FORMULATION AND EVALUATION OF OMEPRAZOLE PELLETS BY USING FLUIDIZED BED PROCESSOR

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ABSTRACT

The current study aims to develop and analyze delayed release Omeprazole pellets using a fluidized bed processor. Using an enteric film coating method, different drug loading, barrier coating, and enteric coating compositions were used to create the different formulations of Omeprazole delayed release pellets. Two types of polymers were employed in the formulation: HPMC K30 and HPMC E5. These polymers were utilized in the production of a capsule designed to have a long-lasting effect by attaching to the intestinal mucosa and relieving an active duodenal ulcer. Omeprazole is an enzyme H+/K+ ATPase inhibitor that is selective and non-competitive. Enteric coated dosage forms are developed to shield the substance from the effects of stomach acid and to stabilize it in low pH circumstances when administered orally. In the formulation of batches, there are variations in the polymer concentration. Therefore, the two elements are addressed in factorial design 2^2. FTIR spectroscopy was utilized to investigate the interaction between the excipients and omeprazole. To study the release rate retarded effect, four suggested formulations (F1–F4) were prepared using different amounts of polymers. The weight fluctuation, particle size determination, flow characteristics, and drug content of the pellets were then assessed. Pharmacopeial criteria were met by every formulation. All batches created by the procedure for drug stacking by employing a fluidized bed processor.

Keyword: *Omeprazole, HPMC, Enteric, Delayed, Fluidized bed Processor*

INTRODUCTION:

The main purposes of delayed release products are to shield the medication from gastric secretions, lessen the discomfort that certain medications cause to the stomach, or make it easier for medications that are better absorbed from the intestine to pass through the digestive tract. A peptic ulcer is a sore on the duodenum or stomach lining. Pepic ulcers are found in the stomach are called as gastric ulcers; the duodenum is called duodenal ulcers. Peptic ulcers are caused by acid and pepsin (an enzyme) produced in the stomach.

Pellets are aggregates of finely ground pills or particles of whole medications and patients. They are mainly meant to be taken orally and are made up of tiny, freely flowing, spherical or semi-spherical solid units that range in size from around 0.5 mm to 1.5 nun. Pellets are another term for tiny, sterile cylinder implants made by compressing medicated masses. Pellets can be prepared in a variety of ways, the most popular being the compaction and drug-layering methods.[1]

Advantage:

1. When it comes to the design and development of oral dosage forms, such as suspension, sachet, tablet, and capsule, pellets provide a great deal of versatility.
2. Pellets offer enhanced flow characteristics that support the creation of formulations, such as the ability to fill capsules easily and without experiencing any issues (leading in a consistent and repeatable fill weight of capsules).
3. Dosage emptying is less likely with pellets.
4. They can minimize local mucosal irritation caused by some irritating medications, maximize drug absorption, and spread easily throughout the GI tract.
5. There is less fluctuation in the intestinal transit time and stomach emptying rate with pellets.

Disadvantages:

1. Pellets range in size from 1 to 2 mm, albeit this depends on the formulation.
2. Low drug loading but a correspondingly greater requirement for excipient.
3. Inadequate efficiency and repeatability in manufacturing.
4. An abundance of process variables.
5. Multiple stages of formulation. [6,7]

Enteric Coatings: To treat several intestinal illnesses and enhance systemic absorption of medications that are unstable in the stomach, oral site-specific drug delivery devices have garnered a lot of attention lately. The creation and optimization of oral medication administration is sometimes impeded by the gastrointestinal tract's surroundings and diverse absorption pathways, which provide challenges for formulation scientists. It is possible to apply an enteric coating to a solid dosage form to deliver a therapeutic substance into the digestive area. Many strategies, such as pH-sensitive drug release and time-controlled drug release, have been tried and documented during the past ten years to an effort to create new techniques for site-specific drug release.

