical Company. The term WOW in Wowtab means without water. The ratio between active ingredients and excipients is kept 50:50. The saccharides of both low and high mouldability are employed to formulate the granules. Mouldability can be expressed as the ability of a substance to be compressed. Tablets with the right amount of hardness are created by combining low and high moldability. In less than 15 seconds, the pills made using Wowtab technology dissolve quickly. For their packing, any type of container will do.^[31]

Flashtab technology is an additional cutting-edge technique for making oro-dispersible pills. Prographarm laboratories invented the flashtab technology. The composition contains microcrystals as the active ingredient. For production, a variety of conventional tablet-making methods can be applied. In less than a minute, the produced end product dissolves in the tongue.^[38,32]

Pharmaburst technology: As the name suggests, this technique's goal is to release the medicament instantaneously in the mouth. This technique was

patented by SPI Pharma, New Castle. In this technique, combinations of specialized excipients are employed, which ultimately gave rise to such a final product which immediately releases the drug from dosage form. One of the specialized ingredients used is mouldability saccharine which forms a rapid melting strong tablet.^[33]

Ora-Quick: The taste-masking has always been a major issue of concern in oral dosage forms. KV Pharmaceutical has developed a novel microsphere technology known as the "micro mask," which can unquestionably go past this barrier. Drugs that are thermolabile can also be treated using this approach. To maintain the tablet's optimal mechanical strength, micro-encapsulated particles are coated on the tablet after formulation. Ora-quick technology ensures flavorful dissolving quickly. Although this technology has not yet been put to use in the market, K.V. Pharmaceutical is prepared to introduce a number of goods that will make use of this cutting-edge technology.^[34]

Characterization of Oral dispersible tablets

1. **Weight variation test:** This test is used to make sure that each pill in a batch contains the same amount of medication as stated on the label. We had to weigh twenty tablets that were chosen at random for this. The average weight of the tablets is determined after they have all been weighed. The batch is approved if the results fall within the specified range, and it is refused if the tablet weights do not fall within the specified range.^[35]
2. **Tablet thickness:** Another crucial evaluative aspect is the thickness of the tablet. A Vernier Caliper is a piece of equipment that makes evaluating it simple. Five tablets are selected at random from the test batch, and each pill is placed one at a time, placed in the equipment and results are interpreted.^[36]
3. **Tablet hardness:** A tablet's ability to withstand mishandling and damage during transit depends greatly on its hardness. However, excessive hardness in dispersible tablets may result in low patient compliance. Therefore, a dispersible tablet's hardness should be lower than that of a regular tablet. The force needed to break a tablet through radial compression is correlated with the tablet's hardness. These days, the Monsanto and Pfizer testers are most likely employed to determine a tablet's hardness.^[37]
4. **Tablet friability test:** The friability of the tablets is typically determined using the friability test apparatus. The purpose of this test is to assess the tablets' resistance to handling and transportation faults. The specified number of pills is swallowed and placed in the test device in accordance with the Pharmacopoeia. The specified number of revolutions and time are followed, and the outcomes are noted.^[38]

5. **Wetting time:** A tablet needs to have adequate wetting capabilities in order to dissolve correctly. For this reason, it is necessary to assess a tablet's wetting capacity. It is also possible to draw conclusions about how various excipients affect a tablet's disintegration time. This is accomplished by placing a tablet on a piece of tissue paper that has been folded twice and placing it in a tiny Petri dish (ID=6.5 cm) with 6 ml of water. The duration of the tablet's complete soaking is then recorded.^[39]
6. **In-Vitro Disintegration Test:** This method typically determines how long it takes for the tablets being tested to dissolve using a disintegration test instrument. Six tubes of the device are filled with tablets that are selected from the batch that is being evaluated. The pharmacopoeia-specified dissolving medium in these tubes is appropriate, and it needs to be kept at $37^{\circ} \pm 2^{\circ}\text{C}$ at all times. The apparatus is started after all the conditions are met. The exam is finished, and the outcome is declared.^[40]

CONCLUSION

Since the development of fast-dissolving dosage forms, many of the issues related to administering medication to pediatric and geriatric patients—who make up a sizable section of the global population—have been resolved. To obtain quick results, ODTs must optimize the tablet matrix's porous structure and add super disintegrating agents at the ideal concentration. Rapid dissolution and disintegration of the tablet, in addition to its superior mechanical strength and ability to disguise taste. Many medications, particularly unpleasant drugs, can be included in ODT. The investigation is still ongoing. There must be more products Commercialized to make appropriate use of this technology. As a result, ODT may soon be produced for the majority of medications on the market.

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