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A Design Research on Formulation and Characterization of Gastro-retentive Tablet to Target Ulcer and Control Emesis

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ABSTRACT

Targeted release of bilayer tablet for combination therapy of pantoprazole sodium and ondansetron hydrochloride for the treatment of gastric and duodenum ulcers associated with vomiting. In bilayer tablet release profiles may be modified by combining layers with various release patterns. Both Ondansetron hydrochloride and Pantoprazole sodium have short biological half-life and frequent administration may lead to patient incompliance. Thus, bilayer tablet is to be prepared imparting delayed release for pantoprazole sodium and sustained release for ondansetron hydrochloride.

Pantoprazole Na, an anti-ulcer drug, has several advantages compared to its analogues (e.g., omeprazole and lansoprazole) such as specific site of binding, greater stability in neutral pH environ-ment, and longer duration of action. Besides, it presents no potential to induce or inhibit the CYP 450. It is a more selective inhibitor of acid secretion than other proton pump inhibitors. Pantoprazole Na is absorbed in the intestine. It possesses an irritant effect on the stomach and is unstable under acidic conditions. Hence enteric delivery system is required. Such formulation would avoid the stomach's acidic exposure, delivering them to a basic pH environment (intestines pH 5.5 and above) and give their desired action.

Ondansetron HCl is a potent, highly selective 5-HT3 receptor-antagonist. It is widely prescribed to control or prevents nausea and vomiting. It has narrow absorption window in stomach. Once a day ondansetron HCl gastroretentive tablets offer better patient compliance through less frequent administration and thus would lower the cost of total therapy. Hence, the focus of present work is to prepare and evaluate gastro retentive floating tablet of the ondansetron HCl to increase its residence time in to achieve prolonged therapeutic action.

KEY WORDS: Bilayer tablet, Pantoprazole Sodium, Ondansetron HCl, Floating tablet, Enteric Coated tablet

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1. INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. [14]

1.1 Floating tablet

1.1.1 Basic Gastrointestinal Tract Physiology[11]

The stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which

is divided into 4 phases as Phase-I (basal phase), Phase-II (preburst phase), Phase-III (burst phase), Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

1.1.2 GRDDSs include: achieving a greater and prolonged therapeutic effect, improve the bioavailability of drugs and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders. Reported methods for the design of gastroretentive systems include mucoadhesion, floatation, sedimentation, expansion and modified shape systems Single and multiple system approaches have also been reported in the literature. A gastric floating drug delivery system (GFDDS) can overcome at least some of these problems and is particularly useful for drugs that are primarily absorbed in the duodenum and stomach.[4] Among these, the floating dosage form has been used most commonly. The floating systems include gas-generating systems, noneffervescent systems and raft forming systems. [1]

The influence of different grades of hydroxypropyl methyl cellulose (HPMC K4M and K10M) and Carbopol 934P on the release kinetics and buoyancy was studied in floating and bioadhesive tablets containing captopril as a model drug. Various polymers, including sodium carboxy methylcellulose (SCMC), were investigated for the evaluation of an oral sustained release floating dosage form of amoxicillin trihydrate; Effervescent tablets with bioadhesive capabilities for ciprofloxacin were made of sodium carboxymethyl cellulose, HPMC, polyacrylic acid, polymethacrylic acid, citric acid, and sodium bicarbonate to lengthen the stay in the absorption region. it was reported that SCMC-containing tablets quickly gelled, losing shape and floating on the surface of the dissolution medium. [6]

1.2 Enteric coated tablet

The tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. It offers many benefits namely – improving the aesthetic quality of the dosage form, masking unpleasant order or test, easing ingestion, improving product stability and modified the release characteristic of the drug. An enteric coating is a barrier applied to oral medication that controls the location in digestive system where it is absorbed. Enteric refers to the small intestine, therefore enteric coatings prevent release of medication before it reaches the small intestine .Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Gastro-oesophageal reflux disease, peptic ulcers, non-ulcer dyspepsia or the use of NSAIDs, are very common. Among the drugs available to inhibit acid secretion, proton pump inhibitors (PPI) have been shown to have the best efficacy-safety ratio. [16]

