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Formulation and Evaluation of Delayed-Release Pantoprazole Tablets

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ABSTRACT

Pantoprazole is a proton pump inhibitor, belongs to a group of benzimidazole, used for the treatment of gastric and duodenum ulcers. Pantoprazole undergoes degradation in the acid medium of the stomach, can be coated with enteric coating polymer that will safely deliver the drug to the small intestine. In this present study, an attempt was made to formulate and evaluate pantoprazole as an enteric-coated tablet. Delayed-release tablets of pantoprazole were prepared by wet granulation method using HPMC, Cassava starch, and polyvinyl pyrrolidine as polymer, Avicel PH 102 (MCC) as filler, and starch as binder. The prepared tablets were evaluated for hardness, weight variation, friability, and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymers such as cellulose acetate phthalate, Eudragit L100, and drug coat L100 by dip-coating method. The in vitro release was studied using pH 1.2 acidic buffer and pH 6.8 phosphate buffer. The in vitro release study revealed that the prepared tablets were able to sustain release drug into the intestine. The release kinetics studies showed that the release was the first-order diffusion-controlled and then values obtained from the Korsmeyer-Peppas model showed that the release mechanism was super case-II transport. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40°C / 75% RH for 1 month. The anti-ulcer activity was evaluated by the water immersion stress-induced ulcer model. The pantoprazole sodium sesquihydrate coated formulations ECF3 at a dose of 10 mg/kg body weight showed a protection index of 100%.

1. INTRODUCTION:

Ulcers are crater-like sores (generally 1/4 inch to 3/4 inch in Hence, ulcers are sores on the lining of the digestive tract. diameter, but sometimes 1 to 2 inches in diameter) which The digestive tract consists of the esophagus, stomach, form in the lining of the stomach (called gastric ulcers), just duodenum (the first part of the intestines) and intestines. Below the stomach at the beginning of the small intestine in the duodenum (called duodenal ulcers) or less commonly in the esophagus (called esophageal ulcers). In general, ulcers in the stomach and duodenum are referred to as peptic. The stomach and duodenum are referred to as peptic An ulcer is the result of an imbalance between aggressive and defensive factors. On one hand, too much acid and pepsin can damage the stomach lining and cause ulcers. On the other hand (and more commonly), the damage comes first from some other causes, making the stomach lining susceptible to even an ordinary level of gastric acid[1].

Hence, ulcers are sores on the lining of the digestive tract. diameter, but sometimes 1 to 2 inches in diameter). The digestive tract consists of the esophagus, stomach, which form in the lining of the stomach (called gastric ulcers), just duodenum (the first part of the intestines), and intestines.

An ulcer may arise at various locations:

• Stomach (called gastric ulcer) in the stomach and duodenum are referred to as peptic ulcer2

• Duodenum (called duodenal ulcer)

• Oesophagus (called Oesophageal ulcer)

• Meckel's Diverticulum (called Meckel's Diverticulum ulcer)

Peptic ulcer:-

A peptic ulcer, also known as ulcus pepticum, peptic ulcer disease (PUD),3 is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. As many as 80% of ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also be caused or worsened by drugs such as aspirin and other non-steroid anti-inflammatory drugs (NSAIDs)[4].

Types of peptic ulcers

• Type I: Ulcer along the lesser curve of the stomach

• Type II: Two ulcers present - one gastric, one duodenal

• Type III: Prepyloric ulcer

• Type IV: Proximal gastroesophageal ulcer

• Type V: Anywhere along the gastric body, NSAID induced

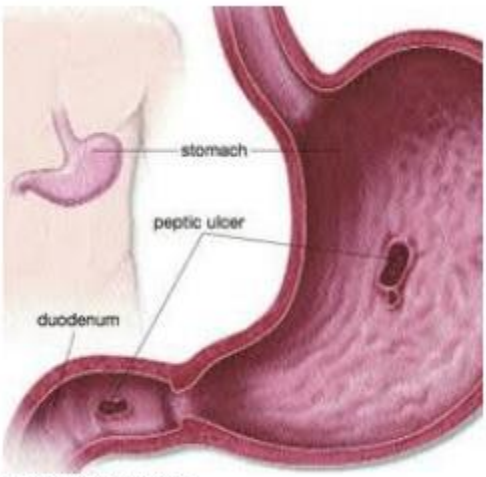

Figure 1. Deep gastric ulcer

Epidemiology:-

The lifetime risk for developing a peptic ulcer is approximately 10%5. In Western countries, the prevalence of Helicobacter pylori infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80, etc). Prevalence is higher in third-world countries. Transmission is by food, contaminated groundwater, and through human saliva (such as from kissing or sharing food utensils). A minority of cases of Helicobacter infection will eventually lead to an ulcer and a larger proportion of people will get non-specific discomfort and abdominal pain or gastritis.

Pathophysiology of peptic ulcer:-

Classical causes of ulcers (tobacco smoking, blood groups, spices, and a large array of strange things) are of relatively minor importance in the development of peptic ulcers. A major causative factor (90% of gastric and 75% of duodenal ulcers) is chronic inflammation due to Helicobacter pylori, a spirochete that inhabits the antral mucosa and increases gastric production. Gastric, in turn, stimulates the production of gastric acid by parietal cells. Glucocorticoids lead to the atrophy of all epithelial tissues. Their role in ulcerogenesis is

relatively small. Stress in the psychological sense has not been proven to influence the development of peptic ulcers. Burns and head trauma, however, can lead to "stress ulcers" and it is reported in many patients who are on mechanical ventilation. Smoking leads to atherosclerosis and vascular spasms, causing vascular insufficiency and promoting the development of ulcers through ischemia. Family history is often present in duodenal ulcers, especially when blood group O is also present. Inheritance appears to be unimportant in gastric ulcers[6].

Signs and Symptoms:-

Symptoms of a peptic ulcer can be abdominal pain, classically epigastric with severity relating to mealtimes, after around 3 h of taking a meal (duodenal ulcers are classically relieved by food, while gastric ulcers are exacerbated by it).