Enteric coating is caused by the following factors:

1. To shield medications that are acid-labile from the stomach acid.
2. To prevent nausea and gastrointestinal distress brought on by medication sensitivity.
3. To provide medications meant to work locally in the intestines.
4. To deliver pharmaceuticals in their most concentrated form to the main absorption location in the small intestine where they are best absorbed.
5. To provide repeating actions with a delayed release component.
6. Prevent the medications from being harmed by the contents of the stomach; several medications, such as omeprazole and pantoprazole, are prone to hydrolyzing in acidic environments. [2]

FLUIDIZED BED PROCESSOR

Figure no.1 Fluidized Bed Processor

Principle Of Fluidization

The principle of operation of fluidized systems is grounded on the fact that if a gas is allowed to flow through a bed of particulate solids at haste lesser than the settling haste of the patches and lower than the terminal haste for curvaceous conveying and equal to the minimal haste of fluidization (V mf), the solids get incompletely suspended in the sluice of overhead moving gas. The gas sluice negates the gravitational pull due to the weight of patches to enable the suspended state of the solid. The attendant admixture of solids and gas behaves like a liquid and therefore correctly solids are called Fluidized. The solid patches are continually caught up in orbits and fall back in an arbitrary boiling stir so that each fluidized flyspeck is girdled by the gas sluice for effective drying granulation or coating purposes. In fluidization, there occurs a violent mixing between the solids or gas performing in invariant conditions of temperature, composition, and flyspeck size distribution throughout the bed [3]

Applications of Fluid bed technology:

A. **Fluid bed drying** is an especially effective way of drying solids. During fluidization, liquid is withdrawn from the entire face of every single flyspeck. The advantages are excellent heat exchange and ideal drying time.
B. **Granulation/ agglomeration** in the fluid bed is an ultramodern system of creating granulates from grease paint-disusing liquid islands. The scattered liquid can be water, an organic detergent, or another binder. The wettest granulates are dried or cooled. As a result, the agglomerates are loose, have a low bulk viscosity, and are outstandingly answerable in water.
C. **film coating** widely influences product characteristics through the operation of defensive flicks. A veritably invariant operation of the coating material is important during coating. The coating must give an absolute seal without mechanical damage or gashes. Film coating is a technically demanding process that can be used over a veritably wide diapason.
D. **Pelletizing**: During pelletizing, grease paint is mixed and moistened. At the same time, a detergent or binding agent can be added. The centrifugal stir produces agglomerates which are spheronized into uniform, thick bullets. picky product characteristics can be realized through direct pelletizing or layering [3,4,5]

DRUG PROFILE

OMEPRAZOLE

Omeprazole is a proton pump inhibitor used to treat GERD-related symptoms such hypersecretion of gastric acid and heartburn, as well as to aid in the repair of ulcers and tissue damage brought on by H. pylori infection and gastric acid.

Background:

The proton-pump inhibitor omeprazole was first authorized by the FDA in 1989 and was prescribed to address conditions linked to stomach acid. GERD, peptic ulcer disease, and various other conditions marked by excessive stomach acid output are examples of these illnesses. Following its licensure, several new proton pump inhibitor medications were developed. This medication was the first in its class to be clinically beneficial. Due to its widespread usage in both adults and children, omeprazole is often well-tolerated and effective.

Structure

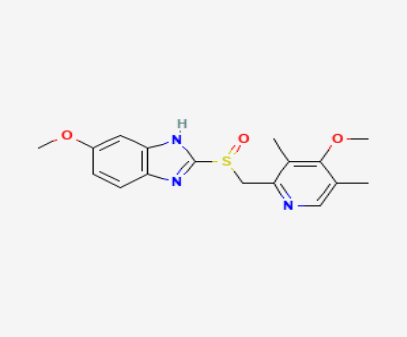

Fig. no.1 Structure of Omeprazole

Generic name: omeprazole

Brand names: First Omeprazole, Omeprazole + SyrSpend SF Alka,PriLOSEC OTC, Zegerid (Original Formulation)

Dosage forms: oral delayed release capsule (10 mg; 20 mg; 40 mg)

Drug class: Proton pump inhibitors.

Chemical Formula: $C_{17}H_{19}N_3O_3S$

Melting point: 146°C (313°F)

Biopharmaceutical classification system (BCS): Class II

Wavelength: 275

pharmacokinetic profile:

- **Bioavailability:** 35–40%
- **Half-life:** >1 hr.
- **Routes:** Oral and intramuscular form
- **Metabolism**: gastric enzyme CYP2C19

Indications and Uses: Omeprazole is a proton pump inhibitor with actions. Once-daily doses should be taken in the morning in the treatment of gastro-oesophagealreflux disease. The usual oral dose is 20 to 40 mg once daily for 4 weeks.[8-9]

MATERIAL AND EQUIPMENT:

Table No.1: List of equipment used for study.

