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Research Article

**FORMULATION OF DELAYED RELEASE OMEPRAZOLE
FOR THE TREATMENT OF ACTIVE DUODENUM ULCER**

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Abstract:

Duodenal ulcers are part of a broader disease state categorized as peptic ulcer disease. While most duodenal ulcers present with dyspepsia as the primary associated symptom, the presentation can range in severity levels, including gastrointestinal bleeding, gastric outlet obstruction, perforation, or fistula development. Proton-pump inhibitors (PPIs) have been very efficacious for the management of ulcer. Omeprazole degrades very rapidly in aqueous solutions at low pH values. Omeprazole degradation is acid-catalysed; with an increase in the pH values, the rate of degradation decreases. So, delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. So, the aim of this study is formulation of delayed release Omeprazole for treatment of Duodenal ulcers. The formulation & evaluation of formulated drug was done according to standard procedures. Particle size analysis result shows that 90 % of particles were in range of 36.031 to 37.592 μm , which showed uniformity of particle size. Moisture content was found to be 0.3%. Weight variation data of core tablets formulated using both direct compression and wet granulation indicated that they were in range of official standards and no significant difference between individual weights of tablets from the average value. Formulation F008 formulated by 4mg of PVP K 30 per tablet along with IPA shows highest drug release among other batches core tablet by wet granulation method. Thus Formulation F008 possesses delayed release property so can be used to cure duodenal ulcers.

Keywords: Duodenal ulcers, Omeprazole, Delayed release, Tablet**Corresponding author:**

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INTRODUCTION:

Duodenal ulcers are part of a broader disease state categorized as peptic ulcer disease. Anatomically, both the gastric and duodenal surfaces contain a defense system that includes pre-epithelial, epithelial, and subepithelial elements. Ulceration occurs from damage to the mucosal surface that extends beyond the superficial layer. While most duodenal ulcers present with dyspepsia as the primary associated symptom, the presentation can range in severity levels, including gastrointestinal bleeding, gastric outlet obstruction, perforation, or fistula development. Therefore, the management is highly dependent on the patient's presentation at the time of diagnosis or progression of the disease. The diagnosis of duodenal vs. gastric ulcer merits consideration in patients with dyspepsia/upper abdominal pain symptoms who also report a history of NSAID use or previous *Helicobacter pylori* diagnosis. Any patient diagnosed with peptic ulcer disease and, most specifically, the duodenal ulcer should undergo testing for *H. pylori* as this is a common cause. According to multiple studies that have evaluated the prevalence of duodenal ulcers, they are estimated to occur in about 5 to 15% of the Western population. Previously, the recurrence and prevalence rates were extremely high due to a lack of identification and effective treatment of *H. pylori*. (Mouly *et al.*, 2013; Marshall BJ, Warren, 1984).

Proton-pump inhibitors (PPIs) have been very efficacious for the management of ulcer. However, as PPIs are acid-labile, they need to be protected from the destructive effects of gastric acid when administered orally. Various types of enteric coating have been developed to protect the PPIs, but they all delay PPI absorption and hinder these delayed-release (DR) formulations (Horn and Howden, 2005).

When a DR-PPI enters the stomach, the enteric coating must be destroyed in order for the PPI to be dissolved and then absorbed. Most PPI absorption takes place in the proximal small intestine. Once absorbed, PPIs circulate widely but are preferentially taken up by parietal cells, particularly when they are actively secreting acid. In the parietal cell, PPIs are excreted via the luminal aspect of the cell into the canalicular space. Therefore, following protonation and conversion to a sulfenamide derivative, the activated PPI molecule binds covalently to cysteine moieties of the membrane-bound H^+, K^+ -ATPase molecule (Corsonello *et al.*, 2018).

In recent years, omeprazole has been widely used as a gastric acid secretion blocker and selectively inhibits the proton pump in the gastric mucosa. Omeprazole

degrades very rapidly in aqueous solutions at low pH values. In aqueous solutions, the rate of degradation proceeds with a half-life of less than 10 min at pH values below 4, 18 h at pH 6.5 and about 300 days at pH 11. Omeprazole degradation is acid-catalysed; with an increase in the pH values, the rate of degradation decreases. So, delivery of therapeutic agent into the intestinal region could be accomplished by the application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH sensitive drug release and time controlled drug release (Clissold, 1986; Wilde and Tavish, 1994).

