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# FORMULATION AND DEVELOPMENT OF PANTOPRAZOLE SODIUM PELLETS IP FOR RAPID ONSET OF ACTION.

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**ABSTRACT :**

Incorporating superior super disintegrates into the pellet core, using an appropriate enteric coating to shield the medication in the stomach, and optimizing the pellet's size and shape to promote rapid disintegration and absorption once it reaches the small intestine—possibly through he use of fluid bed granulation or extrusion spheronization for pellet manufacturing—are the key strategies for creating pantoprazole sodium pellets with a rapid onset of action.

A strong and specific proton pump inhibitor is pantoprazole. Oesophagitis, Zollinger-Ellison syndrome, gastro-esophageal reflux disease (GERD), peptic ulcers, and other GI hyper secretory illnesses can be effectively treated with it. Up to 85–90% of ulcer patients have immediate symptom improvement within an hour of starting medication. Its poor aqueous solubility and mediocre 50% bioavailability limit its absorption and dissolution rate, somewhat delaying the start of action. Sodium starch glycollate (SSG) and croscarmellose sodium are super disintegrates that are obtained by direct compression. All of the pills were evaluated and determined to be within official limits; the formulations' disintegration times ranged from 15 to 25 seconds.

Proton pump inhibitor Pantoprazole sodium is used as an antiulcer medication. The goal of the study was to create enteric-coated pellets of pantoprazole sodium. A thorough product literature analysis was conducted prior to formulation development in order to learn about the MUPS and the kinds of dosage forms that are currently on the market.

**Keywords:** Pantaprazole Sodium, Crospovidone, Croscarmellose sodium

## INTRODUCTION

In delayed release systems, the medicine is released at a predetermined time and location rather than immediately after consumption. Among other therapeutic objectives, this approach guarantees adequate absorption from specific intestinal regions, reduces gastric discomfort, and shields sensitive drugs from stomach fluids. Drugs that are known to cause stomach These systems frequently involve substances that cause distress, are broken down by stomach acid or intestinal enzymes, or are intended to have localized effects in the gastrointestinal tract.

For a variety of reasons, almost 50% of pharmacological medications are taken orally. Because it provides benefits such accuracy in dosing, patient compliance, convenience of administration, and versatility, this route of administration is thought to be the most popular.

One of the major formulation issues that arises with such oral products is undesirable taste.

The stomach, duodenum, or esophageal lining might develop a hole called a peptic ulcer. The terms "gastric ulcer," "duodenal ulcer," and "esophageal ulcer" refer to peptic ulcers of the stomach, duodenum, and esophagus, respectively. When stomach cells release acidic digestion fluids that erode the lining of these organs, an ulcer results. Millions of Americans suffer from peptic ulcer disease each year. One of the primary effects of proton pump inhibitors (abbreviated "PPI") is a significant and sustained decrease in the generation of stomach acid. These medications are used to treat a wide range of illnesses, including Barrett's esophagus, gastroesophageal reflux disease, laryngopharyngeal reflux disease, dyspepsia, and stress gastritis prevention. Proton pump inhibitors work by permanently inhibiting the gastric parietal cell's hydrogen/potassium adenosine triphosphatase enzyme system, often known as the H+/K+ ATPase or, more frequently, the gastric proton pump. Since the proton pump is the last stage of gastric acid production and is directly in charge of releasing H+ ions into the stomach lumen, it is a prime candidate to be inhibited.

Proton Pump Inhibitors (PPIs) are a widely used class of drugs for acid-related disorders. However, their long-term use poses risks such as gut dysbiosis and nutritional deficiencies. Integrating probiotics into PPI therapy offers potential to mitigate these issues.

***1.1The stomach's composition and operations***

At the cardiac sphincter, the stomach joins the oesophagus, and at the pyloric sphincter, it joins the duodenum. There are two curvatures in it. The fundus, body, and antrum are the three sections that make up the stomach. Protecting the gap between the stomach and the duodenum, the pyloric sphincter is located at the distal end of the pyloric antrum. The pyloric sphincter is relaxed and open while the stomach is empty, and it is closed when food is present.

Short-term storage permitting the terminal ileum to produce the intrinsic factor required for the absorption of vitamin B12, prepare iron for absorption, and regulate the transit of stomach contents into the duodenum. The pyloric antrum pushes tiny jets of stomach contents through the pyloric sphincter and into the duodenum1 when the chyme is sufficiently acidified and liquefied.

