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Preparation and Evaluation of Delayed Release Pantoprazole Sodium Enteric Coated Pellets

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ABSTRACT: The goal of this study was to develop a stable, cost-effective, and higher-quality enteric-coated pantoprazole pellet formulation for the treatment of gastro-esophageal reflux disease (GERD). Although pantoprazole and other proton pump inhibitors are effective in treating acid-related diseases, they become unstable in acidic environments. Delay-release formulations are therefore essential to ensuring the efficacy of treatment. Nine different formulations are made using different enteric polymers. Using the solution-suspension layering approach, the formulation process was completed in FBC and compared to the commercial dosage form. Acid-labile drugs such as pantoprazole can be prevented from being broken down by the stomach by the polymers Eudragit L 30 D 55 and Eudragit L 100-55. Rather, the polymers enable the drug to be released into the more neutral pH of the intestine while staying intact in acidic environments. It was revealed by FT-IR research that the medication and polymers got along. With regard to GERD treatment, Formulation F9, which has a particular remark, demonstrated the highest drug release (98%) in phosphate buffer at pH 6.8. Patients with GERD benefit from improved medication stability and effective delivery to the intestinal site of action thanks to this formulation strategy.

KEYWORDS: Gastro-esophageal reflux disease, Enteric coated, Proton pump inhibitor, Delayed release, formulation, Acid-labile.

I. INTRODUCTION

Drugs in delayed release systems are not released right away after consumption; instead, they release the drug at a specific time and place. This strategy minimizes gastric discomfort, protects delicate medications from stomach fluids, and ensures optimal absorption from particular intestinal locations, among other therapeutic goals. Medications that are known to produce gastric distress, are broken down by intestinal enzymes or stomach acid, or are designed to have localized effects in the gastrointestinal tract are commonly used in these systems.

Types of Delayed Release Systems:

1. **Intestinal Release System**

Enteric coatings, which dissolve at pH levels higher than those seen in the stomach, are frequently used in these devices, which are designed to release the medicine in the intestine. This system lessens stomach mucosal irritation while safeguarding medications that are susceptible to acid.

2. **Colonic Release System**

Systems for releasing drugs into the colon are specifically designed for this purpose. This minimizes systemic exposure while permitting localized therapeutic benefits, making it especially useful for treating diseases like Crohn's disease or ulcerative colitis.

Mechanism of Action

Enteric coatings, which dissolve under neutral or alkaline conditions encountered in the intestine but are resistant to acidic surroundings, are frequently used in delayed release formulations. Polymers like EUDRAGIT®, for instance, are frequently utilized for this reason because of their consistent dissolving properties.

Other processes than enteric coatings are as follow:
Pulsatile release: this type of medication has a lag period and then rapid release; it is useful for medications that must synchronize with biological cycles (for example: glucocorticoids used in the treatment of Arthitis).
Matrix Systems: In these systems, the drug is enmeshed in a polymer matrix that uses erosion and diffusion to regulate the rate of release.

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Enteric polymers are gaining popularity because they remain intact in the stomach but dissolve and release the contents once they reach the small intestine. Pharmaceutical formulations that use multiparticulate drug delivery systems—especially pellets—benefit from a number of single-unit systems. Their main advantage is that they can improve the distribution of drugs throughout the GI gut and limit changes in plasma levels, which can lessen the negative effects of medicines.

Benefits of pellets:

- **Pellets for Better Medication Delivery:** The size of pellets is normally between 0.5 and 2 mm, with the aim of being small, spherical beads. Comparing this size to larger single-unit dose forms, it allows for a more equal dispersion across the gastrointestinal tract, which improves absorption characteristics. Drug release is made possible by the numerous units, which lowers the chance of dose dumping and helps to maintain more consistent plasma concentrations. Pellets can be compacted into tablets or enclosed in capsules, offering versatility in the formulation process.
- **Versatility in Formulation:** Pellets offer versatility during the formation of dosage forms because they can also be made into tablets or encapsulated in capsules. Because of its versatility, coated pellets have the flexibility to target particular gastrointestinal tract. Hence they can be used for the co-administration of incompatible drugs.
- **Decreased Local Irritation:** At any given location in the gastrointestinal tract, the smaller size and many units of pellets reduce the local concentration of the active pharmaceutical ingredient (API). This feature reduces irritating effects and improves comfort for the patient.
- **Diminished Variability:** Because pellets slow down stomach emptying and transit time, they can minimize intra- and inter-subject variability in drug concentration.
- **Customization of Release Profiles:** Manufacturers can control the rate at which pharmaceuticals release from pellets by using suitable polymers and coating processes. This enables them to create release profiles that are immediate, sustained, or delayed. This personalization is especially useful for drugs that need to be taken according to certain dosage instructions.

Generally, oral drug delivery methods have advanced significantly with the invention and application of multiparticulate systems like pellets, which solve many of the drawbacks of conventional single-unit dosage forms.

In the pharmaceutical industry, pellets are only tiny, spherical particles that flow freely and are composed of finely ground granules or powder.They can be used to treat a variety of illnesses, albeit tablets are more practical than capsules. Pellet sizes range from 0.5 to 2.0 mm. Because of their small size, the pellets are less likely to be impacted by gastric emptying. With the advantages of several administration routes, this formulation offers an enhanced alternate presentation for all patients needing pantoprazole. The primary goal of this study is to use Eudragit L 30 D in the formulation to slow down the drug release (**Pantoprazole**) into the gastrointestinal system. Pellets are very practical because of their consistent size and shape, which makes them useful in a variety of sectors. Here are a few noteworthy uses:

General Applications

- **Enhancement of Aesthetics:** Pellets give products a more appealing appearance, increasing their visual appeal to customers.
- **Regulated Release:** Producers can attain a regulated release rate of active compounds in pellets by coating them with specified polymers. This is especially helpful for agrochemicals and pharmaceuticals.
- **Enhanced Dissolution and Absorption:** A greater surface area of pellets allows for improved dispersion, solubility, and absorption of the active ingredients in different formulations.
- **Encapsulation of Incompatible Products**: Pellets make it possible to administer chemically incompatible compounds in a single dose form by employing encapsulating techniques.
- **Minimization of Powder Dusting:** The use of pellets reduces powder dusting in the chemical industry, which can be harmful to workers' health and result in material loss.
- **Adaptable Uses:** The versatility of pellets is demonstrated by their use in a variety of goods, including milkshake pellets and powdered detergent with prolonged release.
- **Improved Flow qualities:** The consistency of pellets ensures better flow qualities during

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manufacturing operations, enabling flexibility in formulation creation.

Coatings that are color-coded make it simple to distinguish between beads of varying thicknesses and enable accurate blending in the appropriate ratios.

Pharmaceutical Applications

Pharmaceutical applications for pellets are numerous and include drug delivery methods. Here are a few essential uses:

- **Rapid Dissolution Methods:** Pellets with rapid dissolution and disintegration can be designed for instant release. For traditional oral drug delivery systems, this use is essential for increasing the bioavailability of medications that need to be absorbed quickly.
- **Delivery of Controlled Release Drugs:** It is possible to blend several pellets with incompatible ingredients into a single dose form. This makes it possible to create controlled release profiles, in which different active pharmaceutical ingredients' (APIs') rates of release can be adjusted to suit specific therapeutic requirements.
- **Inhalation Therapy:** Usually non-irritating, inhalation treatment pellets have a maximum particle diameter of around 1 mm. They can also be used to treat various conditions since their size is ideal for targeting the respiratory tract.
- **Implants:** As implants, polymeric spheroidal particles can release APIs steadily and continuously for prolonged periods of time. These pellet implants are frequently made by the extrusion process, which guarantees consistency and stability in the release of the medicament.
- **Self-Emulsifying Drug Delivery Systems (SEDDS):** Drugs with limited water solubility benefit most from this application because it achieves dosage proportionality and lowers subject variability, improving the drug's in vivo behaviour.