Bloating and abdominal fullness

Water brash (rush of saliva after an episode of regurgitation to dilute the acid in the esophagus)

Nausea and copious vomiting

Loss of appetite and weight loss

Vomiting of blood; can occur due to bleeding directly from a gastric ulcer, or damage to the esophagus from severe/continuing vomiting

Melina (tarry, foul-smelling feces due to oxidized iron from hemoglobin)

Rarely, an ulcer can lead to a gastric or duodenal perforation. This is extremely painful and requires immediate surgery. A history of heartburn, gastroesophageal reflux disease (GERD), and the use of certain forms of medication can raise the suspicion of peptic ulcers. Medicines associated with peptic ulcers include non-steroid anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase and most glucocorticoids (e.g. dexamethasone and prednisolone). The timing of the symptoms to the meal may differentiate between gastric and duodenal ulcers. A gastric ulcer would give pain during the meal, as gastric acid is secreted, or after the meal, as the alkaline duodenal contents reflux into the stomach. Symptoms of duodenal ulcers would

manifest mostly before the meal when acid (production stimulated by hunger) is passed into the duodenum. However, this is not a reliable sign in clinical practice[4].

Treatment:-

The gastric mucosa protects itself from gastric acid with a younger patient with ulcer-like symptoms is often treated layer of mucous, the secretion of which is stimulated by antacids. Bismuth compounds may reduce or certain prostaglandins. Non-steroid anti-inflammatory drugs even clear organisms, though it should be noted that the (NSAIDs) block the function of cyclooxygenase 1, which is warning labels of some bismuth subsalicylate products essential for the production of these prostaglandins. Newer indicate that the product should not be used by someone NSAIDs (celecoxib and rofecoxib) only inhibit cox-2, with an ulcer. Patients who are taking non-steroid which are less essential in the gastric mucosa, and roughly inflammatory drugs (NSAIDs) may also be prescribed a halve the risk of non-steroid anti-inflammatory drugs prostaglandin analog (Misoprostol) in our cell. Prevent peptic ulcers, which may be a side-effect of NSAIDs. When Helicobacter pylori infection is present, the most effective treatments are combinations of two antibiotics (e.g. clarithromycin, amoxicillin, tetracycline, and metronidazole) and one proton pump inhibitor (PPI), sometimes together with a bismuth compound. In complicated, treatment-resistant cases, three antibiotics (e.g. amoxicillin + clarithromycin + metronidazole) may be used together with a proton pump inhibitor and sometimes with a bismuth compound. Effective first-line therapy for uncomplicated cases would be amoxicillin + metronidazole + pantoprazole (proton pump inhibitor). In the absence of *Helicobacter pylori*, long-term higher dose proton pump inhibitors (PPIs) are often used. Treatment of Helicobacter pylori usually leads to clearing of infection, relief of symptoms, and eventual healing of ulcers. Recurrence of infection can occur and retreatment may be required, if necessary with other antibiotics. Since the widespread use of proton pump inhibitors (PPIs) in the 1990s, surgical procedures (like "highly selective vagotomy") for uncomplicated peptic ulcers became obsolete. A perforated peptic ulcer is a surgical emergency and requires surgical repair of the perforation. Most bleeding ulcers require endoscopy urgently to stop bleeding with cutlery, injection or clipping[4].

The concept of tablet:-

A tablet is a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipients include binders, glidants (flow aids), and lubricants to ensure efficient tableting; disintegrates to ensure that the tablet breaks up in the digestive tract; sweeteners or flavors to mask the taste of bad-tasting active ingredients, and pigments to make uncoated tablets visually attractive. A polymer coating is usually applied to hide the taste of the tablet's components, to make the tablet smoother and easier to swallow, to make it more resistant to the environment, and to extend its shelf life. The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms and half of these are compressed tablets7. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally but can be administered sublingually, rectally, or intravaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. It consists of an active pharmaceutical ingredient with biologically inert excipients in a compressed solid form. Tablets are one of the most stable and commonly administered oral dosage forms. Since the later part of the nineteen-century, tablets have been widespread and their popularity continues. Tablets remain popular as dosage forms because of the advantages afforded both to the pharmaceutical manufacturers and patients. These include: simplicity and economy of preparation, stable and convenient in packing, ease of transporting and dispensing, the accuracy of single dosage regimen, compactness and portability, and blandness of taste and ease of administration[7].

2. METHODS:

FT-Infrared spectroscopy to find out the compatibility of the drug with polymers:

This was carried out to find out the compatibility between the drug pantoprazole sodium sesquihydrate and the polymer hydroxypropyl methylcellulose (HPMC), Cassava starch, and polyvinyl pyrrolidone. 10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at10 kg/cm2 using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm-1 to 400 cm-1 in the Shimadzu FTIR spectrophotometer. Samples were prepared for drug pantoprazole sodium sesquihydrate, polymer HPMC, Cassava starch,

polyvinyl pyrrolidone, and physical mixture of drug and polymer. The spectra obtained were compared and interpreted for the functional group peaks.

Preparation of standard graphs:

Preparation of standard graph for pantoprazole sodium sesquihydrate using pH 1.2 acidic buffer

A. Determination of absorption maxima (λ max) 100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 ml of pH 1.2 acidic buffer in 100 ml volumetric flask (stock solution). 2 ml was taken from the stock solution and transferred into 100 ml volumetric flask and diluted up to 100 ml with pH 1.2 acidic buffer. The resulting solution was labeled as standard working Solution. 2 ml of the working solution was withdrawn and diluted up to 10 ml with pH 1.2 acidic buffer in a 10 ml volumetric flask. The spectrum of this solution was run in the 200 to 400 nm range in a UV-visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 283.5 nm.

B. Preparation of standard graph:-

From the above standard working solution, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, and 6 ml was withdrawn and diluted up to 10 ml with pH 1.2 acidic buffer in 10 ml volumetric flask to get the concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg, and 12 µg respectively. The absorbance of each solution was measured by a UV-visible spectrophotometer at 283.5 nm using the pH1.2 acidic buffer as blank.