Sr no	name of equipment	Manufacturer	Model
1	Electronic weighing balance	Weser	PGB-300
2	UV-Spectrophotometer	Equiptronics	EQ-826/ EQ-824
3	Fluidized bed processor	ACG-Miniquest-F	Miniquest
4	Dissolution Apparatus	Electro lab USP TDT-08L	
5	Flourier Transform-Infrared Spectroscopy Instrument	Bruker	Alpha II

Table No.2 List of chemicals used for the study.

SR NO	Material	Descriptions
1	Omeprazole	Active pharmaceutical ingredient
2	Sugar spheres	Inert cores
3	Hydroxypropyl methyl cellulose HPMC E5	Film former
4	HPMC k30	Coating material
5	talcum	adsorbent
6	methanol	Solubilizing agent
7	Distilled water	Solubilizing agent

EXPERIMENT WORK

1. **Preformulation studies**

Preformulation can be defined as a process in the research and development process in which scientists determi ne the physical, chemical, and mechanical properties of a new drug substance to develop a stable, safe and eff ective formulation.

Organoleptic properties

- **Solubility analysis:**

Method: Appropriate quantity of drug was weighed and added to the suitable volume of solvent like methanol, ethanol.

Result: The omeprazole is completely soluble in methanol which is used as solvent agent.

- **Melting point**

The melting point of omeprazole was determined by capillary method. A small amount of omeprazole was taken and placed in the device and the melting point was determined according to standard.

Result: Standard Range: 146°C- 152°C Observed Range: 138°C - 144°C

- **Compatibility tests between drugs and excipients.**

An effective analytical tool for examining the chemical interactions between the medication and the other excipient in the formulation is the infrared spectrophotometer. Under an infrared spectrophotometer, the 10 mg medication and excipient are scanned. Using an FTIR spectrophotometer, the spectra was captured by scanning the 4000-400 cm wavelength range.

UV spectroscopy, or ultraviolet-visible

To prepare a stock solution of 1000 µg/ml, 100 mg of omeprazole was precisely weighed and then dissolved in 100 millilitres of filtered water. To create a working standard solution with a concentration of 100 µg/ml, the stock solution was further diluted appropriately. After being appropriately diluted to achieve a concentration of 20 µg/ml, the working standard solution was subjected to a UV scan. A maximum absorption was detected at a wavelength of 275–301 nm. Using a series of 10 ml volumetric flasks, aliquots (5, 10, 15, 20, and 25) ml of the working standard solution (100 µg/ml), or 5–25 µg, were collected and the volume made up with solvent. The methanol solution was used as a blank for the absorbance measurements of these solutions, which were done at 275 nm. Omeprazole's calibration curve was graphed.

- **Physical compatibility**: Omeprazole, HPMC K30, and E5 were physically mixed and kept in a temperature range of 40°C to 20°C and a relative humidity of 75% to 5% for a duration of 15 days. It was found that their physical characteristics had not changed much. Since all of the active and inactive excipients that were the focus of compatibility study communicate with one another, it may be claimed without assurance that they do so. For the current experiment, these chemicals were selected and used. There is always possibility of drug-excipients interactions in any formulations due to their intimate contact. There are no significant changes appeared in the ampules after 15 days in environmental chamber.

Figure.4. Drug Excipient Compatibility Study

- **ChemicalCompatibility:**

• **FTIR Study**: Drug interactions with polymers during storage can be ascertained by IR spectroscopy, a useful scientific technique. As a result, infrared spectroscopy is used to investigate the chemical

interactions between the omeprazole and other excipients used in the formulation. The IR spectra of the drug and the physical combination of the drug and excipients were examined to confirm any possible interactions between the excipients in medicine. The same procedure was used for additional mixes and drug-loaded granules. Valsartan and HPMC K100 powder are combined in a ratio of 1:1. subsequently a tiny portion of the pellet's wavelength range of 4000-400 cm-1 has been established using an FTIR Spectrophotometer.