The enteric coating is done by the different approaches like pH dependent approach, Time dependent approach, Bioadhesive system, Pressure controlled system , Osmotic drug delivery. In which pH and time dependent approaches are mostly used. This approach utilizes the existence of pH gradient in the GIT that increases progressively from the stomach (pH 1.5-3.5) and small intestine (5.5-6.8) to the colon (6.4-7.0). By combining the knowledge of the polymers and their solubility at different pH environments, delivery systems can be designed to deliver drugs at the target site. [18]

The coating of pH-sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid. The problem with this approach is that the GIT pH may not be stable because it is affected by diet, disease and presence of fatty acids, carbon dioxide, and other fermentation products. Moreover, there is considerable difference in inter- and intraindividual gastrointestinal tract pH, and this causes a major problem in reproducible drug delivery to the small intestine.

Table 1.Various pH dependent coating polymers

Polymer	Threshold pH
Eudragit L 100	6.0
Eudragit S 100	7.0
Eudragit L-30D	5.6
Eudragit FS 30D	6.8
Eudragit L 100-55	5.5
Poly vinyl acetate phthalate	5.0
Hydroxypropylmethylcellulose phthalate	4.5-4.8
HPMC phthalate 50	5.2
HPMC phthalate 55	5.4
Cellulose acetate trimellate	4.8
Cellulose acetate phthalate	5.0

1.3 Bilayer tablet

Bilayer layer are novel drug delivery system where combination of two or more drug in single unit having different release profiles improves patient compliance, prolong the drug action, avoid saw tooth kinetics resulting in effective therapy along with better control of plasma drug level. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles.

1.3.1 Advantages

- ✓ Release of both drugs starts immediately Combination of incompatible drugs, Physical/chemical incompatibility can be prevented.
- ✓ Combine different release profiles (Immediate release and sustained release)
- ✓ Reduced Pill Burden By reducing individual dose of two drug due to their additive effect. Example: Salbutamol + Theophylline
- ✓ Reduce the side effects Reduced by using one drug of the combination for this purpose. Amiloride may prevent hypokalemia caused by hydrochlorthiazide
- ✓ Treat different ailments in the same patient (co-morbidity), at the same time and with one pill. Example: Combination of β - blocker and ACE inhibitor or Diuretics is beneficial to treat Hypertention and Heart failure. Only Allows for synergistic combination.

1.3.2 Disadvantages[17]

- ✓ Layer-separation during manufacturing,
- ✓ Insufficient hardness,
- ✓ Inaccurate individual layer weight control,
- ✓ Cross-contamination between the layers,
- ✓ Reduced yield, etc.
- ✓ Not be your best approach to producing a quality bilayer tablet under GMP-conditions. Especially when in addition high production output is required.

1.3.3 Ideal candidate of bilayer tablets

- ✓ Drug produces additive/synergistic effect Anti- asthmatic: Salbutamol + Theophylline
- ✓ Drugs having opposite side effects, may reduce the side effect: Omeprazole + NSAIDS, Hydroclorothiazide + Amiloride
- ✓ Incompatible drugs
- ✓ Low biological half life (ideal for modified release bilayer) Omeprazole, Pantoprazole Na + Domperidone
- ✓ Unstable at intenstinal pH (ideal for bilayer floating)
- ✓ High first pass metabolism with low biological half life (ideal for buccoadhesive bilayer)

1.4 Disease and Disease treatment

1.4.1 Duodenal ulcer

A peptic ulcer in the stomach is called a gastric ulcer. A duodenal ulcer is a peptic ulcer that develops in the first part of the small intestine (duodenum).

A duodenal ulcer is an open sore (ulcer) that develops when there is a break in the lining of the duodenum, the upper part of the small intestine which is connected to the stomach. When food passes from your mouth, it moves through the esophagus and into your stomach. From the stomach, it travels into the duodenum. The duodenum produces chemicals and mucus, which protects the tissues and covers the surface from the acid. Men tend to be affected more frequently by duodenum ulcers than women. It is also more common in people with a family history of duodenal ulcers. Most duodenal ulcers are caused by a chronic infection with a bacteria called H.pylori. Anti-inflammatory medications such as aspirin and ibuprofen and also affects the lining of the duodenum and causes excess stomach acid. Other factors that may increase the risk of developing a duodenal ulcer include nicotine, caffeine, excessive alcohol consumption and stress. Common sign of an ulcer is a frequent burning pain in your abdomen and pain occurs most often when stomach is empty.