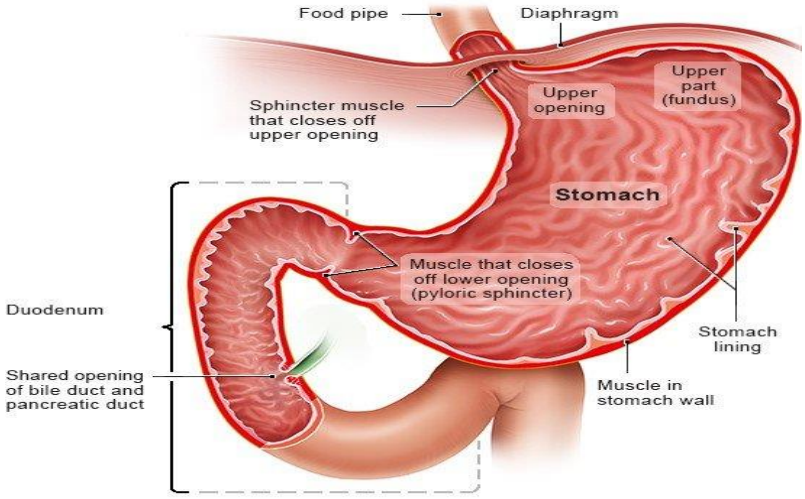



**Figure-1 Structure and functions of the stomach**

***1.2Formation of acid-***

Every day, the stomach secretes roughly 2.5 liters of gastric juice. Proenzymes such prorennin and pepsinogen, which are produced by the chief or peptic cells, and hydrochloric acid (HCl) and intrinsic factors, which are released by the parietal or oxyntic cells, are the main exocrine secretions.The surface cells of the stomach mucosa are abundant in mucus-secreting cells. Bicarbonate In contrast to the much more acidic environment (pH 1-2) in the lumen[2], ions are also released and held in the mucus, forming a gel-like protective barrier that keeps the mucosal surface at a pH of 6-7. H+ secretion by parietal cells is the common endpoint of the intricate, ongoing process of gastric acid secretion, which is influenced by a number of central and peripheral variables.

Acid secretion is controlled by endocrine (gastrin), paracrine (histamine), and neuronal (acetylcholine, ACh) mechanisms. The fundus of the stomach and the basolateral membrane of the body's parietal cells have their particular receptors (M3, H2, and CCK2 receptors, respectively). A GPCR called the H2 receptor triggers the Gs-adenylylcyclase-cyclic AMP-PKA pathway.

***Pellets[5]:***

Made by combining fine powders or granules of bulk medications and excipients using the proper processing equipment, pellets are small, free-flowing, spherical or semi-spherical solid units, usually ranging in size from 0.5 mm to 1.5 mm. They are primarily meant for oral administration. Although there are numerous ways to manufacture pellets, compaction and drug-layering are now the most popular techniques.

1. Pellets must fulfill the following specifications regardless of the manufacturing method. They should have a smooth surface and be almost spherical; these are ideal qualities for a future film covering.

2. The range of particle sizes should be as small as feasible. It is believed that pellets between 600 and 1000mm.

3. To maintain the final dosage form's size within acceptable bounds, the pellets should contain the maximum amount of the active component. They ought to have a smooth surface and be almost round.

4. The range of particle sizes should be as small as feasible. It is believed that pellets between 600 and 1000 mm are the ideal size for usage in medicinal applications.

**Some of the few successful applications of homogenous pellets with smooth surfaces are highlighted below:**

1. A better look for the merchandise.
2. Pellets can be coated with various medications to allow for a regulated rate of release.
3. Better distribution is made possible by a bigger pellet surface area in the case of instant release products.
4. Chemically incompatible compounds can be encapsulated, molded into pellets.
5. It is used to prevent powder dusting in the chemical industry.
6. The pellet form can be used in a variety of ways. For instance, sustained release.
7. Pellets guarantee better flow characteristics and manufacturing and formulation development flexibility.