Preparation of standard graph for pantoprazole sodium sesquihydrate using pH 6.8 phosphate buffer:

A. Determination of absorption maxima (λmax) 100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 ml of pH 6.8 phosphate buffer in 100 ml volumetric flask (stock solution). 2 ml was taken from the stock solution and transferred into 100 ml volumetric flask and diluted up to 100 ml with pH 6.8 phosphate buffer. The resulting solution was labeled as standard working Solution. 2 ml of the working solution was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffer in a 10 ml volumetric flask. The spectrum of this solution was run in the 200 to 400 nm range in a UV

visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 288.5 nm.

B. Preparation of standard graph:

From the standard working solution, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, and 6 ml was withdrawn and diluted up to 10 ml with pH 6.8 phosphate buffer in 10 ml volumetric flask to get the concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg, and 12 µg respectively. The absorbance of each solution was measured by a UV-visible spectrophotometer at 288.5 nm using the pH 6.8 phosphate buffer as blank.

Preparation of pantoprazole sodium sesquihydrate tablets:

Preparation of granules Pantoprazole sodium sesquihydrate granules for tableting was prepared by wet granulation method 42. A specified quantity of pantoprazole, hydroxypropyl methylcellulose (HPMC), Cassava starch, polyvinyl pyrrolidone (PVP), and Avicel PH 102 were weighed according to the formula and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with 5% starch paste to obtain a sluggy mass and this was passed through sieve no 12 to obtain the granules. The granules prepared were dried at 50oC for 4 h. The dried granules were screened through sieves no 22 & 44 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets.

Preparation of pantoprazole sodium sesquihydrate tablets:-

An ideal mixture of granules was directly punched into tablets weighing about 200 mg containing 40 mg of pantoprazole sodium sesquihydrate, using a rotary tablet compression machine (12 stations, Karnavati, India), using 8 mm diameter concave punches. The different batches of pantoprazole tablets were collected and stored in airtight containers. (Table-1).

Characterization of pantoprazole sodium sesquihydrate compressed tablets:

1) Pre-compression parameters

a) Percentage yield

The prepared pantoprazole sodium sesquihydrate granules were completely collected and weighted. The percentage product yield was calculated from its theoretical and practical product yield.

$$\text{percent yield} = \frac{\text{actual yield}}{\text{theoretical yield}} \times 100\%$$

b) Mean granules size analysis by optical microscopy In the present study the granules particle size was determined by the optical microscopy. 1mm of the stage micrometer scale is equal to 89 eyepiece division. Therefore 1 eyepiece division is equal to (1/89) ×1000 Microns i.e. 11.2 µm. The dry granules were uniformly spread on the slide. Granules particle sizes were measured, along the longest axis and the shortest axis (cross-shaped measurement). The average of these two readings given was the mean diameter of particles. The diameter of a minimum number of 50 granules in each batch was calculated.

Table 1 Formula for the preparation of pantoprazole sodium sesquihydrate tablets

Batch no	Ingredients							
	Pantoprazole sodium sesquihydrate (mg)	HPMC (mg)	Cassava starch (mg)	PVP (mg)	Avicel PH 102 (mg)	Starch paste 5%	Talc (mg)	Magnesium stearate (mg)
F1	40	-	-	-	154	qs	2	4
F2	40	24	-	-	130	qs	2	4
F3	40	44	-	-	110	qs	2	4
F4	40	64	-	-	90	qs	2	4
F5	40	84	-	-	70	qs	2	4
F6	40	104	-	-	50	qs	2	4
F7	40	-	24	-	130	qs	2	4
F8	40	-	44	-	110	qs	2	4
F9	40	-	64	-	90	qs	2	4
F10	40	-	84	-	70	qs	2	4
F11	40	-	104	-	50	qs	2	4
F12	40	-	-	24	130	qs	2	4
F13	40	-	-	44	110	qs	2	4
F14	40	-	-	64	90	qs	2	4
F15	40	-	-	84	70	qs	2	4
F16	40	-	-	104	50	qs	2	4

qs- quantity sufficient

c) Bulk density (Db):-

Accurately weighed granules were carefully transferred into a graduated measuring cylinder. The granules bed was then made uniform and the volume occupied by the granules was noted as per the graduation marks on the cylinder as ml. It is expressed in gm/ml and is calculated using the following formula[44].

$$Db=M/vb$$

Where, M - Mass of the powder

Vb - The bulk volume of the powder

d) Tapped density (Dt):-

It is the ratio of the total mass of granule to the tapped volume of granule. The graduated measuring cylinder containing accurately weighed granule was manually tapped 50 times. The volume occupied by the granule was noted. It is expressed in gram/ml and is calculated by the following formula[44].

$$Dt = M/vt$$

Where, M - Mass of the powder

Vt - Tapped volume of the powder

e) Compressibility index and Hausner's ratio:-

Carr's index and Hausner's ratio measure the propensity of granules to be compressed and the flowability of granules. Carr's index and Hausner's ratio were calculated using the following formula.

$$I = Dt-Db/Dt \times 100$$

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

$$\text{Hausner's ratio} = Dt/Db = Vt/Vb$$

Where, Dt – Tapped density of the powder

Db – Bulk density of the powder

f) Angle of repose (θ):-

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole granules were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula[43].

$$\text{Angle of repose } (\theta) = \tan^{-1}(h/r)$$

Where, h – Height of the pile in cm

r – Radius of the pile

2) Post compression parameters

a) Hardness test

The prepared tablets were subjected to a hardness test. It was carried out by using a hardness tester and expressed in kg/cm^2.

b) Friability test

The friability was determined using Roche friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately (W initial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W final) and the percentage friability (F) was calculated for each batch by using the following formula.

$$F = (W \text{ initial}) - (W \text{ final}) / (W \text{ initial}) \times 100$$

c) Weight variation test:-

20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of the weight of each tablet against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%. IP limit for weight variation in the case of tablets weighing more than 80 mg but less than 250 mg is ± 7.5 %.

d) Uniformity of drug content:-

The prepared pantoprazole sodium sesquihydrate tablets were tested for their drug content. Three tablets of each formulation were weighed and finely powdered. About 40 mg equivalent of pantoprazole sodium sesquihydrate was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. 1 ml of the filtrate was

further diluted to 100 ml with pH 6.8 phosphate buffer. The absorbance of the resulting solution was measured by a UV-Visible spectrophotometer at 288.5 nm.