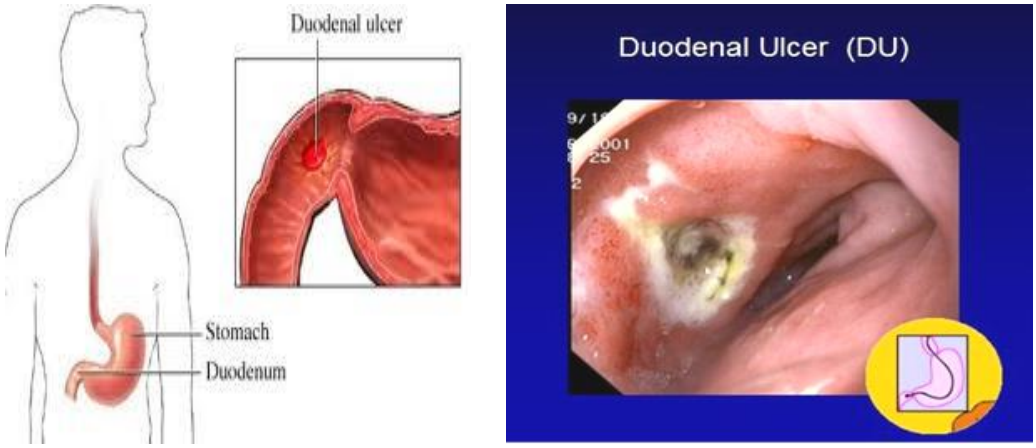


Figure.1: External and Internal structure of duodenal ulcer

1.4.1.1 Symptoms

- ✓ Nausea and Vomiting
- ✓ An ache or burning pain in your abdomen
- ✓ Frequent burning
- ✓ A change in appetite with weight loss
- ✓ Bloody vomit or vomit that looks like coffee grounds
- ✓ Bloody or black tarry stools
- ✓ sharp, sudden, persistent stomach pain

They could be signs of a serious problem, such as
perforation—when the ulcer burrows through the stomach or duodenal wall
bleeding—when acid or the ulcer breaks a blood vessel
obstruction—when the ulcer blocks the path of food trying to leave the stomach

1.4.1.2 Table 2 : Classes of Drugs used to treat Peptic Ulcer

Drug Class	Drugs in the Class
Antibiotics	Amoxicillin, Clarithromycin, Tetracyclin Metronidazole, Levofloxacin
2-Blockers	Cimetidine(Tagamet), Famotidine (Pepcid), Nizatidine (Axid), Ranitidine (Zantac)
Proton Pump Inhibitors (PPIs)	Esomeprazole(Nexium), Omeprazole(Prilosec), Rabeprazole(Aciphex), Pantoprazole Na (Protonix), Lansoprazole (Prevacid)
Cytoprotective Agents	Bismuth subsalicylate, bismuth subcitrate potassium, sucralfate

1.4.1.3 Pantoprazole Na is a proton pump inhibitor belongs to group of benzimidazole. Pantoprazole Na inhibits the H^+/K^+- ATPase enzyme, which is responsible for gastric acid secretion in the parietal cells of the stomach and irreversibly block the final step of acid secretion. It increases motily of GI tract by inhibiting the action of dopamine and fastens gastric emptying. This drug inhabits gastric acid formation and there by it is very efficient for the treatment of gastric and duodenum ulcers. In aqueous media more acidic pH, it suffers decomposition within shorter time. It is sensitive to heat, humidity, light and especially to drugs contains an acidic group. Pantoprazole Na haveing an irritant effect on the stomach, can be coated with a substance that will only dissolve in the small intestine. Dose of the drug is 20-40mg 1-2 times/day.[16] Pantoprazole Na has several advantages compared to its analogues (e.g. omeprazole & lansoprazole)such as specific site of binding, greater stability in neutral pH environment and longer duration of action. Besides, it presents no potential to induce or CYP 450.[2]

1.4.2 Emesis

Nausea and vomiting are not diseases, but are only indications of altered physiological functions. Rational therapy depends on diagnosis of the underlying disorder and may or may not include drugs. antidopaminergic agents