Precision: The intra-day precision was assessed using six determinations at 100% of the test concentration (4mg/ml) for both raw material and injections. Sample solutions of omeprazole were made in accordance with earlier instructions. The same protocol was used, running the analyses across two days in order to assess the inter-day accuracy. The relative standard deviation (RSD) and the omeprazole content were determined for each analysis.

Accuracy: The omeprazole injection was infused with known volumes of the reference standard in order to assess accuracy using the standard addition procedure. The injection was mixed with three different doses of omeprazole standard solutions to obtain final concentrations of 3 mg/mL, 4 mg/mL, and 5 mg/mL, which correspond to 75%, 100%, and 125% of the test concentration, respectively. At each concentration, the solutions were prepared in triplicate and the recovery was calculated.

Formulation and Development

1. **Seal Coating. Table no.3 Formulation table for seal coating**

Sr no	Ingredients	F1	F2	F3	F4
1	Sugar spheres	10	10	10	10
2	HPMC E5	40	40	20	20
3	Talc	10	10	10	10
4	Distilled water	q.s.	q.s.	q.s.	q.s.

2. **drug layering. Table no. 4 Formulation table for drug layering**

5.	Omeprazole	400	400	400	400
6	Coloring agent (food colour)	q. s	q. s	q. s	q. s
7	Talc USP	10	10	10	10
8	Methanol	30	30	30	30

3. **Functional coating Table no. 5 Formulation table for Functional coating**

9.	HPMC K30	40	80	40	80
10.	METHANOL (Solvent)	q.s.	q.s.	q.s.	q.s.

Manufacturing process

A. **Seal coating solution**:

1. After weighing and transferring hydroxyl propyl methyl cellulose into hot water while stirring, an HPMC slurry was prepared.

2. To dissolve HPMC, the remaining amount of dematerialized water was added to the heated slurry while stirring.

3. Stirred the mixture while it cooled to room temperature.

4. After checking the pH and adjusting it to 9 (the acceptable range of 8.5–9.5), pure talc was added and stirred.

5. After thoroughly combining for ten minutes, spray the mixture onto the sugar spheres.

B. Loading of drugs

1. After removing the wet sugar spheres from the fluidized bed coater, let it air dry for a little while.

2. Weigh the omeprazole medication and mix it with the methanol, which acts as an omeprazole solubilizer.

3. Apply this solution to the pellets that have been sealed. 4. Let it sit for a bit before applying the next coating.

C. Functional Coating

1. The functional coating process is carried out once the remaining pellets have dried.

2. The HPMC K30 can be dissolved in appropriate solubilizing agents, including cold water.

3. Maintained the rpm, pressure, and temperature. Keep it in a plastic bag.

EVALUATION OF FORMULATED OMEPRAZOLE PELLETS:

1. Bulk density:

Bulk density is defined as the ratio of the mass of powder and bulk volume.

Method: A given quantity of the Omeprazole pellets was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume was obtained. This volume is bulk, and it includes the true volume of the powder and the void space among the powder particles.

Bulk Density: Bulk Mass/Bulk Volume

2. Tapped density:

Tapped density was determined by using an Electro lab density tester, which consists of a graduated cylinder. Accurate Tapped density =Wt. of sample in gm/Tapped volume.

3. Hausner's ratio:

Its measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5.

It is determined by the ratio of tapped density and bulk density.

Hausner's ratio= vi/V_t

Where, Vt = Tapped volume, vi =untapped volume

4. Angle of repose:

The angle between the open surface of the powder heap and the horizontal plane. The angle of Repose let the pellets fall over the graph sheet on the horizontal plane through a funnel held at a suitable height.

Measure the height of the powder heap. Draw the circumference of the bottom of the powder heap with a pencil. Measure the radius of the resulting circle.

Tan-1 (h/r)

where, h is height, r is radius.

5. Scanning Electron Microscopy:

Photo micro graphs were taken with a scanning electron microscope for visualization of spherocity of the pellets. Pellets were coated with platinum by means of a sputter coater to assure conductivity.