**The following are the most typical benefits of pelletization[6]:**

- The product's look has improved, and its core is elegantly pharmaceutical.
- Pelletization provides versatility in the development and design of dosage forms.
- Pellets are less likely to dump doses.
- It lowers the concentration of irritative medicines locally and increases a drug's safety and effectiveness.
- Pellets provide less fluctuation in transit time and stomach emptying rate.
- In G.I.T., pellets freely dispersion, maximizing medication absorption and minimizing peak plasma fluctuation.
- Pellets guarantee better flow characteristics while developing formulations.

## AIM AND OBJECTIVE

***AIM-***

A common proton-pump inhibitor (PPI) in both hospital and outpatient settings is pantoprazole. The Food and Drug Administration (FDA) has approved pantoprazole for the treatment of a number of disease processes, including pathological hypersecretory conditions like Zollinger-Ellison syndrome and erosive esophagitis linked to gastroesophageal reflux disease. Additionally, the FDA has approved it for the maintenance of healing in erosive esophagitis. In addition, pantoprazole has a number of off-label applications, such as eliminating Helicobacter pylori bacteria and avoiding NSAID-induced ulcers and/or recurrent bleeding from peptic ulcers. Pantoprazole may be used to prevent stress ulcers in critically ill patients. Both adult and pediatric populations can safely get this drug. This exercise goes over how pantoprazole is used and emphasizes the need of the interprofessional team in treating patients with

Peptic ulcer diseases. A substituted benzimidazole derivative called pantoprazole targets the proton pumps in the stomach, which are the last common channel for the secretion of gastric acid. The medication inhibits the production of stomach acid for a long time by covalently attaching itself to the proton pumps. However, the medication irritates the stomach mucosa, which might result in nausea and vomiting. In the stomach's acidic environment, pantoprazole degrades quickly, but in alkaline settings, it remains stable enough. Consequently, the gut should get pantoprazole. In order to address the issue of drug stability in the stomach and release the medication in the intestine, pantoprazole may be formulated as an enteric coated tablet.

***2.2 Objectives:***

- Identify the mechanism of action of pantoprazole.
- Describe the adverse effects of pantoprazole.
- Outline the contraindications of pantoprazole.
- Explain the interprofessional team strategies for improving care coordination and communication to advance the treatment of peptic ulcer disease and improve outcomes.

***2.3 PLAN OF WORK***

**Pre-formulation studies**

a) Physical appearance
b) Melting point
c) Solubility study
d) FTIR
e) HPLC

**Formulation of Enteric coated pellets using fluid bed equipment.**

**Optimization of parameters**

a) pH
b) Homogenization time

**Studies conducted in vitro**

a) Drug release profile in vitro

b) PH

c) Assay

d) Stability study

## ANTICIPATED STUDY RESULTS-

The goal of the study was to address the significant issue of excessively high drug prices. Prescription drug costs put healthcare budgets at risk and reduce funds available for other sectors that require public investment. Pharmaceutical corporations argue that maintaining innovation requires high medicine prices. However, the potential to demand exorbitant rates for each new drug may hold down innovation.

Additionally, choosing a medicine to begin the research was challenging. However, acidity and heartburn are among the most prevalent issues nowadays. Drug selection was therefore based on daily issues. pantoprazole (PPI) relieves the patient by inhibiting the production of excess stomach acid.

Methyl acrylic acid and ethyl acrylate copolymer dispersion was the latest formulation using Drug-coat (polymer). The formulation is rather costly, which raises the cost of the medication. Therefore, a novel formulation was created by substituting DCPD (di-calcium phosphate di-hydrate) for the already utilized polymer. After DCPD was examined, a good polymer and filler were discovered. In addition, it was significantly less expensive than drug-coat. Near the conclusion, at the enteric coating stage, the replacement was made.

- It is anticipated that the new formulation's results will fall within the range.
- Creating a formulation that is economical for both individuals and the business.
- Enhancing the medication's medicinal effects.
- To create a delayed release enteric coated formulation that releases the medication under ideal circumstances and remains stable in an acidic environment.
- Lowering the frequency of dosing in order to reduce the possibility of dosage dumping.