- ✓ 5-HT_3 antagonists
- ✓ H_1 antihistamines

- ✓ cannabinoids
- ✓ corticosteroids
- ✓ benzodiazepines

1.4.2.1 Ondansetron HCl is a potent, highly selective 5-HT3 receptor-antagonist. That will be used to prevent the nausea and vomiting. Ondansetron HCl has a short biological half-life (3.5 ± 1.2 hours) and 62 % absolute bioavailability. Dose of the drug is 8-10 mg 1-2 times/day or 24 mg or 32 mg once daily. [10]

The drugs that are currently used to prevent and treat vomiting belong to the following classes:

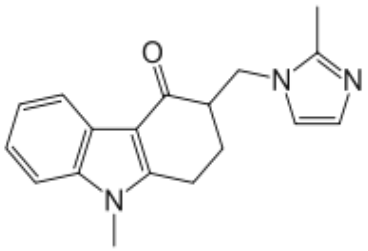
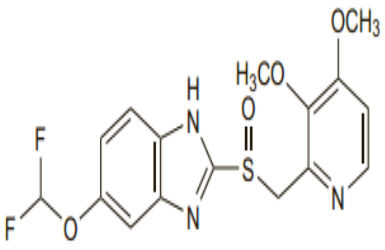
- ✓ anticholinergic agents

1.5 Objectives

- ✓ Optimize the type and concentration of different polymers to give maximum gastro retentive effect with good drug release profile.
- ✓ Application of Design of Experiment for optimizing the formulation.
- ✓ Formulate and evaluate floating tablet of Ondansetron.
- ✓ Optimize the type and concentration of different polymers to give maximum delayed release profile for enteric coated tablet.
- ✓ Formulate core tablet and make it enteric coated with enteric coated polymers, than evaluate enteric coated tablet of Pantoprazole Na.
- ✓ To formulate bilayer sustain release tablet of Ondansetron and Pantoprazole Na using direct compression technology.
- ✓ Evaluation study as per ICH guideline.
- ✓ Improve Patient compliance.

1.6 Drug information [22.23,24,15,19]

Table. 3 Drug information of Pantoprazole Na and Ondansetron HCl

Drug	**Ondansetron HCl**	**Pantoprazole Na**
Synonyms	Zofran, Zophren, Zudan	Pantoprazol, Pantoprazole Na Na, Pantoprazole Na Sodium, Pantoprazolum
IUPAC	(RS)-9-methyl-3-[(2-methyl-1-*H*-imidazole-1-yl) methyl]-2,3-dihydro-1-carbazole-4(9*H*)-one	(*RS*)-6(Difluoromet-hoxy)-2-[(3,4-dimeth --oxypyridin-2-yl) methylsulfinyl]-1*H*-benzo [*d*]imidazole
Appearance	White to Light Beige Solid	White solid Powder form
Mol. Structure		
Mol. Formula	$C_{18}H_{19}N_3O$	$C_{16}H_{15}F_2N_3O_4S$
Mol. Weight	293.3599 g/mol	383.371 g/mol
Solubility in Water	10 mg/ml at 25°C	4.95e-01 g/l
pK_a	7.4	15.76
Partition Coefficient	1.7000	2.18
BCS Class	Class – I	Class – I

Category	Anti-emetic agent	Anti-Ulcer Agents, Proton-pump Inhibitors
Treatment	Nausea, vomiting	Deuodanal ulcer
Dosage	Given orally Adult: 10 mg twice in a day	Oral and intravenous
PHARMACOKINETICS		
Protein Binding	70%-76%	98%
Bioavailability	60-70%	77- 97%
Metabolism	Hepatic: deace- tylation to rhein, later glucuronid- ation and sulfate conjugation	Hepatic: demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4.
Mechanism of Action	Short acting serotonin 5-HT3 receptor antagonist used for nausea and vom- iting 5-HT in small intestine initiating a vomi- ting reflex by activating vagal afferents via 5 HT3 receptors.	Suppresses gastric acid production by forming a covalent bond to two sites of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose- related and leads to inhibition basal and stimulated gastric acid secretion irrespective of the stimulus.
Half-life	3 - 5 h	1 h
Excretion	Renal (30%)	Renal (71%)
Food	Should be taken with or without food.	Take without regard to meals.
Side-effects	Constipation, headache, chest pain, dry mouth.	Nausea, vomiting, headache, abdominal pain.
Market Formulations	Zofran, zofran ODT, Ondarit, Ondon.	PANCARD, Bio-Panto, PANRIT-DSR, Protonox®
Combination in Market	Emtop OD, Ondon P, Vomizen p, Pantorex O, Ondon P (inj).	