Desirable properties of pellets:

In pharmaceutical applications, the unique desired features of coated and uncoated pellets increase their effectiveness. An overview of these properties based on the search results may be found below.

1. **Uncoated pellets:**

- **Uniform Shape and Surface:** To promote flow and packing, the perfect uncoated pellet should have a smooth surface and a uniform spherical shape.
- **Optimal Size:** To balance medication release and handling properties, uncoated pellets should be in the 600–1000 micrometer size range.
- **Better Flow Characteristics:** Accurate dosing depends on consistent filling of tablets or capsules, which is made possible by good flow characteristics.
- **High Physical Strength and Integrity:** To ensure that uncoated pellets retain their integrity throughout manufacture, they must be able to endure handling and processing without cracking or fracturing.
- **Good Hardness and Low Friability:** Pellet breakage during storage and transportation is reduced when there is a high degree of hardness combined with low friability.
- **High Bulk Density:** This characteristic minimizes the volume required for storage by enabling effective packaging and transportation.
- **Ease of Coating:** Uncoated pellets should have surface qualities that facilitate efficient coating, improving the active ingredient's delivery characteristics.
- **Reproducible Packing of Beds and Columns:** For procedures like tablet formulation and controlled release systems, packing behaviour must be consistent.

2. **Coated pellets:**

- **High Active Ingredient Content:** For optimal dosing, coated pellets should incorporate as much of the active components as possible while maintaining a tolerable final dose form size.
- **Desired Drug Release Characteristics:** Depending on the therapeutic needs, the coating must be made to offer particular drug release patterns, such as immediate or sustained release.
- **Coating Quality:** Drug release rates are influenced by coating quality; thinner coatings may allow for faster breakdown, while thicker coatings may slow down release rates.
- **Compressed Consistency:** In order for the coating to properly regulate drug release, coated pellets must preserve their structural integrity during tablet compression procedures.

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These characteristics are essential for guaranteeing that coated and uncoated pellets function as best they can in pharmaceutical formulations, supporting efficient drug delivery systems.

Pelletization Techniques:

In the production of pharmaceuticals, pelletization procedures are essential, especially for producing multiparticulate dosage forms. The three main techniques are balling, agitation, and drug layering. Every technique has its own advantages, uses, and processes.

1. Drug layering:

Drug layering is a technique wherein inert beginning seeds or crystals serve as the nucleus on which successive layers of drug are applied. We can use the following to carry out this process:

a) **Solution/Suspension Layering:** The medication is applied to the nucleus after being suspended or dissolved in a binding solvent. This process is well-liked for creating controlled-release formulations because it enables the pellets to have consistent sizes and surfaces.

b) **Powder Layering:** In this type of method, the beginning seeds are sprayed with a binder solution prior to the addition of the medication powder. In comparison to solution layering, this method may result in a better pellet formation efficiency. The size of the pellets, the rate of manufacture, and the thickness of the coating solution are some of the important factors that determine how successful drug layering is. Consistent drug release profiles and high-quality pellets are guaranteed by proper management of these parameters.

2. Agitation

Agitation is the process of continuously rolling or tumbling tiny particles while adding liquid to form spheroidal forms. This method uses a balling procedure to make pellets using tools like mixers, pans, and discs. Despite being one of the earliest strategies, it is thought to be less effective than more recent approaches like drug layering.

3. Balling

Balling can be accomplished by heating the mixture to promote agglomeration or by applying liquid to the powder. It falls under the following categories:

- **Liquid-Induced Agglomeration:** This process involves forming pellets with a liquid binder.
- **Melt-Induced Agglomeration:** This process uses heat to melt a binder, which cools and solidifies. This method's scalability and efficiency in creating massive amounts of pellets make it popular in sectors like iron ore and fertilizers.

4. Compaction:

Drug granules or particles aggregate under pre ssure to create a pellet with a specific size and shape. Compression With the help of pressure, a mixture of the active components and many excipients are compacted to give the pellet its specific size and shape.

5. Compression

Formulation of pellets using compression is another method of compaction. Using this technique, mixes of excipients and active substances are compressed under pressure to create pellets of predetermined dimensions. Similar to those utilized in the production of tablets, the design and manufacturing variables that affect pellet quality in compression highlight the significance of exact control over variables including pressure and material composition.

6. Extrusion-Spheronization Process:

Extrusion-spheronization is a commonly employed method that yields uniformly sized spherical pellets, mainly for application in oral medication administration systems. This several-step procedure consists of:

- **Damp Massing:** To produce a uniform mass, active substances are combined with a liquid.
- **Extrusion:** To create cylindrical rods or strands, the wet mixture is pushed through an extruder.
- **Spheronization:** Next, these rods pass through a spheronizer, which uses friction to break the extrudates down into smaller, spherical particles, rounding them into spheres.
- **Drying:** In order to reach the appropriate moisture content, the pellets are lastly dried.

The manufactured pellets might have a size ranging from 600 micrometers to several centimeters, contingent upon the particular needs and application.

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By enabling regulated release profiles, this technique not only improves the flow properties of powders but also permits substantial medication loading within tiny pellet sizes, which increases patient compliance.

7. **Cryopelletization:** A specific procedure called cryopelletization is used to turn liquid formulations like solutions, suspensions, or emulsions into pellets. With this method, droplets are quickly frozen by submerging into nitrogen liquid at 160°C. The droplets form into pellets due to the rapid heat transfer made possible by the intense cold. During the next drying stage, the pellets are usually dried using traditional freeze dryers to get rid of any remaining water or organic solvents.

Procedure for Cryopelletization:

- **Droplet Formation:** Fine droplets are created by atomizing liquid compositions.
- **Quick Freezing:** Because liquid nitrogen has a high heat conductivity, the droplets freeze quickly as they come into contact with it.
- **Pellet Formation:** The material solidifies into pellets once it has frozen.
- **Drying:** The frozen pellets are next put in a freeze dryer, which effectively removes moisture and solvents by causing sublimation, which is the direct transition of ice from a liquid phase to vapour. This technique ensures that the finished product maintains its intended qualities by protecting the integrity of delicate chemicals during the drying process.

8. Spray Drying and Spray congealing:

In the formulation of pharmaceuticals, spray drying and spray congealing are two crucial processes that have various applications and methods.

a) **Spray Drying**

One popular technique for turning liquid feeds—like solutions or suspensions—into dry particles is spray drying. In order to do this, the liquid must be atomized into tiny droplets and added to a heated gas stream, usually air. Solid particles, which are typically uniformly sized and spherical, are formed when the solvent evaporates quickly.