MATERIALS AND METHODS:

Lactose monohydrate, Colloidal silicon dioxide, micro crystalline cellulose, Isopropyl alcohol, Sodium starch glycolate, Magnesium stearate of laboratory grade were used.

Preformulation studies

Solubility study:

The sample was qualitatively tested for its solubility in various solvents. It was determined by taking 1 mg of drug sample in 1 ml of solvent as water, methanol, ethanol, ether, ethyl acetate etc., in small test tubes and well solubilized by shaking. Solubility study in different solvents at room temperature that is in distilled water, ethanol, methanol, 0.1N NaOH, Phosphate buffer, in N-octanol and ethyl acetate.

Determination of partition coefficient

The partition behavior of drug was examined in n-Octanol: Water, systems. It was determined by taking 50 mg of drug in three separating funnels containing 50 ml portions of each n-Octanol and 50 ml water. The separating funnels were shaken for 2 hrs in a wrist action shaker for equilibration. Two phases were separated and the amount of the drug in aqueous phase was analysed spectrophotometrically at 234 nm after appropriate dilution.

Preparation of core tablets by direct compression method:

First development was started using direct compression method. Various formulation were planned using list of excipients as mentioned in table 6.1. Preliminary batches were formulated using direct compression method by various ratio of two different directly compressible diluents.

Accurate quantity of each ingredient was weighed. Lactose was divided into two equal parts and first part was passed along with omeprazole through #40 sieve. Other intragranular

were added to second part of Lactose. This blend was co-passed with former blend through #40 sieve.

This blend was dry mixed in Cage blender for 10 min. at 18 RPM.

Table 1: Formula for direct compression preliminary batches

Ingredients	Qty/tab. (mg) F001	Qty/tab. (mg) F002	Qty/tab. (mg) F003	Qty/tab. (mg) F004	Qty/tab. (mg) F005
Omeprazole	10.0	10.0	10.0	10.0	10.0
Direct compressible lactose 11(DCL 11)	130.98	---	43.66	87.30	65.48
Micro crystalline cellulose 102	---	130.98	87.30	43.66	65.48
Sodium starch glycolate	4.0	4.0	4.0	4.0	4.0
Colloidal silicone dioxide	1.68	1.68	1.68	1.68	1.68
Magnesium stearate	3.36	3.36	3.36	3.36	3.36
Total Avg. wt.	150	150	150	150	150

Evaluation of Blends

Bulk Density

Apparent bulk density (pb) was determined by pouring the blend in to a graduated cylinder. The apparent bulk density was calculated by dividing weight of powder by bulk volume. (The British pharmacopoeia, 2005).

Compressibility Index:

The simplest way for measuring of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated by knowing tapped density & tapped volume.

Tapped density (TD)

Weigh accurately 25 g of drug, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 480 times initially and measure the tapped volume (V1) to the nearest graduated units, repeat the tapping an additional 748 times and measure the tapped volume (V2) to the nearest graduated units. If the difference between the two volumes is less than 2% then final the volume (V2) (Splendor *et al.*, 2013).

Carr's index (% compressibility)

The Carr's compressibility index of the powder blend was determined by Carr's compressibility index. It is

a simple test to evaluate the BD and TD of a powder and the rate at which it packed down.

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material (Grey and Beddow, 1969).

Angle of repose

The angle of repose of API powder was determined by the funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel (taken constant) was adjusted in such a way that the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was also calculated (Al-Hashemi *et al.*, 2018).

Particle size distribution

For many active substances, particle size has an impact on powder flow; content uniformity and drug dissolution. In order to assure consistent product quality, the particle size of the API has been characterised. The particle size analyzed by Malvern master seizer is based on the principle of light scattering. The particles can be analyzed by two methods (Hintz *et al.*, 1989).

Moisture content

Moisture content was determined by halogen moisture analyzer. This moisture balance had a heat

source for rapid heating and % moisture content was measured (Bravo-Osuna *et al.*, 2008).

Force Degradation study in Dissolution Medium:

Active Ingredients of the formulation is forced manually to varies extreme condition such as acidic, alkaline, heat, oxidation and check for the extant of the degradation of compound in dissolution medium of dosage form. In Force degradation study Active compound is forced to degradation by various agent and various external condition. Extent of degradation of API where found by force degradation study. Force degradation of omeprazole had performed in Phosphate Buffer pH 8.0.