3) Coating of compressed pantoprazole sodium sesquihydrate tablets:-

a) Preparation of enteric coating solution:

The enteric coating solution was prepared by a simple solution method. It was prepared by 6% w/w of Eudragit L100 or cellulose acetate phthalate or =Drug coat L100 as an enteric polymer, 2.6% w/w of titanium dioxide as an opacifier, diethyl phthalate 1.2% w/w as a plasticizer, and acetone and isopropyl alcohol mixture was used as a solvent. Titanium dioxide was triturated in a glass motor with a small amount of solvent mixture and filtered with muslin cloth into the polymer solution already prepared with one-half of the solvent mixture. Diethyl phthalate was added and made up the volume with the rest of the solvent mixture; this mixture was constantly stirred for 1h with a paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a coating solution was obtained.

Table 2: Composition of coating solution

Ingredients	Quantity (%w/w)
Cellulose acetate phthalate / Eudragit L100 / Drug coat L100	6.0
Titanium dioxide	2.6
Diethyl phthalate	2.0
Acetone	59.4
Isopropyl alcohol	30.0

b) Enteric coating of pantoprazole sodium:-

Sesquihydrate compressed tablets by dipping method The compressed tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate or Drug coat L100) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for their weight variation, thickness, uniformity of drug content, and in vitro dissolution study.

4) Physicochemical evaluation of coating films:-

The same polymer solution was used to prepare the polymeric films and was subjected to film thickness film weight film solubility. The polymeric films were prepared by casting the

acetone –isopropyl alcohol (2:1), the polymer solution was poured on the glass plate. The film was dried for 24 h at room temperature under a special cover with reduced solvent evaporation to obtained smooth homogenous films. The dried films were cut into 1cm^2 area the prepared polymeric film was studied for film thickness, film weight, and film solubility. The thickness of dried films was determined by the thickness Digital micrometer. The 1 cm2 coating film was selected and separately weighed using the digital balance; the weight of the average film was calculated. The film solubility was studied with pH 1.2 and pH 6.8. The 1×1 cm2 coating film was selected, weighed, and transferred in a beaker containing 20 ml of specified pH medium, which was mixed in a magnetic stirrer for 1 h at 37 ± 1°C, and finally, film solubility was examined.

5) In vitro drug release studies:-

USP dissolution apparatus type II was employed to study the in vitro drug release from various formulations prepared. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 10 h. The tablet was kept in the basket. The temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with a fresh dissolution medium. The samples were measured by UV- visible spectrophotometer at 283.5 nm (pH 1.2) and 288.5 nm (pH 6.8) against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time.

6) Stability studies:-

A study was carried out to assess the stability of the pantoprazole sodium sesquihydrate cellulose acetate phthalate coated tablet formulation (ECF3). Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The tablets were packed in a glass container. Stability studies were carried out at 40°C and 75% RH over 1 month. Samples were evaluated on 10th, 20th, and 30th days for different parameters such as physical appearance, hardness, weight variation, drug content, and dissolution.

3. RESULTS AND DISCUSSION

RESULTS:

Drugs Polymer Interaction Study by FTIR spectrophotometer:

FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug pantoprazole and the polymers hydroxypropyl methylcellulose, Cassava starch, polyvinyl pyrrolidone used for the preparation of tablets. The FT-IR was performed for drug, polymer, and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies at a wavelength between 4000 cm-1 to 400 cm-1 are given below.

Table 3 : IR interpretation of drug, polymer and physical mixture of drug-polymer

Sr. No	Interpretation	IR absorption bands (cm^{-1})			
		Pure drug	Drug + HPMC	Drug + Cassava starch	Drug + PVP
1	N-H	3483.56	3487.42	3498.99	3497.06
2	O-H	3358.18	3363.97	3248.23	3362.04
3	CH_2	3176.87	3194.23	3196.15	3203.87
4	CH_3	2960.83	2953.12	2939.61	2945.40
5	C-O	1591.33	1591.33	1591.33	1591.33
6	C-F	1373.36	1373.36	1377.22	1373.36
7	S=O	1049.31	1039.67	1116.82	1033.88