Important Features and Benefits

- **Particle Properties:** The finished powders that are spray-dried have improved flowability, homogeneity, and regulated particle size.
- **Bioavailability:** Increasing the dissolving rates of poorly soluble medications using spray drying helps to increase their bioavailability. When medications are transformed via this method, they become more soluble and dissolve more quickly than when they are in their crystalline form.
- **Uses:** It is widely used in the formulation of oral solid dosage forms and inhalation aerosols. Spray drying is flexible while working with a wide range of medication types, along with biopharmaceuticals and small molecules.
- **Process Efficiency:** The method is effective for large-scale production since it is scalable and automatable. Additionally, it permits the addition of excipients that may help with solubility and stability.

b) **Spray Congealing (Spray Chilling)**

Similar to spray drying, spray congealing concentrates on solid particle formation from melted materials as opposed to solvent evaporation. This method involves melting or dissolving a medication in a hot melt matrix made of fatty acids, gums, or waxes. After being sprayed into a stream of colder air, this melt congeals into spherical pellets.

Important Features and Benefits

- **How Pellets Form:** Spray congealing produces spherical congealed pellets as its main product, which can be utilized in formulations for controlled release. Drug release characteristics can be modulated by encapsulating medications within a solid matrix using this technique.
- **Process Control:** In a process equivalent to spray drying, variables like temperature and air flow may be changed to produce the appropriate pellet properties. For the purpose of guaranteeing product performance and consistency, having control over manufacturing conditions is essential.

Factors affecting pelletization Techniques:

The quality and properties of the resulting pellets are determined by a number of important parameters that impact the pelletization process. There is a brief overview of these parameters:

1. Moisture Content

Since moisture improves the cohesiveness of powder mixture, it is essential during the

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pelletization process. The right amount of moisture promotes efficient spheronization, which results in well-formed spherical pellets. On the other hand, too much moisture might lead to agglomeration during spheronization, which would lower the quality of the pellet.

2. **Rheological Characteristics**

For the wet mass to flow properly during extrusion, its rheological characteristics are essential. While differences can cause irregularities in pellet production, ideal rheological circumstances aid in the development of homogenous extrudates.

3. **Drug and Excipient Solubility** Pellet formation is dependent on how soluble drugs and excipients are in the granulating fluid. While proper wetting improves plasticity but can additionally result in a sticky mass that hinders processing, excessive amount of liquid can cause over-wetting.

4. **Composition of Granulating Fluid**

Granulation can be done with a variety of liquids, such as alcohol, water, and polymer dispersions like PVP and HPMC. The wetting and binding characteristics necessary for pellet formation are impacted by the granulating fluid selection.

5. **Physical Characteristics of Starting material**

Qualities of the materials utilized, such as swelling properties and particle size, have a major impact on how quickly pharmaceuticals escape from pellets. Differences in the final pellet quality might result from variations in material grades.

6. **Spheronizer Speed**

Pellet characteristics such as size, hardness, sphericity, and density are influenced by the spheronizer's operating speed. Pellets produced at higher speeds usually have less friability and better sphericity.

7. **The Extrusion Screen** Extrusion screen design and size are critical; bigger pellets are often produced by larger orifice sizes, and some modifications might affect the extrudate's surface properties and overall quality.

These elements work together to influence the pellets' physical characteristics and performance in pharmaceutical applications, as well as the process' overall efficacy and efficiency.

II. MATERIALS AND INSTRUMENTS

Materials:

Each and every reagent was analytical grade. Pantoprazole sodium's basic material was purchased from Metrochem API Private Limited, a pharmaceutical distributor. We bought disodium hydrogen phthalate from East India Chemials. We bought sugar pellets and non-pareil seeds from I.H. Pharmaceuticals Private Limited. HPMC and sugar syrup were bought from Chuzang-chuban and M B sugars and pharmaceuticals; magnesium carbonate was bought from Hari om chemicals; Eudragit L30 D was bought from Evonik industries; Diy chemicals supplied sodium hydroxide; Koel Colors Private Limited supplied brilliant blue supra; and Nishant Organic Private Limited supplied diethyl phthalate.

Table: Materials used in the formulation of delayed release pantoprazole sodium EC pellets

S.NO	Chemical name	Category
1	Pantoprazole sodium	Proton pump inhibitor
2	Disodium hydrogen phthalate	Alkalizing agent
3	HPMC (E5)	Binding agent
4	Magnesium carbonate	Antacid
5	Eudragit L-30 D	Enteric polymer
6	Sodium hydroxide	Alkalizing agent

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7	Diethyl Phthalate	Plasticizer
8	Brilliant blue supra	Colorant
9	Non pareial seeds	Core material
10	Sugar pellets	Core material
11	Sugar syrup	Binding agent

APPARATUS:

Volumetric Flasks (1000ml, 100ml, 10ml), Beakers (50, 100, 500ml), pipette (1, 2, 5, 10ml), Rubber bulb, Test tubes, Syringe (5ml), Micro Pipette (0.1ml), Measuring cylinder (10, 100ml), Glass rod, Conical flask.

Instruments:

Table 4: Different Equipment along with their models

S. No	Equipment	Make/Model
1	Weighing Balance	Shimadzu- ATY224
2	Pulvurizer	Rieco-4TH
3	Double cone blender	Upm-001
4	Colloidal mill	Accura-300
5	Coating pan	Chitra impex- 36
6	Fludized Bed Coater	DEBU (DB-30)
7	Shifter	VE- 12/1/8/24
8	UV-Visible spectrophotometer	Shimadzu UV-1800
9	Dissolution test apparatus	Labindia DS 8000
10	High performance Liquid Chromatography (HPLC)	Shimadzu LC-2030C
11	Sieve shaker	Harrisons-12

Figure 2: UV-Visible spectrophotometer, model 1800, Shimadzu.

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Fig: Fluidized Bed Coater


Fig: Shifter


Fig: Double Cone blender


Fig: Pulverizer machine

III. EXPERIMENTATION

UV-visible spectroscopic method for Pantoprazole sodium:

Standard Curve of Pantoprazole sodium in 0.1N Hcl:

- To make the standard stock solution, put 100 mg of the medication into a 100 ml volumetric flask and then add 100 ml of 0.1N Hcl.
- A volumetric flask containing 100 mg of the medication was filled with a few ml of 0.1N Hcl, and the volume was then filled with another 100 ml of 0.1N Hcl (1000 ppm).
- Take 1 ml of the aforesaid solution and add 10 ml of (100 ppm) 0.1N Hcl to make it up.
- Take 1 ml of the above solution, add 0.1N Hcl (10 ppm) to bring the volume up to 10 ml. Dilutions were created from the stop solution to yield concentrations of 10, 20, 30, 40, and 50 ppm.
- Using the photometric approach, the absorbance was measured at 290 nm. Based on the results, a calibration curve (standard plot) was created, with the slope and y intercept.

Standard curve in phosphate buffer (pH 6.8):

- To create the standard stock solution of pantoprazole (100 µg/ml), 10 mg of the medication was dissolved in 100 ml of

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phosphate buffer (pH 6.8) in a volumetric flask.

- A stock solution in phosphate buffer 6.8 containing 100 µg/ml was made. From the stock solution, various dilutions of 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 µgm/ml were made.
- Using the photometric approach, the absorbance was measured at 290 nm. Based on the results, a calibration curve (standard plot) was created, and the slope and y axis intercept were computed.
- A graph was created by plotting concentration on the X-axis and absorbance on the Y-axis. Within the selected concentration range, the graph complied with Beer Lambert's law.

Method:

Preparation of pantoprazole Enteric coated pellets

Pulverization:

The excipients and the medication are ground up independently. Install and run the pulverizer, then fill the hopper with the amounts of the outer layer and the sucrose blend separately. Pulverize the substance.