Identification By Fourier Transform Infrared Spectroscopy

The FTIR absorption spectrum of the finely ground sample in KBr dispersion compressed into a disc should exhibit maxima only at the same wavelengths as that of a similar preparation of working standard.

Differential Scanning Calorimetric (DSC) procedure

Differential Scanning Calorimetry (DSC) analysis of the samples was carried out by Mettler Toledo DSC. Differential scanning calorimetry (DSC) measures the heat loss or gain (Melting point) resulting from physical or chemical changes within a sample as a function of temperature. Quantitative measurement of endothermic and exothermic processes has many applications in preformulation studies including purity, polymorphism, degradation and excipients compatibility with drugs. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 100C/min over the temperature range of 5 and 3000C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in² (Freire *et al.*, 1995).

Drug-excipients compatibility study

The primary objective of this investigation was to identify a stable storage condition for drug in solid state and identification of compatible excipients for its formulation. In this method different excipients were selected and mixed separately with drug in

proportion generally used for tablet formulation. Eleven sets of each mixture were prepared, from which 1 set was used for FTIR study, 1 for initial visual analysis without moisture, 1 for initial visual analysis with moisture and 1 set for initial impurity analysis. Remaining 7 sets were kept at 40°C ± 2°C, from which 2 sets were kept in without moisture condition for 1 and 2 month and 2 set in with moisture condition for 1 and 2 month and were used for visual analysis. From remaining 3 sets, 2 sets were kept in moisture condition for 1 and 2 month and were analyzed for presence of impurity. Then remaining final sample was used for DSC study that clarifies if any interaction was occurred between Drug-excipients. Here moisture condition means 75% RH (Schlich *et al.*, 2021).

Preparation of core tablets by Wet granulation method:

Accurate quantity of each ingredient was weighed. Lactose was divided in to two equal parts and first part was passed along with Drug X through #40 sieve. Again added second part of Lactose in step 2 bland and passed it through #40 and mix it in a polybag (geometric mixing). Then, Passed SSG type A through #40 and mixed with former bland. Prepare binder solution by dissolving PVP K-30 in purified water (150g) under stirring. Blend was charged in Rapid Mixing Granulator (RMG) and mass was granulated using binder solution and additional purified water OR IPA if required until dough mass obtained. The prepared granules were then dried in Fluid Bed (FBD) at 48°C to 55°C till LOD was obtained less than 2%. Dried granules were sifted through the #20 screen of Oscillator granulator (OG). Then Seized granules of were mixed with Extragranular materials (sifted through #40 sieve) for 10 minutes in cage blender. This blend was further lubricated with Magnesium stearate (#60) for 3 minutes in cage blender. The LOD of blend ready for compression should be NMT 1-1.5%. The blend ready for compression was compressed into tablets using Cadmach 'D' tooling 16 Station Rotary tablet compression machine with 9/32" Round shallow concave punch.

Table 2: Formula of wet granulation preliminary batches

Ingredients	Qty/tab. (mg) F006	Qty/tab. (mg) F007	Qty/tab. (mg) F008	Qty/tab. (mg) F009
Intragranular				
Drug-X	10.0	10.0	10.0	10.0
Micro crystalline cellulose 101	46.0	42.0	46.0	42.0
Lactose monohydrate	26.0	26.0	26.0	26.0
Sodium starch glycolate	6.0	6.0	6.0	6.0
Poly vinyl pyrrolidone K 30	4.0	8.0	4.0	8.0
P. water	q.s	q.s	---	---
Iso propyl alcohol	---	---	q.s	q.s
Lubrication				
Micro crystalline cellulose 102	46.0	46.0	46.0	46.0
Sodium starch glycolate	4.0	4.0	4.0	4.0
Colloidal silicone dioxide	2.86	2.86	2.86	2.86
Talc	0.18	0.18	0.18	0.18
Magnesium stearate	3.34	3.34	3.34	3.34
Total Avg Weight (mg)	150.0	150.0	150.0	150.0

Evaluation of Core Tablet

Description: The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture avoid of sticking etc. Brown colored, round shape, biconvex, enteric coated, plain on both sides.

