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Formulation Development and Evaluation of Pantoprazole Enteric Coated Tablets

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Abstracts: Pantoprazole 5-(difluoromethoxy)- 2-[(3,4-dimethoxypyridin-2-yl) methylsulfinyl]- 3*H*-benzoimidazole is a proton pump inhibitor belongs to group of benzimidazole . This compound inhabits gastric acid formation and there by it is very efficient for the treatment of gastric and duodenum ulcers. In aqueous media more acidic than pH 4 it suffers a practically complete decomposition within a period shorter than 10 minutes. Even in solid state it is sensitive to heat, humidity, light and especially to substances containing an acidic group. Pantoprazole which have an irritant effect on the stomach, can be coated with a substance that will only dissolve in the small intestine. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action. This stumulate us to formulate and evaluate pantoprazole as a enteric coated tablet.

Key-words: Pantoprazole**,** Enteric Coated, Development and Evaluation.

1. Introduction:

The tablet coating is perhaps one of the oldest pharmaceutical processes still in existence[1]. 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 [2].An enteric coating is a barrier applied to oral medication that controls the location in the 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 (GORD), 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 [3].Drugs such as pantoprazole which have an irritant effect on the stomach and must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric delivery systems are required. Similarly, certain groups of Azoles (Esomeprazole, omeprazole, and all grouped azoles) are acid-unstable . For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action. The purpose of this study was to prepare and formulae the Entericoated Pantoprazole tablets.

2. Material and Method:

2.1 Chemicals and Materials

Pantoprazole sodium sesquihydrate are obtained from Ranit Pharma Ltd. Microcrystalline cellulose IP , Sodium Methyl Paraben IP (Nipagin Sodium)and Sodium Propyl Paraben IP (Nipasol Sodium) were obtained from Neelraj Agencies . Sodium lauryl Sulphate IP and Sodium Metabisulphate IP/USP were obtained from Ranbaxy Fine Chemicals Ltd. Castor Oil , Lake of col. Quinoline Yellow WS , Starch IP and Talcum Powder IP were obtained from Mukesh Chemicals .All the chemicals used

in the study were of pharmacopoeia quality (IP).

2.2 Method

While developing a pharmaceutical dosage form, it is very much important to determine the physico-chemical properties of the drug molecule & the other derived properties of the drug powder. This first phase of the studies is known as pre-formulation studies which provide lots of information about the formulation development.

2.3 Analytical method

This involves the identification of the API (Active pharmaceutical ingredient), evaluation of pharmacopoeial compliance & development of analytical procedure [4, 5].

2.4 Evaluation of the granules: [6]

Angle of repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such away that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of
the powder cone was measured & angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

where, h & r are the height & radius of the powder cone.

Bulk density:

Both loose bulk density (LBD) & tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. LBD & TBD were calculated using the following formulas:

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility Index:

Carr's index (%) = [(TBD – LBD) * 100] / TBD

Where: LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

2.5 Evaluation of tablets : [7,8]

Thickness:

The thickness of the tablet was determined using a thickness gauge (Mitutoyo). Six tablets from each batch were used & average values were calculated (Table no: 2).

Weight variation test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance & the test was performed according to the official method. The USP limit for weight variation in case of tablet weight between 107.3 to 124.7 mg that is 7.5%.

Hardness & friability:

For each formulation the hardness of 6 tablets were determined using tablet hardness testers. The friability of 20 tablets was determined using Roche friabilator. The limit for friability is NMT 1%.

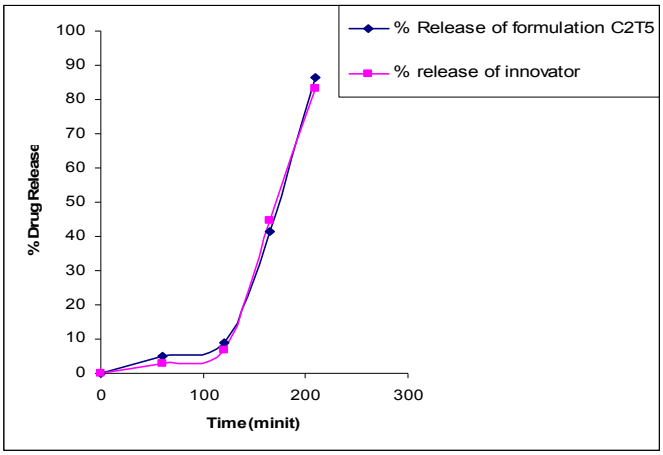
In Vitro Release Studies:

The in vitro dissolution studies [8] for all the formulations were carried out in two steeps, using USP apparatus type II at 100 rpm. The dissolution medium consisted of Hydrochloric acid buffer solution pH - 1.2 (900 ml), and Phosphate buffer pH – 6.8 (900ml), maintained at 37 ^{0}C ± 0.5 ^{0}C. The drug release at different time intervals was measured by UV-1700 UV-visible spectrophotometer at 280 nm (Hydrochloric acid buffer solution pH - 1.2) and at 265 nm (Phosphate buffer pH – 6.8). The release studies were conducted in triplicate (6 tablets in each set) and dissolution procedure are given in the table no 1.