2. MATERIALS AND METHODS

2.1 Proposed Materials[1,2,4,5,16,]

Table. 4 Proposed material used for formulation of tablet

Ingredients	**Floating tablet**	**Enteric coated tablet**
Drug	Ondansetron	Pantoprazole Na
Polymers	HPMC K4M, HPMC K15M, HPMC K100M, EC, Carbopol 934P, Sodium alginate, Xanthan gum, Guar gum	HPMCP, CAP, PVAP, HPMC acetate phthalate Eudragit L-100, Eudragit L-30 D-55,
Gas generating Agent	Sodium bicarbonate, citric acid, tartaric acid, $CaCO_3$	---------
Binders	PVP K 30, HPMC, HPC, MC, Alginate	
Diluents	MCC, Spray dried Lactose, Emdex, Celutab	
Lubricants	Talc and Magnesium stearate	

2.2 METHODS

2.2.1 Preparation of floating tablets[1]

Gastroretentive tablets of Ondansetron HCl will be prepared by direct compression methods employing sodium bicarbonate as a gas generating agent. HPMC K4M, HPC and Carbopol 934P will be used as a rate controlling polymers. All the ingredients (Table 1) will be weighed accurately. The required quantity of drug will be mixed with release rate retarding polymers and other excipients in ascending order of their weight. The powder mix will be blended for 20 minutes so as to have uniform distribution of drug. The powder mix, 150mg will be weighed accurately and fed into die of single punch tablet machinery and compressed.

2.2.2 Preparation of enteric coated tablets[5,16]

Pantoprazole Na core tablets will be compression-coated with pH-depe ndent dependent polymers. Each core tablet will be consisted of Pantoprazole Na, super disintegrant and anhydrous lactose as direct compression vehicle. Pantoprazole Na and other ingradients will be thoroughly mixed and passed through mesh. The mixture will be compressed into core tablets with single punch tablet machine equipped with flate punch 6 mm in diameter. The core tablets will be compression-coated with 400 mg different coat polymers. About 50% of the coat polymer was placed in the die cavity and the core tablet will be then placed in the center of the die cavity, which was filled with the remainder of the coat polymer. Then, it will be compressed around the core tablets using 12 mm flate punches.

2.2.3 Compression of bilayer tablets[17]

In this method, Floating tablet and enteric coated tablet will be compress together by keeping buffer layer between two tablet.

3. EVALUATION PARAMETERS

3.1 Preliminary evaluation tests

3.1.1 Spectrophotometric scanning of Ondansetron HCl & Pantoprazole Na [20,21]

The determination of λ_{max} is identified by scanning the suitable diluents solution of Ondansetron HCl and Pantoprazole Na in spectrophotometer.

3.1.2 Standard curve[20,21]

3.1.2.1 Calibration curve of Ondansetron HCl in 0.1N HCl buffer

A stock solution of pure drug will be prepared by dissolving accurately weighed(100 mg) drug in 100 mL solution of 0.1N HCl. From the stock solution, suitable dilution will be made and absorbance will be measured at appropriate wavelength using UV-Visible spectrophotometer.

3.1.2.2 Calibration curve of Pantoprazole Na in 0.1N HCl buffer

A stock solution of pure drug will be prepared by dissolving accurately weighed(100 mg) drug in 100 mL solution of 0.1N HCl. From the stock solution, suitable dilution will be made and absorbance will be measured at appropriate wavelength using UV-Visible spectrophotometer.

3.1.2.3 Calibration curve of Pantoprazole Na in pH 6.8 phosphate buffer

A stock solution of pure drug will be prepared by dissolving accurately weighed(100 mg) drug in 100 mL solution of phosphate buffer pH 6.8. From the stock solution, suitable dilution will be made and absorbance will be measured at appropriate wavelength using UV-Visible spectrophotometer.

3.1.2.4 Calibration curve of Pantoprazole Na and ondansetron HCl in methenol

A stock solution of pure drugs will be prepared by dissolving accurately weighed(100 mg) drug in 100 mL methanol. From the stock solution, suitable dilution will be made and absorbance will be measured using UV-Visible spectrophotometer.