6. **In vitro dissolution study**:

Method: The USP-II paddle technique was utilized to conduct dissolution experiments for each formulation. For the first hour, the dissolving media was 500 ml of 0.1 N HCL, and for the second hour, 900 ml of phosphate buffer pH-6.8. Temperature equilibration of 37 +0.5" was permitted in the medium. With the pellets inside, the vessel was sealed and run for five hours at 75 rpm in 0.1 N HC1 and for one hour in ph-6,8 phosphate buffer for a total of one hundred minutes. An equal volume of new dissolving media was added to the aliquot of sample every time a certain amount of time, 5 ml at a time. With the use of a UV spectrophotometer, the samples were examined spectrophotometrically at 281 mm.[10-11]

RESULTS AND DISCUSSION

A. Calibration Curve of Omeprazole

Linearity: Linearity is the relation between absorbance and concentration of drugs. That was shown by plotting the X-axis and Y-axis plots at concentrations 5 to 25 ppm.

Table No 6:. calibration curve of omeprazole

Sr.No.	Concentration	Absorbance	Wavelength
1	5	0.058	310
2	10	0.105	
3	15	0.162	
4	20	0.225	
5	25	0.275	

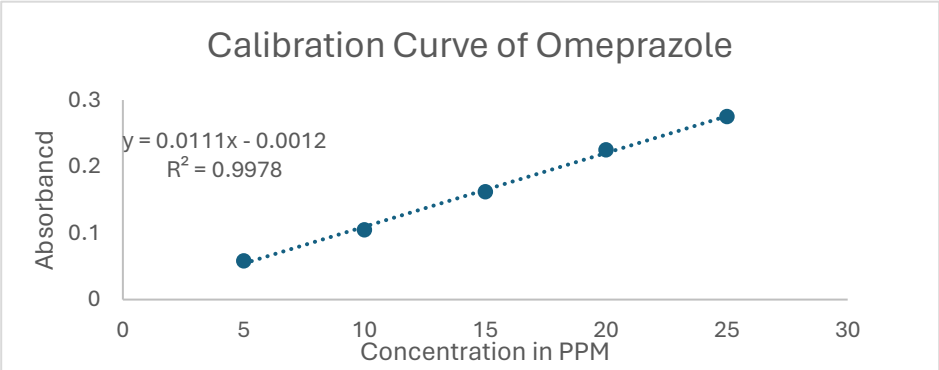

Chart No. 1 Graph of linearity

FTIR spectrum of omeprazole and Excipient:

The FTIR spectra of pure showed peaks in wave numbers (cm) which corresponds to the functional group present in the structure of the drug FT-IR spectrum of Omeprazole as shown in