Pulverization-2: Charge the pantoprazole and sucrose mixture in order to set up and run the pulverizer.

Blending: In a double cone blender, the material from Pulverization-2, disodium hydrogen phthalate, and magnesium carbonate were combined. The remaining amount of medication was then put into the blender and stirred for ten minutes.

Binder solution preparation: After adding water and HPMC to the container and turning on the stirrer, the mixture was stirred for ten minutes. A nylon cloth was used to filter the solution before it was transferred to a different container.

Drug loading:

- Drug loading involves first setting up and running the coating pan before adding sugar spheres to it. Attach the air pressure tube to the spray gun.
- Next, attach the solution tube to the spray gun by inserting one end into the binder solution and the other end through a peristaltic pump. First, moisten the sugar sphere by using a peristaltic pump to spray the binder solution using a spray gun.
- First, load the drug-blended mixture using a scoop. Wet the binder preparation once more, dust the mix material.
- Proceed by gradually increasing the amount of mix material while continuously spraying. Once the mixed substance is finished, dust the outer layer.
- Resume the cycles until the blended and outer layer materials are finished. After every hour, note the observations.
- After the procedure is finished, use a scoop to carefully dump the pellets into the tray dryer's trays after wetting them with binder solution. After that, move the pellets to a tray dryer to finish drying.

Drying: The drug-loaded pellets from the pan were evenly distributed among the trays and allowed to dry for roughly three hours at 60°C. Following drying, the pellets were sieved to obtain the uniformly sized pellets and remove any particles.

Sieving: Pass the pellets through #12-#18 sieve.

Barrier Coating:

Preparation the barrier coating solution: Hypromellose 5cps (HPMC E5) is added to a container of filtered water while being constantly stirred.

Procedure:

- Setup and operate the FBC and then load drug loaded pellets into the product bowl of the FBC through loading port by setting the parameters in the HMI.
- Start the fluidization by starting process on, heating on and spray on in HMI. Allow the drug loaded pellets to warm up till the product temperature is not less than 40°C
- After warm up of the drug loaded pellets, start spraying the barrier coating solution and increase the inlet temperature, peristaltic pump RPM and atomization pressure gradually within limits.
- After completion of barrier coating solution, dry the pellets with the bed temperature 47±3ºC for 1 hour by reducing the inlet air temperature using controller.
- After drying allow the pellets to cool at room temperature by switching OFF the heating to reduce the temperature, and then unload the dried pellets.

Enteric coating:

Preparation of EC Solution: Diethyl phthalate, sodium hydroxide, Eudragit L-30D, and Brilliant Blue supra were placed in a jar. After 15 minutes of mixing in a homogenizer, they were filtered

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through nylon fabric and placed in a different container.

Procedure:

- The process involved charging the sub-coated pellets into the fluidization basket. Coating of enteric In order to maintain the materials' fluidized state, a solution of polymer is dispersed onto them while air was permitted to circulate inside the basket. For ten minutes, the fluidization process was maintained.
- After two hours of drying at room temperature, the coated pellets were sorted through a sieve to gather pellets of uniform size.

Fig: Pantoprazole sodium EC pellets

Table 5: Formulation table of Pantoprazole sodium EC pellets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1)Drug loading:									
Pantoprazole sodium	173.85	173.85	173.85	173.85	173.85	173.85	173.85	173.85	173.85
Disodium hydrogen phthalate	206.15	206.15	213.15	257.15	284.02	227.49	200.23	229.18	155.23
HPMC E-5	-	-	24.04	31.04	31.04	31.04	31.04	31.04	31.04
Magnesium carbonate	112.09	112.09	112.09	112.09	112.09	112.09	112.09	112.09	62.09
Non-pareial seeds	198.69	-	-	-	-	-	198.69	198.69	-
Sugar pellets	-	198.69	198.69	198.69	198.69	198.69	-	-	198.69
Sugar syrup	31.04	31.04	-	-	-	-	-	-	-
Water	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req
2)Barrier coating:									
HPMC	-	-	93.13	93.13	120	93.13	93.13	93.13	93.13
Water	-	-	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req
3)Enteric coating:									
L-30D	-	-	-	120.34	120.34	150	171.34	200	271.34
Sodium hydroxide	-	-	-	1.71	1.71	1.71	1.71	2	2.49

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Brilliant blue supra	-	-	-	8.5	8.5	8.5	8.5	8.5	8.5
Diethyl phthalate	-	-	-	3.5	3.5	3.5	3.5	3.5	3.5
Water	-	-	-	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req	Qua.req

IV. EVALUATION TESTS:

A) Gastric Resistance by HPLC:

Standard Preparation:

1. Weighing: Fill a 50 ml volumetric flask with precisely 45 milligrams of pantoprazole sodium.
2. Dissolution: Sonicate 25 ml of 0.1N NaOH until it dissolves entirely.
3. Dilution: Use 0.1N NaOH to dilute to volume and stir well.
4. Final Preparation: Pour 2 ml of this solution into a 25 ml volumetric flask, be sure to mix thoroughly, and dilute with the mobile phase to volume.

Preparing the Sample:

- Weighing the pellets: Weigh each pellet to 40 mg of pantoprazole, then place it in one of six dissolution bowls filled with 1000 ml of 0.1 N hydrochloric acid at 37°C ± 0.5°C.
- Pellets should be tapped with a glass rod to make sure they sink to the bottom.
- Dissolution Process: Turn on the device right away and let it run for two hours.
- Post-Dissolution Handling: Lift the paddles and drain the medium without losing any pellets after two hours have passed. Using a funnel, move each pellet into a 50 ml volumetric flask. Pellets should be dissolved by adding about 20 milliliters of 0.1N NaOH, sonicating until dissolved, then diluting with 0.1N NaOH to volume and stirring.
- Filtration: Use 0.45µ nylon syringe filter to filter the resultant solution.
- Preparing the Final Sample: Pour 2 ml of the clear supernatant into a 25 ml volumetric flask, dilute with mobile phase to volume, and swirl.

Methodology

- Fill the liquid chromatography system with 20 µl of filtered blank, five replicate injections of the standard preparation, and one injection of each sample preparation (G1–G6).
- Estimate the responses for the primary peaks after recording the chromatogram.

Calculation of Pantoprazole Release Percentage

Release of Pantoprazole in Acid Medium = % Pellet Assay − Acid Medium Content of Pantoprazole

%Assay of pellets − Content of Pantoprazole in Acid Medium = Release of Pantoprazole in Acid Medium

Pellets assay = Assay result in % w / w × 100

B) Dissolution by HPLC

- Weighing: Fill a 50 ml volumetric flask with precisely 45 milligrams of pantoprazole sodium.
- Dissolution: Sonicate 25 ml of 0.1N NaOH until it dissolves, then use dissolution media to dilute it to volume and mix well.
- Final Preparation: Pour 5 ml into a 100 ml volumetric flask, add the dissolving media to dilute it to volume, and thoroughly mix.

Preparing the Sample

- Weighing Pellets: Weigh an amount equivalent to 40 mg of Pantoprazole and transfer them into six dissolution bowls containing 1000 ml of equilibrated 0.1 N Hydrochloric Acid at 37°C ± 0.5°C.
- Pellets should be lightly tapped to settle them and get rid of air bubbles.
- Dissolution Process: Turn on the device right away and let it run for two hours. After two hours, remove the paddles and slowly drain the pellets without losing any. Then, add 1000 ml of equilibrated phosphate buffer (pH 6.8) and run for another forty-five minutes.
- Sample Withdrawal: Take samples halfway between the rotating blade's top and surface, sifting them through a 0.45µ membrane filter and throwing away the first milliliters.