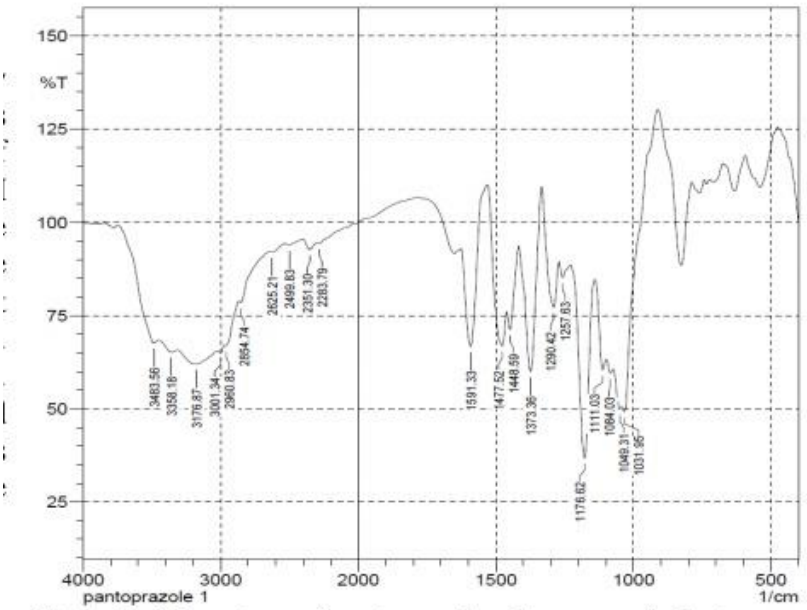

Figure 2:- IR spectrum of pantoprazole sodium sesquihydrate

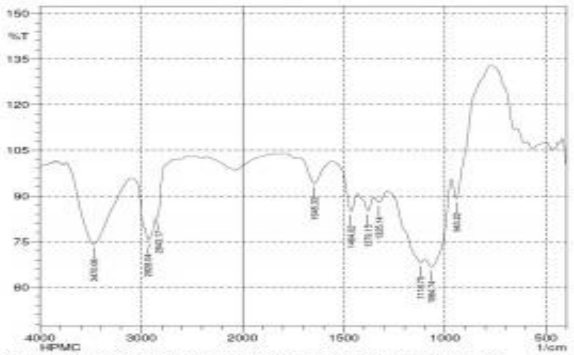

Figure 3 :- IR spectrum of hydroxypropyl methylcellulose

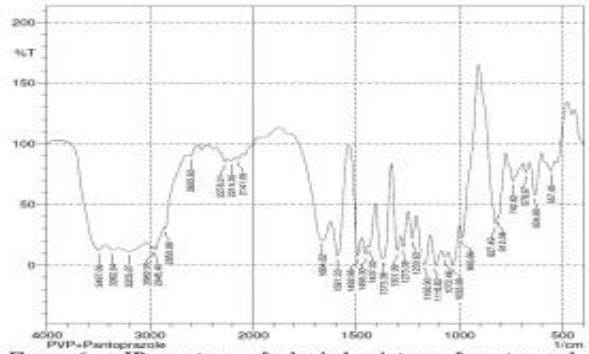

Figure 6:- IR spectrum of physical mixture of pantoprazole sodium sesquihydrate and polyvinyl Pyrrolidone

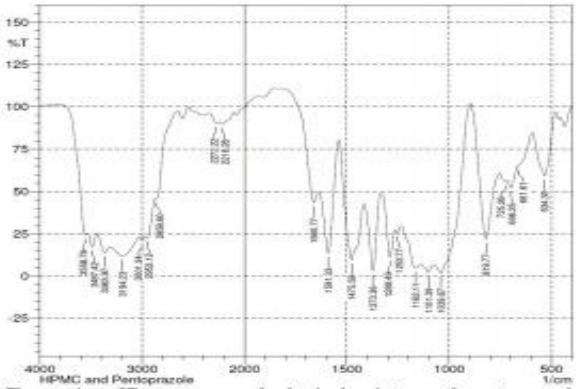

Figure 4:- IR spectrum of physical mixture of pantoprazole sodium sesquihydrate and hydroxypropyl methylcellulose

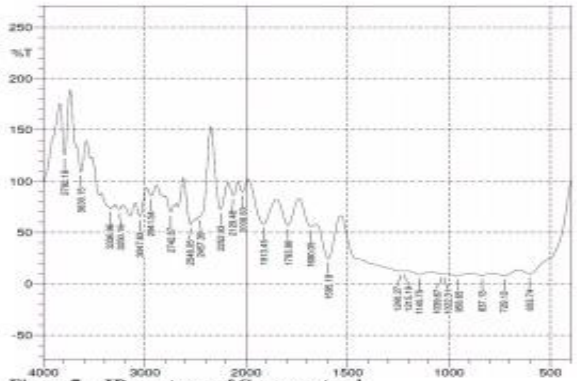

Figure 7:- IR spectrum of Cassava starch

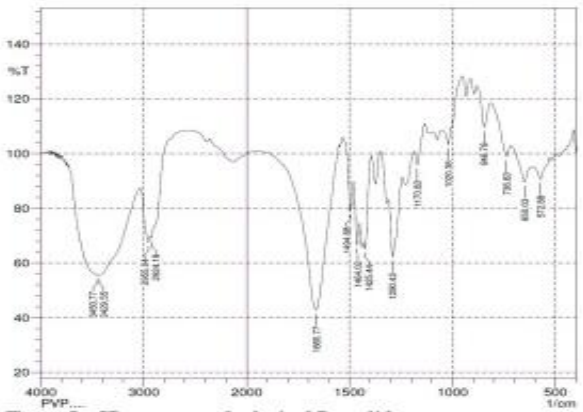

Figure 5:- IR spectrum of polyvinyl Pyrrolidone

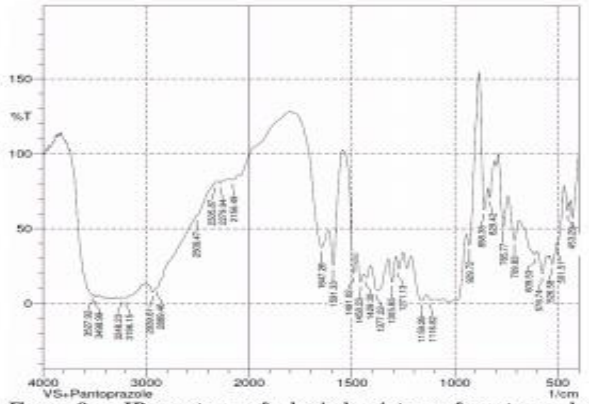

Figure 8:- IR spectrum of physical mixture of pantoprazole sodium sesquihydrate and Cassava starch

Preparation of standard graphs:-

The standard graph for the drug pantoprazole sodium sesquihydrate was done separately in pH 1.2 acidic buffer and pH 6.8 phosphate buffer. Tables show the concentrations of pantoprazole sodium sesquihydrate in pH 1.2 acidic and pH 6.8 phosphate buffers and the respective absorbance. The Figures show the calibration curves of pantoprazole sodium sesquihydrate in pH 1.2 acidic buffer and pH 6.8 phosphate buffer respectively.

and pH 6.8 phosphate buffer respectively.

Table 4:- Spectrophotometric data for standard graph of pantoprazole sodium sesquihydrate in pH 1.2 acidic buffer

Concentration (µg/ml)	Absorbance
2	0.06
4	0.12
6	0.182
8	0.237
10	0.306
12	0.365

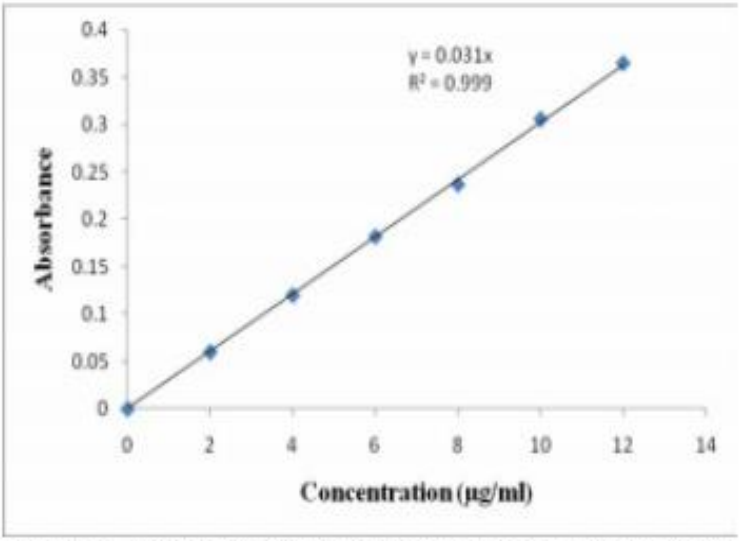

Figure 9:- Standard curve of pantoprazole sodium sesquihydrate in pH 1.2 acidic buffer