Average weight: Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight. ^[56]

Hardness: Tablets require certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester. ^[56] Ten tablets were randomly selected and hardness was measured in Schleuniger hardness tester. The average was taken as hardness of the tablet.

Thickness and diameter: Ten Tablets were selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement.

Friability: Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. A maximum mean weight loss from three samples of

not more than 1 % is considered acceptable. Ten tablets were accurately weighed and transferred into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final weight). Friability was calculated as below formula

Disintegration time: For disintegration test of tablet put it in to the apparatus and note the time at which it completely disintegrates.

pH study: For pH study one tablet was placed in 20 mL of distilled water and sonicated for 5 min. pH was measured at initial time point and after 5 min.

Content uniformity: Content uniformity were carried out same as under section 5.3.

Dissolution study

The release rate of tablet containing omeprazole was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 0.1 N HCl as dissolution medium for invitro study of gastric resistance and using phosphate buffer pH 7.2 + 0.5% SLS as dissolution medium for invitro study of drug release at $37 \pm 0.5^\circ\text{C}$ and 100 rpm for 2 hours and 1 hour respectively. A 10 ml aliquot was withdrawn at different time intervals and filtered using a 0.45μ nylon disc filter; each sample was replaced with 10 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed by measuring the absorbance at 248 nm. The dissolution experiments were conducted in triplicate (Agyilirah *et al.*, 1999; Vitz *et al.*, 2009).

RESULTS AND DISCUSSION:

Omeprazole was observed to be white crystalline powder which is slightly soluble in water, ethanol and chloroform, soluble in methanol, Sodium hydroxide and acetonitrile. practical melting point of drug found out 150 to 154°C . The partition coefficient was found to be 2.20. The Bulk density & Tapped density was found to be 0.201 (g/cm³) & 0.258 (g/cm³) respectively. Hausner's ratio was found to be 1.28 & Carl index was found to be 22.09% while angle of contact was found to be 1.28. Particle size analysis result shows that 90 % of particles were in range of 36.031 to 37.592 µm. which showed uniformity of particle size. Moisture content was found to be 0.3%.

Solution stability study at different pH suggested that as pH increase towards alkaline condition it lead to decrease in degradation of drug. Forced degradation study revealed that drug was more susceptible towards oxidation than any other condition such as acidic, alkaline and heat. Diffential screening colometric data revealed that drug and excipients shown that there was no significant incompatibility occurred when drug was mixed with other ingredients used in formulation of tablets. omeprazole showing sharp endothermic peak at 150.4°C corresponding to its melting point, indicating its crystalline nature. The compatibility results revealed that drug was compatible with all the excipients which was used in formulation development and result found to be satisfactory.

Weight variation data of core tablets formulated using both direct compression and wet granulation indicated that they were in range of official standards and no significant difference between individual weights of tablets from the average value. Hardness of all tablets kept between 10-12Kp. Friability test for both wet granulation and direct compression was in the range of less than 1 %. All the batches by direct compression method failed in content uniformity test it may be because of improper distribution of drug into blend or difference of density between drug and diluent. Assay result of core tablet of direct compression method was too low. Content uniformity test was complied in all the batches prepared by wet granulation method.

%CDR from the tablets of all batches of preliminary study by direct compression and wet granulation method was very low. Drug release was found to be same in core tablets of both preliminary batches method. Core tablets of different wet granulation batches showed drastic difference in %CDR. %CDR of core tablets of batch F006 and F007 showed less drug release when compared with batch F008 and F009 it may be due to water used as solvent in former batches which may produce hard granules in comparison while in previous batches IPA was used as solvent. F008 formulated by 4mg of PVP K 30 per tablet along with IPA shows highest drug release among other batches core tablet by wet granulation method. Based on this result of F008 was selected from preliminary study.