## DRUG AND EXCIPIENT

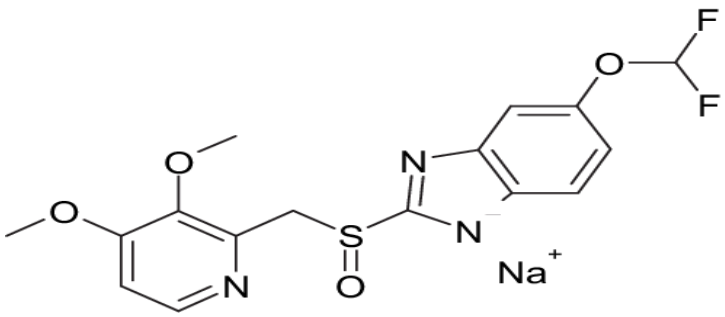
**PANTOPRAZOLE** [25, 26]

**Chemistry**

Chemically speaking, sodium 5-(difluoromethoxy)-2[[(3,4,dimethoxy-2pyridinyl)methyl] sulfinyl] is what pantoprazole sodium sesquihydrate is. -1H sesquihydrate of benzimidazole.

**Molecular formula:** 1.5 H2O C16H15F2N3O4S

**Weight in moles:** 432.4 gm/mol.




**Structure of pantoprazole sodium**

By covalently attaching to the (H +,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell, pantoprazole, a proton pump inhibitor (PPI), inhibits the last stage of stomach acid generation. Regardless of the stimulus, this action results in the suppression of both basal and induced stomach acid output. For all studied doses, the antisecretory effect lasts longer than 24 hours as a result of binding to the (H +, K +)-ATPase.

***Pellets' excipients:***

Pharmaceutical dosage forms are supplemented with formulation aids or excipients primarily to ensure adequate drug distribution to the target location, to give the dosage form advantageous properties, and to make product manufacturing easier. The excipients used in pellet dosage forms are usually the same as those used in tablet or capsule formulations because pellets are meant to be taken orally.

Example- Disintegrates, surfactants, excipients, adjusting pH, separating agents, and spheronization

**Table 1: Commonly used Excipient examples**

| | |
|---|---|
| **FILLER** | MCC, Lactose, Mannitol, Starch, and Sucrose |
| **BINDER** | Gelatin, Starch, MC, PVP, HPC, and HPMC |
| **LUBRICANT** | PEG, Magnesium Stearate, Glycerin, and Calcium Stearate. |
| **AGENT OF SEPARATION** | Silicon dioxide, Talc, and Kaolin. |
| **DISINTEGRANT** | Alginates and Sodium Croscarmellose |
| **ADJUSTER FOR PH** | Meglumine, Phosphate, and Citrate. |
| **THE SURFACTANT** | SLS and Polysorbate |
| **ENHANCER OF SPHERONIZATION** | MCC and Sodium CMC |
| **GLISTENING** | Mg. Stearate, Talc, and Starch. |
| **MODIFIER OF RELEASE** | Shellac, Carnauba wax, and Ethyl cellulose. |

**Materials for enteric coatings:**

Enteric coatings function by being selectively insoluble compounds that dissolve at the higher pH of the small intestine but not in the stomach's acidic fluids. The majority of enteric coatings are insoluble in liquids with a pH below 5.5. Enteric coatings that are frequently used can be made from the following:

Example- acetate copolymers made of methacrylic acid; Hydroxypropyl methyl cellulose.

## MATERIALS AND METHODS

**TECHNIQUES FOR MAKING PELLETS-**

In the pharmaceutical sector, the two most popular pelletization methods are compaction and drug stacking. Extrusion and spheronization are the most often used compaction procedures. But lately, melt pelletization has been widely employed to create compaction pellets with a different kind of machinery, like a high-shear mixer. Pharmaceutical pellets are also developed using other pelletization techniques, such as globulation, balling, and compression, but on a smaller scale.

**Powder layering:**

Using binding solutions, powder layering is the process of applying consecutive layers of dry drug and Excipient powders to prepared nuclei or cores. Because powder layering entails applying dry powders and binding agents simultaneously, specialist tools like a spheronizer are needed. In order to prevent powder loss beneath the product chute before it is scooped up by the wet mass of pellets that is being layered, the main need in this procedure is that the product container have solid walls without any perforations.

**Solution/suspension layering:**

This technique entails covering the starter/non-pareil seeds—an inert substance—with consecutive layers of drug substance and binder suspensions or solutions, or crystals or granules of the same medication. Actually, solution or suspension layering technology can use the coating procedure used in general. As a result, this process has been employed to produce pellets using centrifugal granulators, wurster coaters, fluidized beds, and standard coating pans. The type of equipment utilized has an impact on both the process's efficiency and the quality of the pellets that are generated.