3. Results:

In case of coating tablets trial no. C_1T_1, and C_3T_6 show less color, poor dissolution, poor disintrigation time and more color, poor dissolution, increase disintrigation. Tablets trial no. C2T5 show excellent hardness, disintrigation and coating. The dissolution data and comparison profile between C_2T_5 and innovator were also given in the table no 3 and graph no 1.

Graph no: 1: Comparison profile between C_2T_5 and innovator



4. Conclusions:

Series of experiments were performed during pre-formulation studies to select suitable excipient .Combination of different excipient were used to formulate pantoprazole enteric coated tablet .Various percentage of the excipient were also used to get best formulations with high bioavailability. Evaluation experiments such as friability, hardness, content-uniformity, thickness, weight variation, disintegration time were carried out and found that the results were satisfactory. Dissolution method was developed and validated. Dissolution of three batches of pantaparazole enteric coated tablet were carried out and found that RSD (Relative standard deviation) is below 2% including good reproducibility from batch to batch. Results of evaluation experiments were compared with marketed formulation .

Table 1: Specifications for dissolution procedure

Medium	Vessels temp	Bath temp	Dissolution Medium	Dissolution time	Volume of Dissolution Medium	λ_{max} (nm)	Aliquot withdrawn	Aliquot replaced	Dissolution Apparatus	Agitation rate
Acidic	37 ^{0}C ± 0.5 ^{0}C	37 ^{0}C ± 0.5 ^{0}C	Hydrochloric acid buffer pH - 1.2	2 Hours	900ml	280 nm	10 ml	10 ml of the fresh dissolution media	USP type I (Basket)	100 RPM
Buffer	37 ^{0}C ± 0.5 ^{0}C	37 ^{0}C ± 0.5 ^{0}C	Phosphate Buffer pH - 6.8	90 minutes	900ml	265 nm	10 ml	10 ml of the fresh dissolution media	USP type I (Basket)	100 RPM

Table 2: E valuation of tablets

Formulation	Hardness (kg/cm^2)	Disintrigation Time (min)		Friability	Result	Decision
		pH 1.2	pH 6.8			
T_1	6	3.0 ± 0.2	6	0.2%	Dissolution Very poor	Increasing Binder concentration
T_2	3.5	3.0 ± 0.2	3.5	0.5%	Poor Hardness & Friability	Chang the exceipient ratio
T_3	7	3.0 ± 0.2	7	0.2%	Good Dissolution	Chang the exceipient ratio
T_4	4	3.0 ± 0.2	4	0.2%	Poor Hardness	Chang the exceipient ratio
T_5	8	3.0 ± 0.2	8	0.2%	Excellent Hardness & D.T	-----

Table 3: Dissoluation data

Formulation. No	Condition	Average % drug Release	Stander deviation (SD)	Relative stander deviations (RSD)	Disintegration test (min) pH 1.2	Disintegration test (min) pH 6.8	Result`	Decision pH 6.8
C_1T_1	Acidic medium (pH 1.2) After 60minit	17.29	0.816	0.047	96	8	Less color, Poor Dissolution & D.T	Chang the exceipient ratio & increase color
	Acidic medium (pH 1.2) After 120minit	30.87	0.846	0.274				
	Buffer medium(pH 6.8) After45 minit	41.92	0.906	0.0216				
	Buffer medium(pH 6.8) After90 minit	61.16	0.455	0.0074				
C_2T_5	Acidic medium (pH 1.2) After 60minit	4.48	0.417	0.093	121	13	Excellent, Hardness, D.T & Coating	----------
	Acidic medium (pH 1.2) After 120minit	8.91	0.411	.046				
	Buffer medium(pH 6.8) After45 minit	41.27	0.0518	0.0125				
	Buffer medium(pH 6.8) After90 mini	86.52	0.550	0.0063				
C_3T_6	Acidic medium (pH 1.2) After 60minit	20.98	0.810	0.038	135	18	More color, Increase D.T & Poor dissolution	Chang the exceipient ratio
	Acidic medium (pH 1.2) After 120minit	42.74	0.810	0.038				
	Buffer medium(pH 6.8) After45 minit	50.84	0.896	0.017				
	Buffer medium(pH 6.8) After90 minit	72.59	0.881	0.014				
Innovator	Acidic medium (pH 1.2) After 60minit	2.93	0.411	0.140	125	14	Excellent Hardness, D.T,& Coating	----------
	Acidic medium (pH 1.2) After 120minit	6.85	0.479	0.0699				
	Buffer medium(pH 6.8) After45 minit	44.60	0.850	0.190				
	Buffer medium(pH 6.8) After 90 minit	83.345	0.723	0.0086				

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