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Review Article

A Review Article on Conversion of Pantoprazole Crystalline Form to Amorphous Form to Study the Effect of Solubility

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ABSTRACT

Proton pump inhibitors (PPIs), like pantoprazole, are used to treat a number of ailments linked to high stomach acid. It is frequently recommended to treat acid reflux-induced erosive dysphagia, Zollinger-Ellison syndrome, and gastroesophageal reflux disease (GERD). It lessens the generation of acid by blocking the stomach lining's proton pump. One way to increase pantoprazole's bioavailability is to transform it from a crystalline to an amorphous form. Increased Solubility, Quicker Rates of Dissolution, Stability Enhancements Compared to crystalline forms, amorphous forms may be less thermodynamically stable, which could eventually cause recrystallization. To preserve the amorphous state and its advantages, proper formulation and storage conditions are crucial. One method that shows promise for increasing pantoprazole's solubility and bioavailability is converting it to its amorphous form.

INTRODUCTION

In the creation of pharmaceuticals, solubility is essential to the formulation and administration of drugs. One of the main factors affecting a drug's absorption, distribution, and, eventually, bioavailability is its solubility. Drugs with poor solubility frequently have trouble breaking down in the gastrointestinal system, which reduces absorption and diminishes therapeutic efficiency. Therefore, increasing solubility is crucial to maximizing a drug's therapeutic effects and increasing its bioavailability. In its crystalline form, pantoprazole, a proton pump inhibitor (PPI) used to lower gastric acid output in situations such as gastroesophageal reflux disease (GERD), is poorly soluble in water. Because crystalline medications typically have low energy states due to their ordered and stable molecular structures, they are difficult to dissolve in watery environments like the gastrointestinal tract. The insoluble nature of crystal

Pantoprazole: Pharmacological and Physicochemical Properties:

1. Drug Name:

Pantoprazole (Brand names: Protonix, Pantoloc)

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2. Chemical Structure:

IUPAC Name: 5-(Difluoromethoxy)-2-[[(3,4-dimethoxypyridin-2-yl)methyl]sulfinyl]1H-benzimidazole

Molecular Formula: C16H15F2N3O

Brand Names: *Protonix, Pantoloc, among others*

Drug Class: proton Pump Inhibitor

Chemical Structure: Pantoprazole is a substituted benzimidazole compound with a pyridine ring and a sulfoxide group, contributing to its proton pump inhibitory activity.

Mechanism of Action: mechanism of Action: Similar to other proton pump inhibitors (PPIs), pantoprazole targets and irreversibly inhibits the H+/K+ ATPase enzyme in the stomach's parietal cells. The last stage of gastric acid secretion into the stomach lumen is carried out by this enzyme. Pantoprazole efficiently decreases the formation of gastric acid, which lowers stomach acidity by inhibiting this pump. This lessens the symptoms of acid reflux and improves the repair of duodenal and stomach ulcers.

Crystalline Nature and Solubility Limitations: One of the main physicochemical characteristics of pantoprazole is its crystalline structure. The most common form of pantoprazole is crystalline, with molecules grouped in a highly structured, lattice-like structure. Although this crystalline structure has strong solubility restrictions, it is energetically stable. Compared to their amorphous cousins, crystalline medicines usually have lower energy states and are less soluble in water. The low water solubility of pantoprazole's crystalline form makes it difficult for the medicine to be absorbed, particularly when taken orally. Because the medicine must dissolve in the gastrointestinal fluids before passing through the intestinal wall for oral absorption to occur, pantoprazole's weak solubility may cause partial or delayed absorption, which would lower its bioavailability. Therefore, administering medication at bigger doses or more frequently.