Table: 3: Result of Particle Size analysis

Percentage of particles	Particle Size (µm) Conc:- 0.0215 %	Particle Size (µm) Conc:- 0.0220 %	Particle Size (µm) Conc:- 0.0225 %
10 %	6.102	6.127	5.610
50 %	16.352	16.085	16.940
90 %	37.204	36.031	37.592

Table: 4 Result of Solution stability of omeprazole at various pH

Sl. No.	pH	% Degradation in 1 hr
1	6.8	15.59 %
2	7.2	13.71 %
3	7.5	12.21 %
4	8.0	6.8 %
5	7.2 + 0.5% SLS	6.0 %

Table 5: Result of force degradation study

Reaction	% Degradation
Acid Degradation	32.09 %
Alkali Degradation	46.44 %
Heat Degradation	50.36 %
Oxidative Degradation	75.64 %
phosphate buffer pH 7.2 Degradation	0.26%

Table 6: Result of Interpretation of FT-IR Spectra of omeprazole

Functional Group	Peak Intensity (%)	Practical Value from IR Spectra (cm ⁻¹)
Methoxy	2850–2815	2814
Aerometric Ring	1615–1580	1593
C-C double bond	1680-1620	1675
C-N Secondary amine	1350–1280	1286
C-N Tersary amine	1360–1310	1320
Alkyl-substituted ether, CO stretch	1150-1050	1066
Organic sulfates	1200–1180	1200

Table 7: Result of Drug-excipients compatibility study

Drug-excipients	Ratio	Total Max. Impurity		Result	
		Room Temp.	40° C/75% RH	Room Temp.	40° C/75% RH
Drug		0.6	0.43	Compatible	Compatible
Drug + MCC 101	1:1	0.41	0.17	Compatible	Compatible
Drug + MCC 102	1:1	0.24	0.69	Compatible	Compatible
Drug + DCL 11	1:1	0.18	0.34	Compatible	Compatible
Drug + Lactose	1:1	0.17	0.47	Compatible	Compatible
Drug + SSG	1:1	0.14	0.31	Compatible	Compatible
Drug + Aerosil	1:1	0.84	0.29	Compatible	Compatible
Drug + Talc	1:1	0.43	0.18	Compatible	Compatible
Drug + Light MgO	1:1	0.4	0.62	Compatible	Compatible
Drug +Magnesium stearate	1:1	0.51	0.38	Compatible	Compatible
Drug + Magnesium hydroxide	1:1	0.19	0.41	Compatible	Compatible
Drug + Sodium sulfate	1:1	0.94	0.58	Compatible	Compatible
Drug + HPMC 6 cps	1:1	0.27	0.64	Compatible	Compatible
Drug + all excipients	1:1	0.42	0.18	Compatible	Compatible

Table: 8: Micromeritic properties of powder blends of preliminary batches

Powder blend	Angle of Repose ($^{\circ}$)	Bulk Density (g/cc)	Tapped Density (g/cc)	Carr's Index (%)	Hausner's ratio
F001	27	0.503	0.597	15.75	1.19
F002	29	0.432	0.519	16.76	1.20
F003	24	0.421	0.504	16.47	1.20
F004	30	0.397	0.493	19.47	1.24
F005	28	0.49	0.604	18.87	1.23
F006	24	0.527	0.603	12.60	1.14
F007	23	0.418	0.521	19.77	1.25
F008	22	0.436	0.526	17.11	1.21
F009	26	0.432	0.51	15.29	1.18

Table: 9: In Process Quality Control Test Result of Core Tablet

Batch No.	Avg. wt (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration Time (min)
F001	150±0.59	3.90 ± 0.05	10-12	0.43	2-3 min
F002	150±0.94	3.94±0.14	10-12	0.40	2-3 min
F003	150±0.47	3.90±0.02	10-12	0.44	2-3 min
F004	150±1.06	3.95±0.07	10-12	0.42	2-3 min
F005	150±0.97	3.96±0.068	10-12	0.54	2-3 min
F006	150±1.22	3.90±0.06	10-12	0.39	4-5 min
F007	150±0.76	3.98±0.014	10-12	0.48	5-6 min
F008	150±0.93	3.93±0.01	10-12	0.48	3-4 min
F009	150±1.02	3.92±0.04	10-12	0.54	3-4 min

Table: 10: Result of Assay and Content Uniformity of Preliminary batches core tablet.