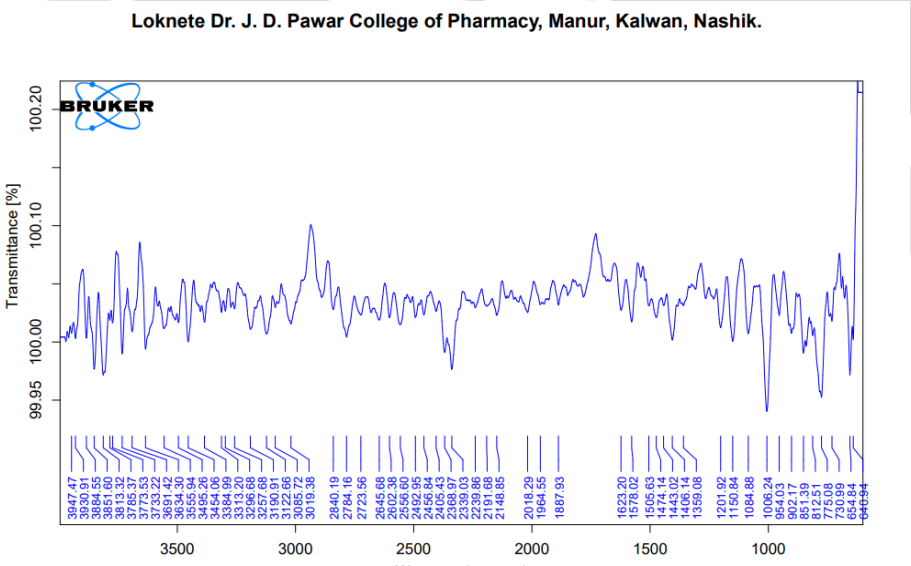

Chart No. 2 FTIR graph of omeprazole

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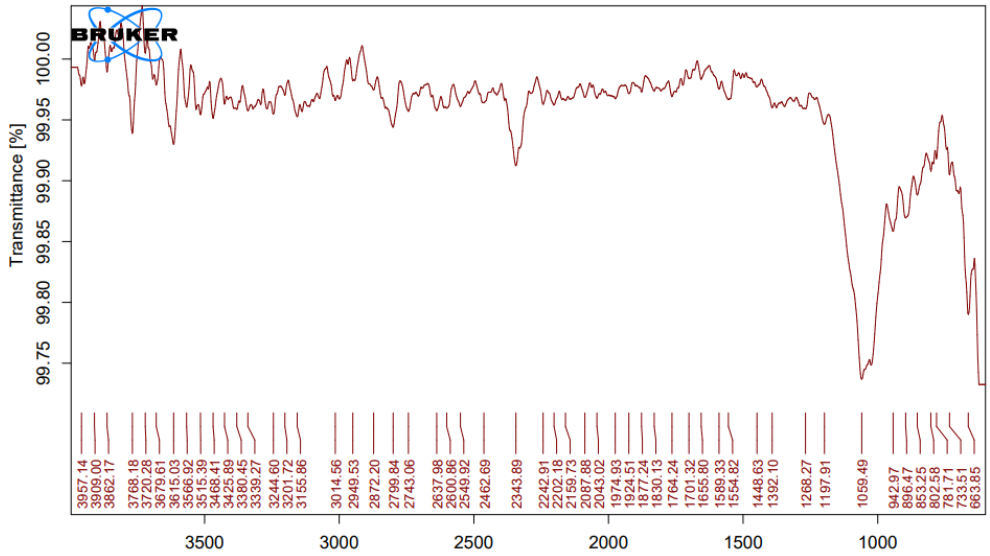

Chart No. 3 FTIR graph of polymer HPMC 30

Evaluation Parameter

Sr.no	parameters	F1	F2	F3	F4
1	Bulk density	0.923±0.02	0.937±0.03	0.921±0.02	0.940±0.03
2	Tapped density	0.991±0.04	1.0048±0.05	0.989±0.03	1.028±0.04
3	Hausner ratio	1.07±0.01	1.08±0.05	1.09±0.04	1.08±0.05
4	Angle of repose	26.50	27.50	28.30	27.20

Scanning Electronic Microscopy:

The surface morphology of the coated pellets was compact, continuous, homogeneous, and porous in character, giving the impression that they were discrete spherical pieces. The spherical form of the pellets was shown by SEM. The pellets' average size was determined to be 1085±5 µm.

fig 6 Scanned pellets under electronic microscope

In vitro dissolutions studies

In vitro dissolution studies for first two hours in acidic medium had revealed the acid resistance capacity of pellets. Followed by dissolution behavior of pellets in basic medium (phosphate pH 7.4) revealed the in vitro drug release characteristics.

Table no.7 Invitro % Drug Release

Cumulative percent drug release in phosphate Buffer pH 6.8			
Time	innovator	F1	F2
15 min	89.6	85.2	89.5
30min	95	89.2	90.4
45min	93	92.6	94.8
60min	92	93.5	91.5

CONCLUSION

The purpose of this study was to develop and evaluate delayed-release capsules. The omeprazole delayed-release capsule formulation was developed using an enteric film coating process that changes the composition of the drug load, barrier coating, and enteric coating using HPMC E5 and HPMC K30 as predicted. The F2 build is probably the best batch of the final product.

ACKNOWLEDGEMENT

I expressed wholehearted gratitude to my guide Dr. Rajendra Surwase, professor of Loknete Dr. J D Pawar College of Pharmacy, Manur, Kalwan for Suggesting Solutions to problems face by me and providing guidance and encouragement at every step of this work. I thankful to my seniors, classmates, and all non-teaching staff. Special thanks to Tejal Bhadane, Arpit Batham, Mohini Bhamare, Aakash Rathod, Shubham Bhadane, Vinay Kothawade, Deshmukh Sir. I thank all the people who have helped me directly or indirectly to complete this research.

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