Methodology

Add one injection from each sample preparation (D1–D6), five replicate injections of the standard preparation, and a filtered blank (20 µl) to the liquid chromatography.

Measure the main peak responses and record chromatograms.

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Calculation:

$$\frac{At}{As} \times \frac{Ws}{50} \times \frac{5}{100} \times \frac{1000}{Wt} \times \frac{100}{Assay} \times \frac{383.38}{405.40} \times P$$

C) Assay by HPLC:

- Weighing: Fill a 100 ml volumetric flask with precisely 45 milligrams of pantoprazole sodium.
- Dissolution: Sonicate 70 ml of methanol until it dissolves, then dilute with methanol to volume and stir well.
- Final Preparation: Pour 5 ml into a fresh 50 ml volumetric flask, dilute with the solvent mixture, and thoroughly mix.

Preparing the Sample

- First Sample Preparation: Accurately weigh 200 mg of pellets into a 250 ml volumetric flask. Add 200 ml of methanol, sonicate until it dissolves, dilute as necessary, and then filter through a 0.45µ nylon syringe filter.
- Pour 5 ml of the filtered supernatant into a fresh 100 ml volumetric flask, dilute with the solvent mixture, and thoroughly mix.

Methodology

Add one injection from each sample preparation (A1 & A2), five replicate injections of the standard preparation, and a filtered blank (20 µl) to the liquid chromatography.

Keep track of graphs and determine the primary peaks.

- For sample preparation-2, follow the same

Calculation:

$$\frac{At}{As} \times \frac{Ws}{50} \times \frac{5}{100} \times \frac{1000}{Wt} \times \frac{100}{Assay} \times \frac{383.38}{405.40}$$

a) UV spectroscopy determination of absorption maxima in 0.1N Hcl

The wavelength at which the most absorption occurred in the spectra of pantoprazole sodium was 290 nm. It was discovered that the correlation coefficient R2 was 0.999, which is quite close to 1.

Table 7: Calibration data of Pantoprazole sodium at 290nm in 0.1N Hcl

Concentration (µg/ml)	Absorbance
0	**0000 000000000000**
10	0.135± 0.528
20	0.276± 0.347
30	0.418± 0.641
40	0.556± 0.472
50	0.696± 0.234

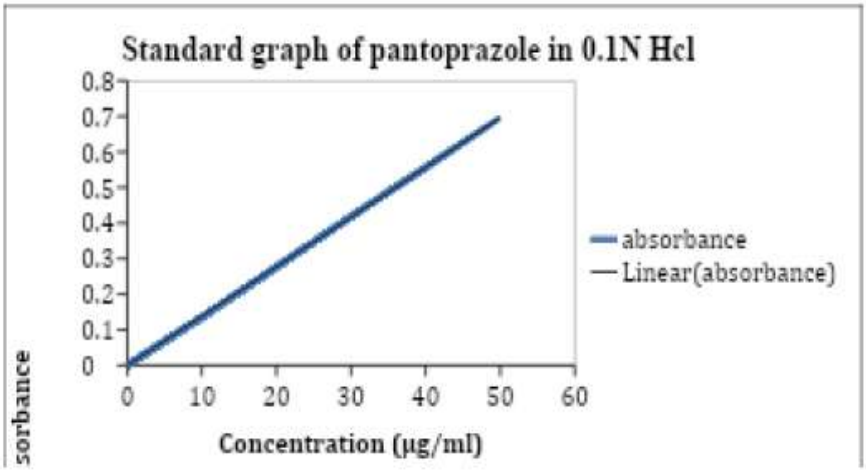

Figure: Standard graph of Pantoprazole sodium in 0.1N Hcl at 290nm

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Determination of absorption maxima by UV Spectroscopy in Phosphate buffer (pH 6.8)

The wavelength at which the most absorption occurred in the pantoprazole sodium spectrum was 290 nm.It was discovered that the correlation coefficient R2 was 0.9989, which is close to 1.

Table: Calibration data of Pantoprazole sodium at 290nm in buffer

S.NO	Concentration (µg/ml)	Absorbance
1	2	0.082± 0.326
2	4	0.149± 0.742
3	6	0.233±0.641
4	8	0.301± 0.845
5	10	0.372± 0.743
6	12	0.476± 0.572
7	14	0.549± 0.843
8	16	0.630± 0.562
9	18	0.698± 0.480
10	20	0.792±0.504

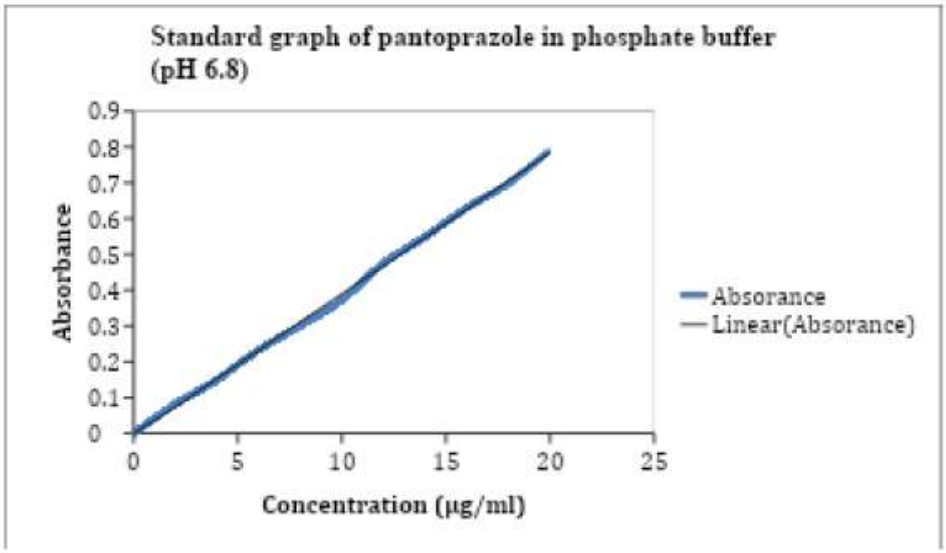

Figure: Standard graph of Pantoprazole sodium in buffer (pH 6.8) at 290nm

Table: Evaluation results of various parameters

Formulation	Angle of repose	Bulk Density	Tapped density	Carr's Index	Moisture content	Assay
F4	25.52	0.952	1.037	5.71	1.97±0.142	98.85±0.217
F5	25.48	0.937	1.032	5.47	1.95±0.179	98.23±0.261
F6	25.37	0.934	1.004	5.39	1.94±0.201	99.12±0.342
F7	24.23	0.928	0.996	5.21	1.91±0.097	99.39±0.198
F8	24.15	0.923	0.991	5.11	1.91±0.152	99.87±0.294
F9	23.52	0.915	0.989	4.96	1.88±0.087	101.17±0.302
Innovator	23.61	0.911	0.988	4.38	1.87±0.225	101.24±0.273

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Drug-excipient interaction study by using FTIR:

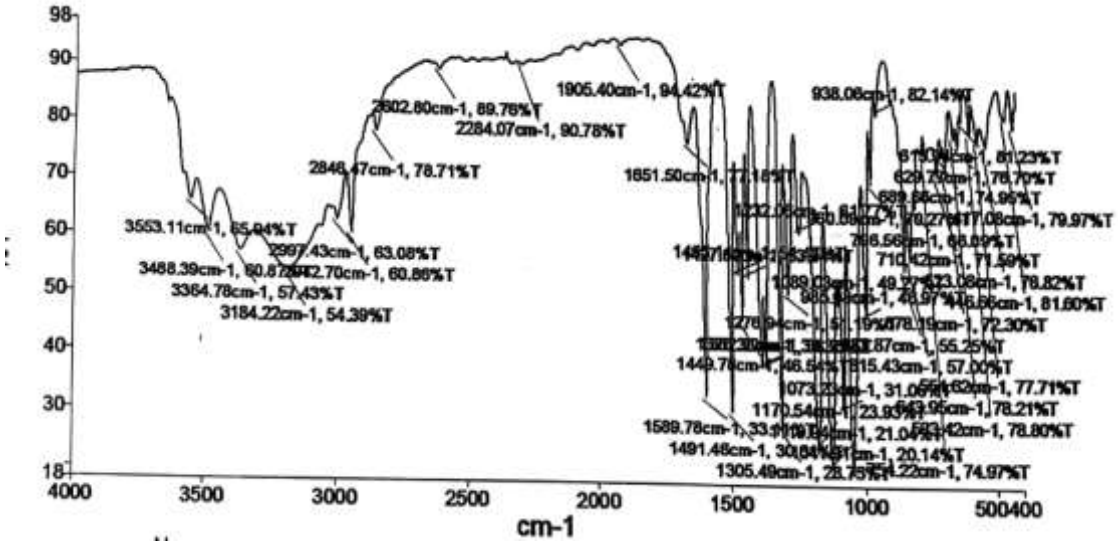

Figure: FTIR spectra of Pantoprazole

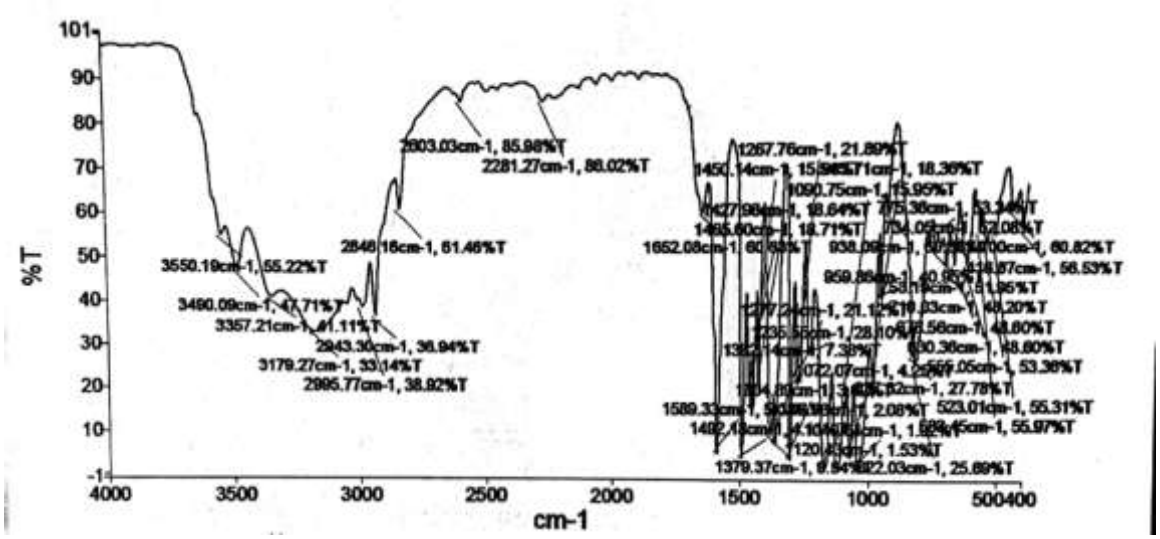

Figure: FTIR spectra of pantoprazole sodium

Resistance to Acid:

Table: Acid Resistance of pantoprazole sodium EC pellets

Innovator	F4	F5	F6	F7	F8	F9
97.36	76.34	80.5	86.42	89.43	92.17	98.03

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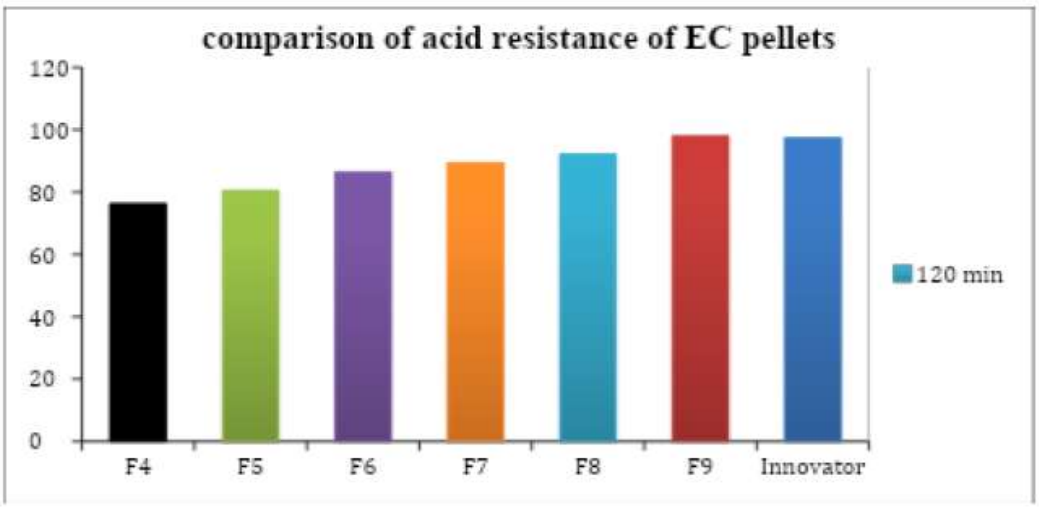

Figure: Acid resistance of pantoprazole sodium EC pellets in compared with innovator

Drug Release:

Table: Drug release of pantoprazole sodium EC pellets in acid stage

Time	Innovator	F4	F5	F6	F7	F8	F9
After 2 hrs	0.7	25.8	21.6	15.8	12.4	9.3	0.1

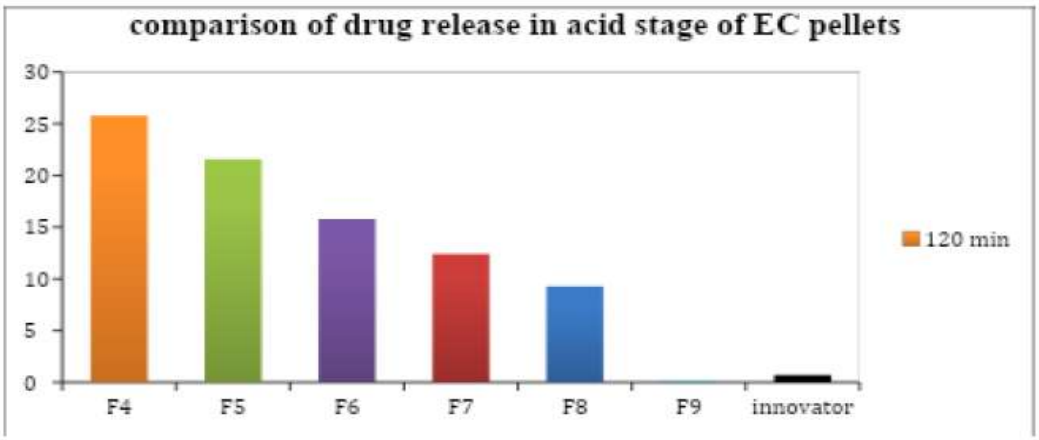

Fig: Comparison of percentage release of drug in acidic stage of pellets with the innovator