Comparison crystalline form to amorphous form:

Property	**Crystalline Form**	***Amorphous Form***
Structure	Ordered, well-defined lattice	Disordered, noncrystalline
Solubility	Lower solubility, pH dependent	Higher solubility, better across pH range
Dissolution Rate	Slower dissolution	Faster dissolution
Stability	More thermodynamically stable	Less stable, prone to recrystallization
Shelf Life	Longer shelf life	Shorter shelf life, requires careful storage
Bioavailability	Lower bioavailability	Higher bioavailability
Manufacturing	Established methods for formulation	Requires specialized techniques (e.g., spray drying, milling)
Applications	Commonly used in standard formulations	Suitable for advanced formulations (e.g., solid dispersions)
Patient Compliance	Standard dosage forms	Potential for more patient-friendly forms (e.g., fast-dissolving)
Therapeutic Effect Onset	Slower onset of action	Faster onset of action

Effect of Amorphous form on:

Solubility and Dissolution Rate of Amorphous Pantoprazole: The solubility and dissolution rate of pantoprazole are greatly enhanced by its transformation from its crystalline to an amorphous state. Although pantoprazole is more stable and organized in its crystalline form, its decreased solubility is caused by the limited interaction between the drug molecules and solvent. The amorphous form, on the other hand, has more molecular mobility and free energy since it lacks a well defined crystalline lattice. This accelerates the rate of dissolution by increasing the surface area accessible for contact with the solvent. According to studies, medications that are amorphous, like pantoprazole, dissolve more quickly than those that are crystalline. According to one study, the breakdown rate of amorphous pantoprazole was almost three times higher than that of the crystalline form.

Role of Supersaturation:

The increased solubility of amorphous pantoprazole can be largely explained by the idea of supersaturation. When a drug is in a supersaturated condition, its concentration in solution is greater than its equilibrium solubility in the crystalline form, which increases the driving force for absorption.

Because of its high internal energy, the amorphous form can dissolve more quickly and reach a supersaturated condition in the gastrointestinal tract (GIT). Because of the enhanced concentration gradient provided by this supersaturated solution, medication is absorbed through the intestinal barrier more quickly. It is difficult to keep the amorphous form in this supersaturated state for long because it tends to recrystallize into the more stable crystalline form.

Impact on Bioavailability:

Pantoprazole's bioavailability is directly impacted by the increased solubility and dissolution rates brought about by amorphization. The percentage of a medicine that is delivered and enters the systemic circulation in an active state is referred to as bioavailability. The rate of dissolution in the gastrointestinal tract (GIT) frequently limits the bioavailability of medications, such as pantoprazole, which is poorly soluble in water.

Because amorphous pantoprazole dissolves more quickly and is more soluble, it can reach higher quantities in gastrointestinal fluids, which improves the absorption of the medication. In the end, this improves the medication's bioavailability over its crystalline form. More of the medication enters the systemic circulation when it has increased bioavailability, which may lead to better therapeutic outcomes, such as a faster beginning of action and better symptom relief in diseases like gastroesophageal reflux disease (GERD). Pantoprazole is changed into an

Numerous efficient procedures or approaches can be employed to change pantoprazole from its crystalline form to an amorphous one.

1. Utilizing Spray Drying:

One of the most popular methods for preparing amorphous medication forms, such as pantoprazole, is spray drying. Using this technique, pantoprazole is atomized into fine droplets in a solution or suspension and quickly dried by a hot gas stream. An amorphous solid is produced when the drug molecules are unable to arrange themselves into a crystalline form due to the solvent's quick evaporation.

Overview of the Process:

- A appropriate solvent is used to dissolve pantoprazole.
- Droplets of the solution are atomized.
- Rapid evaporation of the solvent leaves behind amorphous particles.
- It gathers the amorphous powder.

Benefits

- Repeatable and scalable: Fit for large-scale production.

- Particle size control: It is possible to regulate the size of the particles, which can improve dissolving even further.
- Flexibility: Suitable for a variety of solvent types

2. Hot Melt Extrusion (HME)

Another well-liked method for creating amorphous solid dispersions is hot melt extrusion. This procedure involves heating and forcing a slurry containing pantoprazole and a polymeric carrier via an extruder. The medication melts and disperses molecularly within the polymer matrix due to the heat and shear stresses, which prevents it from crystallizing when it cools.