Table 5:- Spectrophotometric data for standard graph of pantoprazole sodium sesquihydrate in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
2	0.071
4	0.145
6	0.215
8	0.287
10	0.357
12	0.430

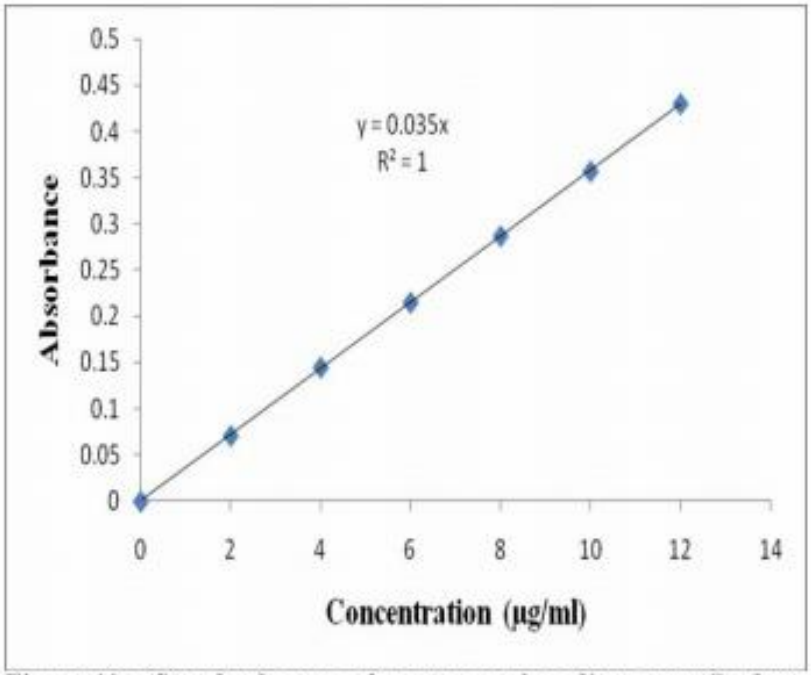

Figure 10:- Standard curve of pantoprazole sodium sesquihydrate in pH 6.8 phosphate buffer

Characterization of pantoprazole sodium sesquihydrate tablets:

1) Pre-compression parameters:

The pantoprazole sodium sesquihydrate granules were prepared by the wet granulation method. The granules were evaluated for percentage yield, granules particle size, angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index, and the results are shown in Table. The percentage yield was ranged between 86.13 to 97.82%. The particle size of the granules was ranged between 0.498 ± 0.05 mm to 0.559 ± 0.12 mm. The bulk densities of the granules were found to be in the range of 0.306 ± 0.03 to 0.418 ± 0.03 gm/ml. The angle of repose varied from 25.47 ± 0.12 to 30.79 ± 0.26. The tapped densities were ranged between 0.313 ± 0.04 to 0.472 ± 0.05 gm/ml. Hausner's ratio was ranged between 1.055 ± 0.04 to 1.129 ± 0.07, while the compressibility index was in the range of 5.28 ± 0.16 to 11.44 ± 0.12. (table-6)

Table 6:- Physicochemical evaluations of pantoprazole sodium sesquihydrate granules

Batch no	Yield (%)	Mean patricle size (mm)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (θ)
F1	97.82	0.498	0.306	0.326	6.13	1.065	25.79
F2	94.82	0.545	0.312	0.335	6.86	1.073	26.95
F3	95.37	0.527	0.358	0.358	7.01	1.075	26.33
F4	94.12	0.542	0.357	0.384	7.03	1.075	28.31
F5	93.43	0.533	0.359	0.394	8	1.097	27.2
F6	91.68	0.535	0.384	0.429	10.48	1.117	30.27
F7	94.23	0.512	0.312	0.334	6.58	1.07	29.52
F8	95.89	0.548	0.286	0.313	8.62	1.094	26.13
F9	97.14	0.536	0.306	0.334	8.38	1.091	26.78
F10	94.42	0.559	0.294	0.324	9.25	1.102	28.09
F11	93.57	0.538	0.307	0.34	9.7	1.107	28.74
F12	94.6	0.507	0.384	0.406	5.41	1.057	25.47
F13	94.86	0.537	0.394	0.416	5.28	1.055	28.47
F14	96.13	0.523	0.416	0.457	8.97	1.098	29.79
F15	97.37	0.567	0.384	0.41	6.34	1.067	26.32
F16	86.13	0.545	0.418	0.472	11.44	1.129	30.79

(n=3 ± S.D)

Post compression parameters:-

The pantoprazole sodium sesquihydrate tablets were prepared by the wet granulation method. The results of the physicochemical evaluation of prepared tablets are shown in Table 7. The tablets were evaluated for Average weight, hardness, friability, and drug content. The drug content was found to be between 95.42 ± 0.38% to 99.42 ± 0.26%. The hardness was found to be from 4.73 ± 0.42 to 8.40 ± 0.002 kg/cm2 and in all the cases the friability was less than 1%. (table-7).