3.1.2.5 Simultenious estimation of ondansetron HCl & pantoprazole Na in 0.1N HCl[20]

Using the Spectrum mode with medium scan speed, the zero-crossing point (ZCPs) of ondansetron HCl at which the Pantoprazole Na showed some derivative response will be recorded. The wavelength where the derivative response for ondansetron HCl is zero will be selected for the quantitation of pantoprazole Na and vice-versa.

3.2 Floating tablets

3.2.1. Physical characterization tests

3.2.1.1 Weight variation [4]

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit.

$$\%\boldsymbol{Deviation} = (\textbf{Avg. weight of tablet} + \textbf{Initial weight}\ )/(\textbf{Avg. weight of tablet}) \times \mathbf{100} \quad (\mathbf{1})$$

Table 4 IP standards of percentage of weight variation

Average weight of a tablet	% deviation
80mg or less	10
>60mg but <250mg	7.5
250mg or more	5

3.2.1.2 Hardness[4]

Hardness of the tablets can be measured by Monsanto hardness tester (Rolex) for formulated tablets. The experiment was carried out in triplicate and mean values will be recorded.

3.2.1.3 Thickness[4]

The thickness of 10 tablets will be measured using screw gauge micrometer and will be tried to control within 5% variation of the standard value.

3.2.1.4 Friability[4]

Ten tablets will be weighed and placed in the Roche friabilator (Veego) test apparatus. The tablets will be exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions, the tablets were reweighed. The friability will be determined using following formula.

$$\%\ \textbf{Friability} = (\textbf{Initial weight} - \textbf{Final weight}\ )/(\textbf{Initial weight}) \times \mathbf{100} \quad (\mathbf{2})$$

3.2.2 Swellability study floating tablets[10]

A floating tablet were placed in simulated gastric fluid (pH 1.2) and allowed to swell for the required period of time at 37±0.5°C in the dissolution apparatus. The floating tablet were periodically removed and then their change in weight was measured until attainment of equilibrium. The swelling ratio (SR) was then calculated using the following formula:

$$\boldsymbol{SR} = (\mathbf{Wg} - \mathbf{Wo}\ )/\mathbf{Wo} \times \mathbf{100} \quad (\mathbf{3})$$

Where, *SR*= Swelling ratio; *Wg*= Final weight of tablet; *W0* = Initial weight of tablet.

3.2.3 Drug content estimation for Ondansetron HCl floating tablet[6]

Prepared 10 tablets will be accurately weight and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to 1 mg/ml of prepared tablet was transferred in to a volumetric flask and the drug will be extracted with methanol as the solvent. The contents of the flask will be diluted with 0.1 N HCl as the solvent. The samples will be analyzed spectrophotometrically at 293 nm.

3.2.4 *In vitro* buoyancy studies[10]

The *In vitro* buoyancy study will be determined by lag time and floating duration. The floating lag time and the duration of floating will be determined in the USP dissolution apparatus II paddle type apparatus using 900ml of 0.1 N HCl at paddle rotation of 50 rpm at 37± 0.5°C. The time interval between the introduction of the tablet into the dissolution medium and its floating to the top of dissolution medium will be taken as floating lag time and the floating duration of the tablets will be determined by visual observation.

3.2.5 *In Vitro* Drug dissolution Profile for Ondansetron HCl floating tablet[13]

In vitro drug release of the formulation was carried out by using USP II apparatus (paddle method). The dissolution will be performed using 900 ml of 0.1 N HCl (pH=1.2), at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution will be withdrawn at a regular interval of one hour for initially six hours, every two hours up to 12 hours and every four hours till 24 hours. The samples will be replaced with fresh dissolution medium of same quantity. Absorbance of these solutions was measured at 310.00 nm using a Shimadzu UV-1700 double beam Spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

3.2.6 Drug release kinetic study[4]

Data obtain from *in vitro* release studies will be fitted to various kinetic equation to find out the mechanism of release of Ondansetron HCl floating tablet.

3.3 Enteric coated tablets

3.3.1 Physical Characterization test [4]

The enteric coated tablets will be evaluated for hardness, weight variation, friability (percent), and disintegration time as per the USPXXII procedure.

3.3.1.1 Weight Variation

Weight variation test will be carried out using 20 tablets and determining their weight with the help of electronic balance.

3.3.1.2 Thickness

Thickness will be measured by Screw gauge micrometer.