**Pelletization via extrusion and spheronization[8]:**

This method entails first creating extrudes from the powder material, which are subsequently transformed into beads by use of a spheronizer. Any type of powder could be used as the powder material, including detergent powder, nuclear powder, food component powder, ayurvedic powder, and medicine powder. It is possible to create beads as fine as 0.6mm.

**Other methods of pelletization:**
Pharmaceutical pellets are also prepared using other pelletization techniques, such as globulation, cryopelletization, balling, and compression, but on a smaller scale.

## METHOD OF CORE PELLETS PREPARATION

The extrusion and spheronization methods were used to create the core pellets.After precisely weighing and sifting the necessary amount of pantoprazole sodium through sieve 30, a blend was created using microcrystalline cellulose, sodium carbonate, sodium lauryl sulphate, hydroxyl propyl methyl cellulose, and disintigrant (crosspovidone or crosscarmelose sodium). Talc and magnesium steareate, antitacking agents, were run through sieve 60. In purified water, hydroxyl propyl methyl cellulose was dissolved. Additionally, it serves as a granulating fluid in granulation processes. After thoroughly mixing all the materials and adding the HPMC solution, the produced wet mass was run through an extruder to generate cylindrical extrudates, which were then placed in a spheronizer to smooth them out. The LOD of the wet pellets was evaluated after the extrudate rotated in a spheronizer for 10 minutes at various RPMs of 75, 100, and 125. The pellets were dried using a fluid bed dryer at a temperature lower than 40 °C.

**Parameters:**

- The LOD of wet mass is 30%.
- The LOD of wet pellets is 27%.
- LOD of pellets that have been dried: 1.5%

## RESULTS

**OUTCOMES OF THE PRE-FORMULATION ANALYSIS.**
**The preformulation**
**Physical attributes**
**1) CALCULATING THE TAP AND BULK DENSITIES**

After carefully pouring a precisely weighed amount of the powder (W) into the granulated cylinder, the volume (Vo) was measured. After that, a lid was placed over the graduated cylinder.placed into the bulk density equipment, which was configured for 500, 750, and 1250 taps (density determination).The volume (Vf) was then measured, and the process was repeated until the two subsequent readings were equal. The calculations were used to determine the bulk density and the tapped density.

**W/Vo for Bulk Density**
**W/Vf Tapped Density**
**Where W is the powder's weight.**
**Vo: The starting volume**
**Vf: The last volume.**

The powdered pantoprazole's bulk density was 0.39 grams per milliliter.
It was discovered that the tap density of pantoprazole powder was 0.62g/ml.

**2) Hausner ratio:**

- It measures the powder's flow characteristics by dividing .
- Density of taped to bulk.
- Tapped density divided by bulk density is the Hauser ratio.

| NO | Hausner ratio | Properties |
|---|---|---|
| 1 | 0-1.2 | Free flowing |
| 2 | 1.2-1.6 | Cohesive powder |

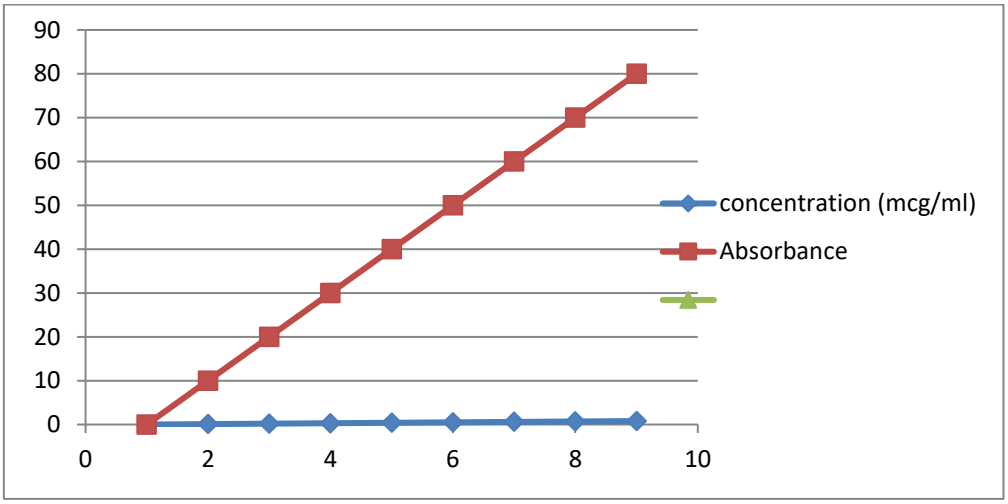
*Table No.1:* **Range of hausner ratio and its properties**