Table 7:- Physicochemical evaluations of pantoprazole sodium sesquihydrate tablets

Batch no	Parameter			
	Hardness (kg/cm2)*	Friability (%)**	Average weight (g)**	Drug content (%)***
F1	8.4	0.011	0.201	98.85
F2	5.8	0.012	0.199	97.71
F3	6.2	0.016	0.204	98.85
F4	4.9	0.005	0.203	97.42
F5	4.93	0.023	0.208	96.85
F6	4.73	0.024	0.205	97.14
F7	5.66	0.24	0.199	98.55
F8	8.2	0.017	0.209	99.42
F9	5.6	0.11	0.198	96.85
F10	5.73	0.11	0.203	96.28
F11	5.12	0.09	0.206	95.78
F12	8.06	0.011	0.198	94.57
F13	7.66	0.019	0.207	95.42
F14	5.56	0.051	0.206	95.71
F15	5.83	0.032	0.204	95.71
F16	6.21	0.023	0.199	96.01

*(n=5 ± S.D)
**(n=20 ± S.D)
***(n=3 ± S.D)

In vitro drug release studies:-

The in vitro dissolution studies were carried out for the prepared tablets using USP apparatus type II. The in vitro release profiles of pantoprazole sodium sesquihydrate tablets are shown in Tables. The cumulative percentage of the release of pantoprazole sodium sesquihydrate from the prepared tablets was varied from 65.02 ± 0.42% to 99.26 ± 0.16% depends upon the drug-polymer ratio for 12 h. (table-8, Fig.- 11).

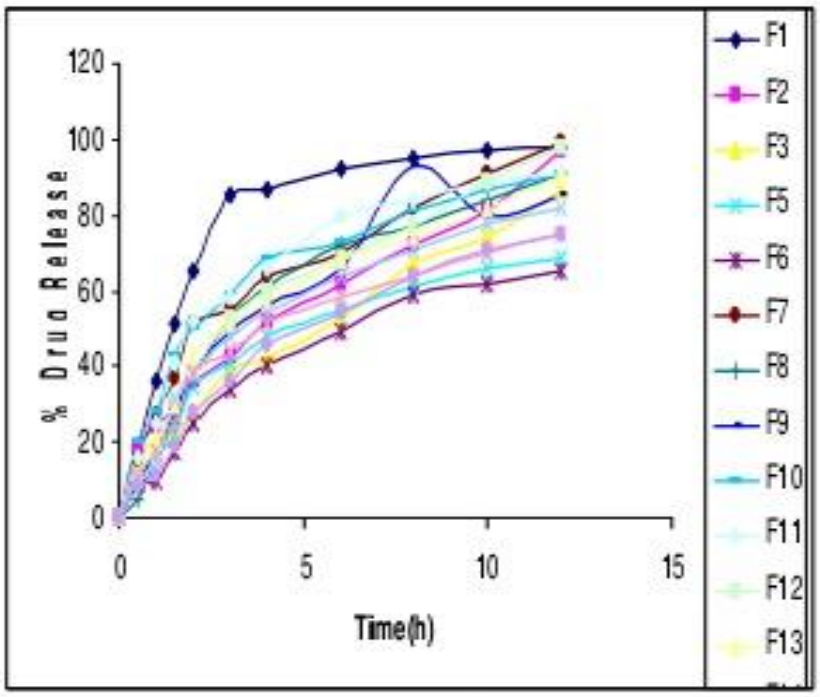

Figure 11:- ***In vitro*** **drug release profile of pantoprazole sodium sesquihydrate from various tablet formulations (F1 to F16)**

Table 8:- *In vitro* drug release profile of pantoprazole sodium sesquihydrate from various tablet formulations (F1 to F16)

Time (h)	Cumulative percentage of drug released														
	F1	F2	F3	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	17	19	15	9	9	15	5	9	20	16	10	11	10	11	8
1	36	24	21	16	10	27	15	17	28	25	15	20	15	17	11
1.5	51	29	23	22	17	37	25	28	43	41	31	30	31	24	19
2	65	36	28	35	25	51	37	39	50	52	38	43	38	38	28
3	85	42	39	41	34	55	53	49	59	58	53	51	48	44	36
4	87	52	42	48	40	64	61	56	69	66	60	57	54	51	46
6	92	62	53	55	49	70	72	66	73	80	69	68	64	58	54
8	95	72	67	61	59	82	77	93	81	84	77	74	71	64	64
10	97	81	74	66	62	91	84	80	87	89	89	82	78	70	71
12	98	97	87	69	65	99	91	85	91	91	98	90	82	75	75

4. DISCUSSION:

FT-Infrared spectroscopy to find out the compatibility of the drug with polymer This was carried out to find out the possible interaction between selected drug pantoprazole and polymers hydroxypropyl methylcellulose, Cassava starch, and polyvinyl pyrrolidone. FT-IR of pantoprazole showed the following peaks at 3483.56, 3358.18, 3176.87, 2960.83, 1591.33, 1373.36, and 1049.31nm due to N-H, O-H, CH2, CH3, C-O, C-F, and S=O functional groups. The physical mixture of drug with polymer hydroxypropyl methylcellulose, Cassava starch, and polyvinyl Pyrrolidone clearly shows the retention of these characteristic peaks of pantoprazole thus revealing no interaction between the selected drug and polymers.

Preparation of pantoprazole tablets:-

This method produced granular particles and very few fines. The pantoprazole sodium sesquihydrate tablets were prepared by the wet granulation method. Hydrophilic matrix systems are widely used in oral sustained drug delivery because they make it easier to achieve a desirable drug release profile, they are cost-effective and they have broad US FDA acceptance. The Cassava starch and PVP are also used as the polymer in the other formulation49. The hydrophilic polymer matrix system consists of a hydrophilic polymer, drug, and other excipients distributed throughout the matrix. Sustained delayed-release can be achieved by formulating drugs as matrix devices using HPMC, PVP, and/ or other polymers 50,51,52. The solubility of HPMC is pH-independent. In this study HPMC, Cassava starch, and PVP were used as a hydrophilic release retarding polymer in different concentrations and the Avicel pH 102 (MCC) as filler and starch paste (5%) as a binding agent. During the optimization of granules, less moisture sluggy masses were found to have more fines and high friability and the high moisture sluggy masses were sticky in the sieving process. Hence, optimum moisture (paste 5%) was used for preparing the granules. Drying of granules was performed at 50°C temperature. This method produced narrow-shaped granular particles with very few fines. The obtained granules were smooth and almost uniform-sized.