Batch No.	Assay (%)	Content Uniformity
F001	80.9	Do not Complies
F002	83.5	Do not Complies
F003	76.2	Do not Complies
F004	84.2	Do not Complies
F005	78.6	Do not Complies
F006	85.48	Complies
F007	86.13	Complies
F008	86.7	Complies
F009	85.3	Complies

Table: 11: % CDR of core tablets prepared by direct compression method

Time	F001	F002	F003	F004	F005
10 min	20.4	24.2	25.1	25.7	22.6
20 min	27.6	33.4	39.6	38.5	45.8
30 min	53.4	47.6	45.3	49.2	53.7
40 min	64.8	60.7	58.2	62.1	58.3
50 min	69.3	68.7	64.4	67.4	59.4

Table: 12: % CDR core tablets prepared by Wet granulation method

Time	F006	F007	F008	F009
10 min	21.8	25.4	20.4	23.6
20 min	35.7	31.6	43.8	41.4
30 min	51.8	45.8	50.9	48.7
40 min	59.7	53.2	58.3	56.9
50 min	70.4	61.7	68.7	64.2

CONCLUSION:

After the results of preliminary batches of core tablet, it was concluded that wet granulation method is the preferred method over to direct compression because of core tablets of direct compression method were failed in content uniformity test. Other preformulation study were also in the range as per officials requirement.

REFERENCES:

1. Mouly C, Chati R, Scotté M, Regimbeau JM. Therapeutic management of perforated gastro-duodenal ulcer: literature review. *Journal of visceral surgery*. 2013 Nov 1;150(5):333-40.
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984 Jun 16;1(8390):1311-5.
3. Cave DR. Transmission and epidemiology of *Helicobacter pylori*. *Am J Med*. 1996 May 20;100(5A):12S-17S; discussion 17S-18S.
4. Pounder RE, Ng D. The prevalence of *Helicobacter pylori* infection in different countries. *Aliment Pharmacol Ther*. 1995;9 Suppl 2:33-9.
5. Shiotani A, Graham DY. Pathogenesis and therapy of gastric and duodenal ulcer disease. *Medical Clinics*. 2002 Nov 1;86(6):1447-66.
6. Horn JR, Howden CW. Similarities and differences among delayed-release proton-pump inhibitor formulations. *Alimentary pharmacology & therapeutics*. 2005 Dec;22:20-4.
7. Corsonello A, Lattanzio F, Bustacchini S, Garasto S, Cozza A, Schepisi R, Lenci F, Luciani F, Maggio MG, Ticinesi A, Butto V. Adverse events of proton pump inhibitors: potential mechanisms. *Current drug metabolism*. 2018 Feb 1;19(2):142-54.
8. Clissold SP, Campoli-Richards DM. Omeprazole. *Drugs*. 1986 Jul;32(1):15-47.
9. Wilde MI, McTavish D. Omeprazole. *Drugs*. 1994 Jul;48(1):91-132.
10. Splendor D, Gonçalves IM, Costa P, Sousa Lobo JM. Note on the measurement of bulk density and tapped density of powders according to the European Pharmacopeia. *AAPS PharmSciTech*. 2013 Sep;14(3):1098-100.
11. Grey RO, Beddow JK. On the Hausner ratio and its relationship to some properties of metal powders. *Powder Technology*. 1969 Sep 1;2(6):323-6.
12. Al-Hashemi HM, Al-Amoudi OS. A review on the angle of repose of granular materials. *Powder technology*. 2018 May 1;330:397-417.
13. Hintz RJ, Johnson KC. The effect of particle size distribution on dissolution rate and oral absorption. *International Journal of Pharmaceutics*. 1989 Apr 1;51(1):9-17.
14. Bravo-Osuna I, Ferrero C, Jiménez-Castellanos MR. Drug release behaviour from methyl methacrylate-starch matrix tablets: effect of polymer moisture content. *European journal of pharmaceutics and biopharmaceutics*. 2008 May 1;69(1):285-93.
15. Freire E. Differential scanning calorimetry. Protein stability and folding. 1995:191-218.
16. Schlich M, Lai F, Maria Fadda A, Sinico C, Pini E. Drug-Excipients Compatibility Studies in Proniosomal Formulation: A Case Study with Resveratrol. *Journal of Nanoscience and Nanotechnology*. 2021 May 1;21(5):2917-21.
17. Agyilirah GA, Green M, Banker GS. Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet. *International journal of pharmaceutics*. 1991 Sep 20;75(2-3):241-7.

18. Vitz J, Erdmenger T, Haensch C, Schubert US.
Extended dissolution studies of cellulose in

imidazolium based ionic liquids. Green
chemistry. 2009;11(3):417-24.