**2) TYPICAL PANTOPRAZOLE SODIUM SESQUIHYDRATE CURVE-**

| Concentration | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.131 |
| 20 | 0.272 |
| 30 | 0.414 |
| 40 | 0.552 |
| 50 | 0.692 |

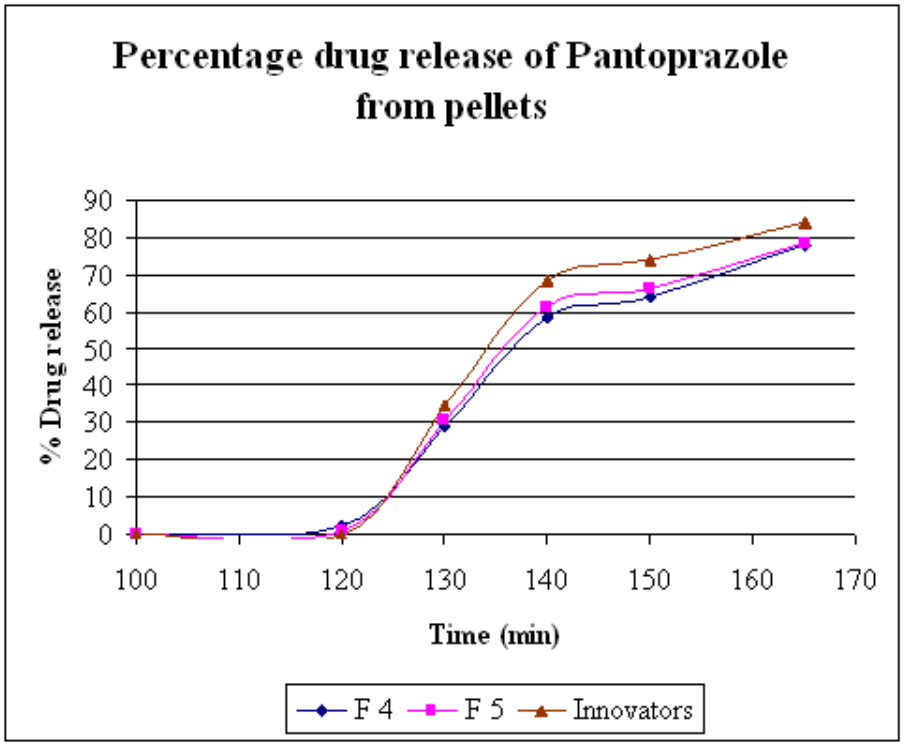
**Table No.2 Conc. and absorbance for standard curve**

**Graph 2.Std curve for enteric-coated pellets of pantoprazole sodium sesquihydrate.**




**3) DISSOLUTION TEST IN VITRO-**

| Media Dissolution trials | Sampling Time | Drug release percentage across | | | | | USP Details |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F 5 | |
| 0.1 N HCl | 2hr | ---------- | | | 2.5% | 1% | NMT 10% drug release |
| 6.8 pH phosphate buffer | 10min | F1,F2,F3 trial batches | | | 29.% | 30.7% | |
| | 20 min | were partially or fully | | | 58.% | 61.5% | |
| | 30min | Dispersed in 0.1 N HCl | | | 64% | 66.2% | |
| | 45min | ---------- | | | 77.% | 78.2% | NMT 75% drug release |




**Graph 1:** Pantoprazole Sodium Sesquihydrate Enteric Coat Pellets Released In Vitro.

**3) DESCRIPTION**: round, blue in color, with pellets coated in enteric.

**4) DIMENSIONS**: Using a vernier caliper, determine the pellets' size, which ranges from 1.28 to 1.40 mm.

**5) HARDNESS**: Dr. Schieuniger's hardness tester measured the pellets' hardness, which ranged from 9 to 17 N.

| **Formulation** | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|
| **Hardness** | 9N | 10N | 14N | 17N | 17N |

**Table No. 12 - Hardness of pellets of various formulations.**

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