Overview of the Process:

A polymer (such as PVP, HPMC, or Eudragit) is combined with pantoprazole.

The mixture is heated and combined inside an extruder. An amorphous solid dispersion is formed by rapidly cooling the extrudate.

Benefits

No solvent is needed. Since HME doesn't use solvents, there is a lower chance of solvent residue.

Enhanced stability: The amorphous state is stabilized by the polymer matrix and

3. Lyophilization via Freeze Drying

Freeze drying, often called lyophilization, is a process that sublimates the solvent (usually water) under vacuum to transform crystalline medicines into amorphous particles. Since this approach does not require high temperatures, it is perfect for medications like pantoprazole that are sensitive to heat.

Overview of the Process:

In a solvent (often water or a combination of water and organic solvent), pantoprazole is dissolved.

A solid is created by freezing the solution. Sublimation under vacuum is used to remove the frozen solvent, leaving the amorphous drug behind. might deteriorate in a heated environment.

Minimized degradation: There are no harsh solvents or high temperatures used.

The finished product has a porous structure that facilitates dissolving.

Problems:

Freeze drying is an intricate and time-consuming procedure that needs careful control.

4. Evaporation of Solvents

One easy and popular method for changing crystalline medications into amorphous solids is solvent evaporation. In this process, pantoprazole is dissolved in a volatile solvent, which is subsequently evaporated under controlled conditions, leaving behind the medication in an amorphous state. is given time to gradually vanish.

After the solvent is removed, the resultant amorphous solid is collected.

Benefits

Simplicity: The approach is simple and readily scalable.

Low-temperature method: Ideal for medications that are thermally labile and susceptible to:

An organic solvent or combination of solvents is used to dissolve pantoprazole. To protect medications that are susceptible to heat, the solution is sprayed on, applied as a thin coating, and then cured at room temperature or slightly higher temperatures.

Flexibility: May be mixed with surfactants or polymers

5. **Milling (Mechanical Amorphization)**

By applying strong mechanical pressures that break the crystalline lattice, the mechanical process of milling, also known as ball milling, can cause crystalline medications to become amorphous. Pantoprazole is pulverized into fine particles using this process, frequently with the use of a polymer or stabilizing ingredient.

Overview of the Process:

A ball mill is used to grind pantoprazole along with other milling materials, including beads or balls.

The crystalline structure is broken down by the mechanical motion, taking on an amorphous shape. During milling, the amorphous shape can be stabilized with the assistance of a polymer.

Benefits

No solvents required: stays away from using organic solvents.

Easy to use and reasonably priced: The procedure is simple to carry out and reasonably priced.

Scalable: Capable of expanding to an industrial production level.

Problems:

6. Melt quenching, or quench cooling

In order to stop the drug molecules from building a crystalline lattice, quench cooling, also known as melt quenching, entails melting pantoprazole in its crystalline form and quickly chilling the mixture.

Overview of the Process:

The temperature of pantoprazole is raised over its melting point. The amorphous form is produced by quickly cooling (quenching) the melt, usually on a cold surface or by submerging it in a cold liquid.

Benefits Simpleness: There is no need for solvents in this easy-to-follow procedure.

High purity: The product is free of any remaining solvents.

Quick processing: The procedure can be completed in a timely manner.

Problems:

Thermal stability: It's important to take into account pantoprazole's heat sensitivity because too much heat can cause degradation.

Stabilizing agents are necessary since recrystallization during storage may not always be avoided by rapid cooling.

CONCLUSION

Pantoprazole's transformation from crystalline to amorphous form is a viable tactic for raising the medication's solubility and rate of dissolution, which will eventually increase its bioavailability and therapeutic effectiveness. Since crystalline pantoprazole is poorly soluble in water, amorphization provides a solution by creating a higher-energy, disordered solid state that dissolves more easily in biological fluids. Research has indicated that the conversion of pantoprazole into its amorphous form significantly improves its solubility and dissolution. This can result in faster absorption and better therapeutic outcomes for patients with acid-related diarrhea.

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