Characterization of pantoprazole sodium sesquihydrate tablets:-

a) Pre-compression parameters:

The prepared pantoprazole granules for tableting were prepared by the wet granulation method. The prepared pantoprazole granules were evaluated for percentage yield, mean

granule particle size, angle of repose, bulk density, tapped density, Hausner's ratio, and compressibility index. This method was able to produce narrow-shaped granular particles with fewer fines. The obtained granules were smooth and almost uniform sized. The percentage yield of the granules was ranged between 86.13 to 97.82% w/w. This could be considered a satisfactory product yield value of granules and this was due to the polymer binding properties of granules. The particles were found to possess a narrow range of size distribution and have an average particle size in the range of 0.498 ± 0.05 to 0.559 ± 0.12 mm. The bulk densities of the granules were found to be in the range of 0.306 ± 0.03 to 0.418 ± 0.03 gm/ml, while the tapped densities were ranged between 0.313 ± 0.04 to 0.472 ± 0.05gm/ml. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The low values of compressibility (5.28 ± 0.16 to 11.44 ± 0.12%) signify good flowability. The angle of repose of all formulations was less than 30° (25.47 ± 0.12 to 30.79 ± 0.26) also indicates the good flowability of the prepared granules. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets[44].

b) Post compression parameters:-

The pantoprazole tablets were prepared by the wet granulation method and shown in Figure. The tablets were evaluated for their hardness, weight variation, content uniformity, friability, and in vitro drug release. The hardness test is one of the control parameters during the manufacturing of tablets. Generally, the tablet prepared with low compression force was dissolved faster than that with high compression force. Hardness must be controlled to ensure that the product is firm enough to with and handling without breaking or crumbling and not so hard that the disintegration time is unduly prolonged. The recommended value for a tablet is 4 to 8 kg/cm2. The average hardness of the tablets to be in range was found within 4.73 ± 0.42 to 8.40 ± 0.002 kg/cm^2. The average weight variation of tablets was found within the limits of 7.5% (I.P.). The friability value which is also affected by the hardness value of tablets should be in the range of 0.5 to1% limits, which is the usual friability range of tablets. The friability of the prepared tablets was found less than 1% w/w. The uniformity of drug pantoprazole sodium sesquihydrate present in tablets formulation ranged from 95.42 ± 0.38 to 99.42 ± 0.26%. The physicochemical parameters of the prepared tablets were compared with the marketed tablet (Pantosec 40 mg, Cipla, India) containing 40 mg of pantoprazole. It was

found that the physicochemical parameters of the prepared tablets, as well as the marketed tablets, comply with the standards.

5. CONCLUSION:

Ulcers are crater-like sores that form in the lining of the stomach, just below the stomach at the beginning of the small intestine in the duodenum. An ulcer is the result of an imbalance between aggressive and defensive factors. Pantoprazole is a substituted benzimidazole derivative that targets gastric acid proton pumps, the final common pathway for gastric acid secretion. The drug covalently binding to the proton pumps, causing prolonged inhibition of gastric acid secretion. The stability of pantoprazole is a function of pH and it rapidly degrades in the acid medium of the stomach but has acceptable stability in alkaline conditions. Therefore, pantoprazole should be delivered into the intestine. Hence, an attempt was made to formulate a delayed-release drug delivery system for pantoprazole by using various enteric coating polymers. The main objective of the study was to develop delayed-release tablets of pantoprazole. The study led to the following conclusions:

The drug pantoprazole was selected for the study, because of its availability, proved activity, and better clinical applications. The compatibility studies using FT-IR revealed that there was no interaction between the selected drug pantoprazole and the polymers HPMC. The pantoprazole granules were prepared by the wet granulation method. The physicochemical parameters of the granules observed support the ideal flow nature of the formulated granules. The pantoprazole tablets were prepared by the wet granulation method. The physicochemical evaluation of the prepared tablets was found within the standard's pharmacopeial limits. The effect of enteric coating on the in vitro drug release, none of the CAP enteric-coated tablets showed drug release during the first 2 h in pH 1.2. While the Drug coat L100 and Eudragit L100 coated formulation showed a drug release of 0.5% to 1% during the first 2 h in pH 1.2. Release of drug from the tablets was the first-order diffusion-controlled as indicated by higher r2 values in the First-order kinetic and Higuchi model. The n value of the Korsmeyer Peppas equation indicated that the release mechanism was super case-II transport.

The optimized formulation was stable and retained the pharmaceutical properties at room temperature and 400C / 75% RH over 1 month. The pantoprazole sodium sesquihydrate coated tablet formulation ECF3 showed its antiulcer activity. Based on the observations, it can be concluded that the formulated delayed-release tablets of pantoprazole using widely

accepted and physiologically safe polymers and other excipients were capable of exhibiting sustained release properties for a period of 12 h. The enteric-coated, especially the CAP coated tablets, did not release the drug in the acidic pH 1.2 for a period of 2 h. They are thus may be reducing the dose intake, prevent the degradation of the drug in acidic pH 1.2, minimize the blood level oscillations, dose-related adverse effects, and cost and ultimately improve patient compliance and drug efficiency.

6. SUMMARY:

The present study aimed to formulate and evaluate the delayed-release drug delivery system of pantoprazole sodium sesquihydrate tablets by using HPMC, Cassava starch, and polyvinyl pyrrolidone. FT-IR study was carried out to check any possible interactions between the drug and the polymers HPMC, Cassava starch, and polyvinyl pyrrolidine, the study confirmed that no interaction between the selected drug and the polymers. Pantoprazole sodium sesquihydrate granules were prepared by wet granulation method using different concentrations of HPMC, Cassava starch, and PVP as release retarding polymers, Avicel pH 102 (MCC) as filler, and starch paste (5%) as a binding agent. Magnesium stearate and talc were used as glidants and lubricants respectively. The granules were evaluated for percentage yield, mean particle size, angle of repose, bulk density, tapped density, and compressibility index. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility index and angle of repose signify good flowability of the granules for all the batches. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets. The compressed tablets were evaluated for their hardness, weight variation, content uniformity, and friability. The in vitro dissolution studies were carried out for compressed and coated tablets using USP dissolution apparatus type II. The cumulative percentage of drug release from the tablets varied and depends on the type of polymer used and its concentration.

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