3.3.1.3 Hardness

Hardness measurement will be carried out by Monsanto tester.

3.3.1.4 Friability

Friability (percent) will be calculated by taking 20 tablets with the help of Roche's friability tester by using 25 rpm for 4 min.

3.3.2 Drug content estimation for Pantoprazole Na enteric coated tablet[6]

Enteric coated tablet will be accurately weight and finely powdered by pestle in a mortar. This fine powder will be transferred in to a volumetric flask and the drug was extracted with methanol as the solvent. The contents of the flask will be diluted with methanol the solvent. The samples will be analyzed spectrophotometrically at 300 nm.

3.3.3 Disintegration Time[1]

Disintegration test will be carried out in USP XXII disintegration test apparatus using 900 mL of pH 6.8 phosphate buffer.

3.3.4 *In Vitro* Drug dissolution for Pantoprazole Na enteric coated tablet[13]

After 2 hrs , enteric coated tablet containing Pantoprazole Na tablet will be taken out from 0.1 N HCl solution and put it after 2 h into 900 ml 6.8 pH containing phosphate buffer at 37 ± 0.5 °C and 50 rpm agitation. Five ml sample aliquots will be withdrawn and an equal volume of the fresh medium will be replaced. The drug release at different time intervals was measured by UV-1700 UV-visible spectrophotometer at 280 nm (HCl buffer solution pH-1.2) and at 265 nm (Phosphate buffer pH-6.8).

3.3.5 Drug release kinetic study[4]

Data obtain from *in vitro* release studies will be fitted to various kinetic equation.

3.4 Bilayer tablets

3.4.1 Physical Characterization test [4]

The bilayer tablets will be evaluated for hardness, weight variation, friability (percent), and disintegration time as per the USPXXII procedure.

3.4.1.1 Weight Variation

Weight variation test will be carried out using 20 tablets and determining their weight with the help of electronic balance.

3.4.1.2 Thickness

Thickness will be measured by Screw gauge micrometer.

3.4.1.3 Hardness

Hardness measurement will be carried out by Monsanto tester.

3.4.1.4 Friability

Friability (percent) will be calculated by taking 20 tablets with the help of Roche's friability tester by using 25 rpm for 4 min.

3.4.2 Drug content estimation for bilayer tablet formulation[6]

The optimized bilayer tablet formulation will be powdered and a quantity equivalent the average weight of tablet will be accurately weighed and dissolved in a suitable quantity of solvent. The solution will be made up to the mark and mixed well. A portion of

sample will be filtered. After making suitable diluents the final solution will be analyzed. The absorbance of the resultant solution will be measured at appropriate wavlength using simultaneous UV specrtophotometric method.

3.4.3 *In Vitro* Drug Release for the novel bilayer tablet formulation containing Ondansetron HCl floating tablet and Pantoprazole Na enteric coated tablet[13]

Dissolution studies of the optimized formulation of bilayer tablet will be conducted using USP II apparatus (paddle). The dissolution medium will be 900 ml of 0.1 N HCl and after 2 h enteric coated tablet placed in pH 6.8 phosphate buffer at 37 ± 0.5 °C and agitation rate of paddle was 50 rpm. 5 ml aliquots will be withdrawn up to 12 hr and an equal volume of the fresh medium was replaced. The drug content will be determined spectrophotometrically.

3.4.4 Stability study[14]

Stability studies will be carried out at 25°C ± 2°C / 60% RH ± 5 % and 40°C ±2°C / 75% RH ± 5% for a period of 30 days with selected formulations.

3.4.5 Compactibilty study

3.4.5.1 FT-IR Spectroscopy study[1]

FT-IR spectroscopy will be used to determining the solid state of the drug (molecular dispersion, amorphous, crystalline or a combination) in the carrier regardless of the state of the carrier. It also used to study the interaction occur between drug and polymer by matching the peaks of spectra. The absence of any significant change in the IR spectral pattern of drug and polymer physical mixture indicate the absence of any interaction between the drug and the polymer.

3.4.5.2 Differential Scanning Calorimetry (DSC) study[25]

It can be used to detect the amount of crystalline material. It help to study the changes in the physical state of optimized bilayer tablets may occur during heating, and the presence of polymer may influence the melting behavior of drug (e.g. melting point depression).

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