Table: In vitro dissolution in buffer stage

Time (min)	Pentablo c	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	22.28± 0.070	Pellets not having strengt h	pellets forme d as twins and dumb-	During sub coating pellets broken into fine	79.64± 0.084	68.79± 0.073	42. 24± 0.091	47.18± 0.080	39.32± 0.166	31.08± 0.071
10	42.61± 0.096				92.14± 0.095	75.03± 0.087	51.09± 0.163	56.23± 0.085	51.29± 0.091	53.64± 0.078
20	59.06± 0.084					97.42± 0.094	57.43± 0.076	61.45± 0.061	64.53± 0.082	72.17± 0.093

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30	78.03± 0.089		bell shaped	partiles			62.17± 0.139	69.05± 0.064	77.03± 0.082	86.54± 0.135
45	97.36± 0.145						68.42± 0.178	76.43± 0.075	89.17± 0.093	98.03± 0.152

The information in this table is displayed as mean ± SD, with n = 3.

Table: Comparative dissolution profile of enteric coated pellets (F6- F9)

Time (min)	%CDR (F6)	%CDR (F7)	%CDR (F8)	%CDR (F9)	Innovator
0	0	0	0	0	0
5	42. 24± 0.091	47.18± 0.080	39.32± 0.166	31.08± 0.071	22.28± 0.070
10	51.09± 0.163	56.23± 0.085	51.29± 0.091	53.64± 0.078	42.61± 0.096
20	57.43± 0.076	61.45± 0.061	64.53± 0.082	72.17± 0.093	59.06± 0.084
30	62.17± 0.139	69.05± 0.064	77.03± 0.082	86.54± 0.135	78.03± 0.123
45	68.42± 0.178	76.43± 0.075	89.17± 0.093	98.03± 0.152	97.36± 0.145

The information in this table is displayed as mean ± SD, with n = 3.

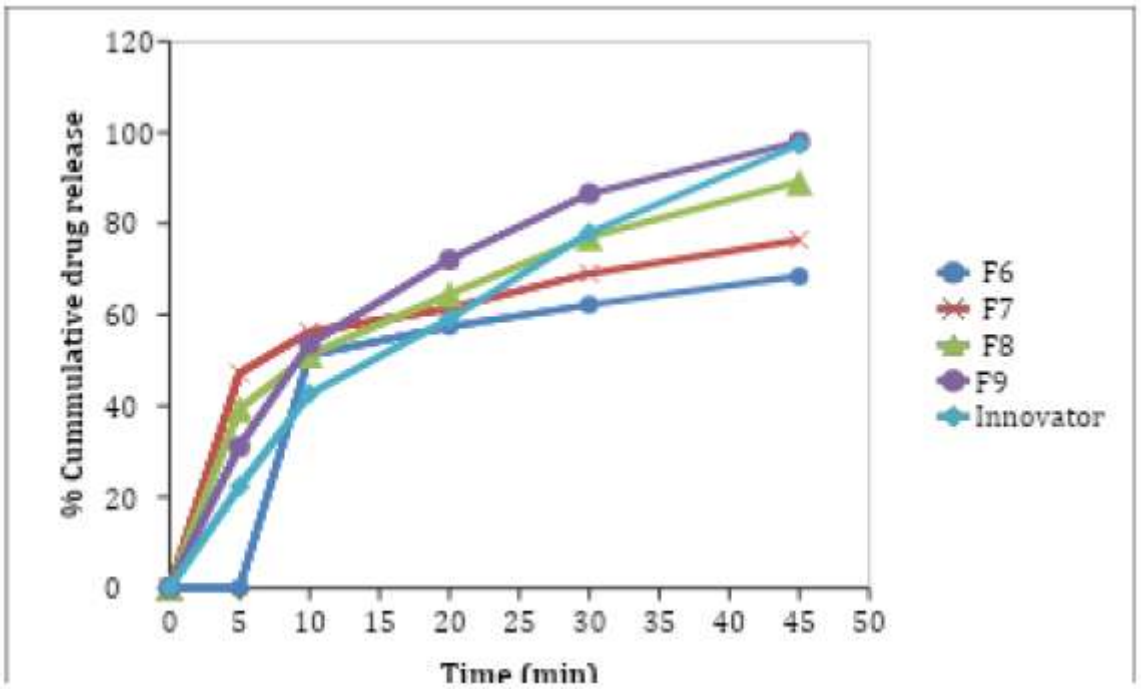

Figure: Comparative In vitro dissolution profile of Enteric coated pellets

Assay by HPLC:

Table: Assay results of F9 formulation was compared with the innovator

Assay limit	Assay (F9)	Assay(Innovator)
90-110%	101.17%	101.2%

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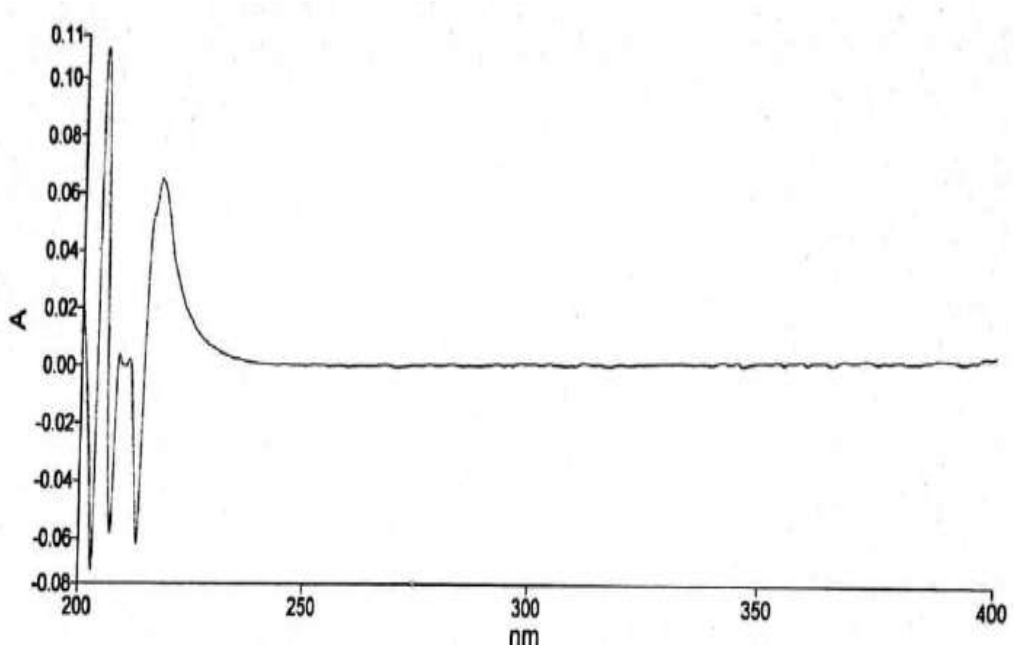
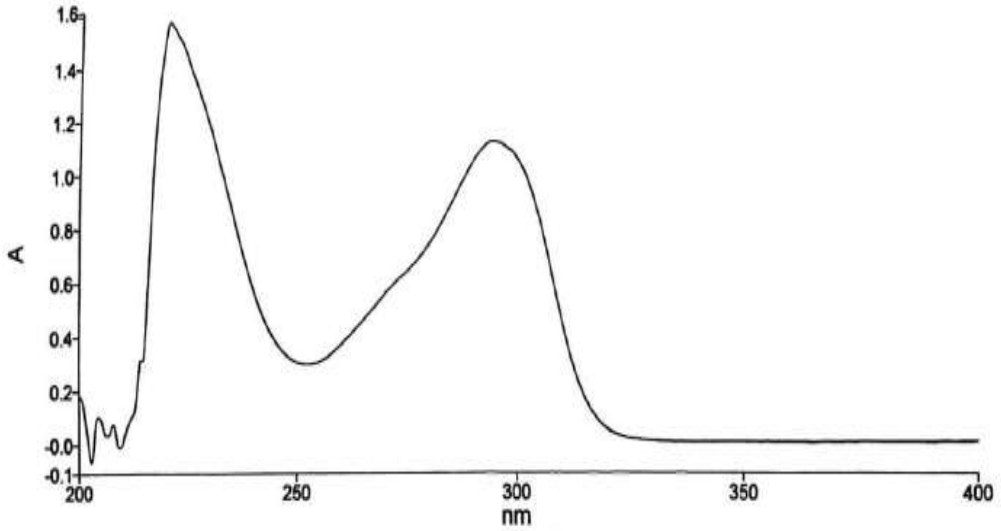
Chromatograms of optimized formulation:

Blank



Product name	Position (nm)	Intensity
Blank	204.5	0.1103

Standard



Product name	Position (nm)	Intensity
Standard	294.3	1.108
Standard	220.3	1.577

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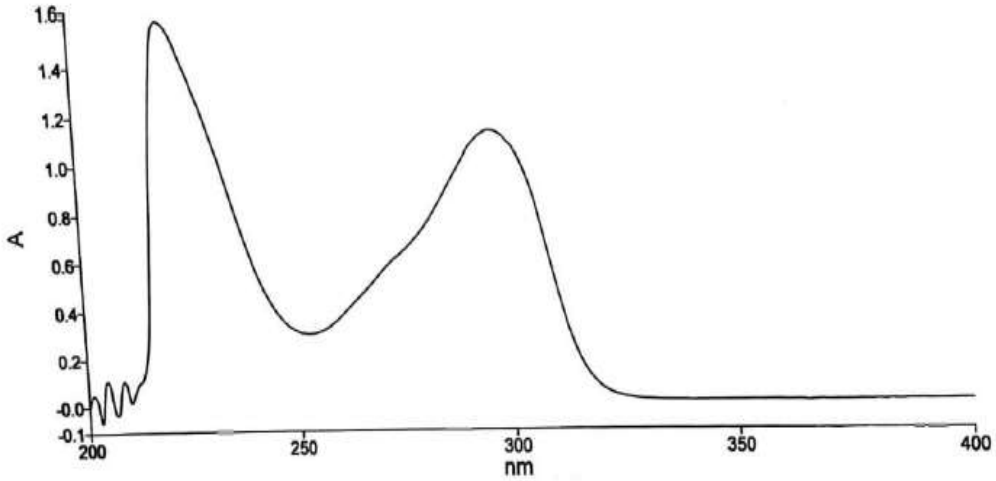
Sample:



Product name	Position (nm)	intensity
sample	295.1	1.110
sample	220.4	1.582
sample	204.5	0.1093

Stability studies:

According to ICH recommendations, stability tests are conducted on the chosen formulation for three months at 30°C and 65% relative humidity and 40°C and 75% relative humidity.

Parameter	Initial	1 month	2 month	3 month
Storage conditions:		30°C/ 65 % RH		
Appearance	good	good	good	good
% friability	0.60± 0.023	0.60± 0.023	0.59± 0.04	0.57± 0.04
Moisture content	1.96%	1.96%	1.92%	1.90%
Assay	101.17± 0.042	101.02± 0.042	100.47± 0.042	100.17± 0.02
Dissolution studies	Acidic stage : 0.1% Buffer stage :98.03%	Acidic stage : 0.1% Buffer stage :97.62%	Acidic stage : 0.1% Buffer stage :96.74%	Acidic stage : 0.1% Buffer stage :96.12%

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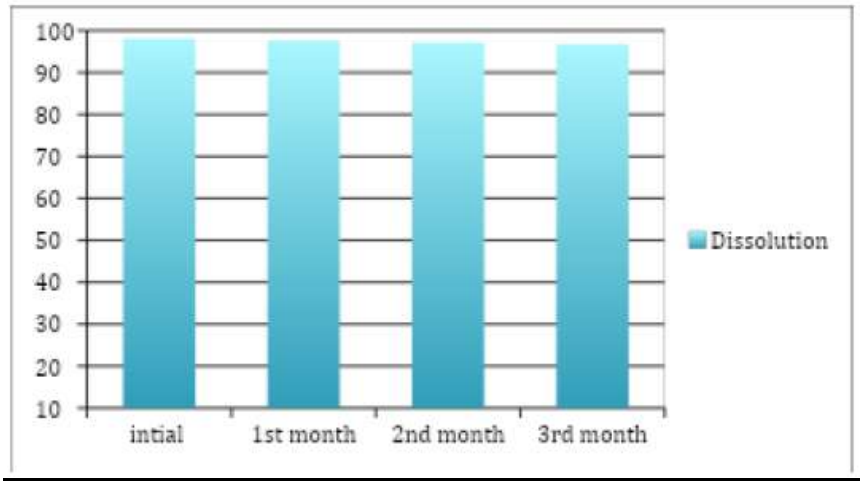

Figure: Dissolution profile of selected stability sample i.e. F9

CONCLUSION

The current study's goal was to create and assess enteric coated pellets with delayed release that were on par with the innovator product. Utilizing Eudragit L 30D and HPMC Phthalate as enteric polymers, different drug loading, barrier coating, and enteric coating compositions were used to create the formulations of pantoprazole delayed release pellets utilizing the enteric film coating procedure. The solution-suspension layering technique was used in FBP to carry out the formulation process. As an acid-labile medication, pantoprazole breaks down in the stomach's acidic pH. The formulation must postpone the release and provide it in the proximal small intestine in order to avoid the stomach. Enteric coating is one way to accomplish this. Enteric polymer was used in the study to postpone the release of pantoprazole.

Pre-formulation of the medicine and excipients, formulation, evaluation, and stability studies of pellets are all included in the study. Drug coating, sub coating (barrier coating), enteric coating, and the inert core material (sugar sphere) were applied.

Sugar spheres were loaded with drugs using various binders, such as HPMC, at varying concentrations. Drug-loaded pellets were subcoated to prevent direct contact with the enteric coating. Eudragit L30 D was used to apply enteric coating to pantoprazole pellets. The release profile and enteric-coated pellets were contrasted with those of Innovator. Plasticizer is a key component in pellet film production in enteric coating. F9 enteric coated pellets were determined to be the best after they were tested for assay, acid resistance and dissolution.

After evaluating these pellets, it was discovered that the outcomes were more comparable with innovator. After accelerated stability experiments and optimization, the formulation F9 was chosen because it demonstrated superior results and the highest cumulative drug release characteristics compared to the innovator. The formulation remained stable for three months under accelerated settings.

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