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DESIGN, DEVELOPMENT AND EVALUATION OF ENTERIC COATED PANTOPRAZOLE TABLETS

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Abstract

The purpose of the present research was to develop and evaluate pantoprazole enteric coated tablets utilizing Eudragit L100 as the enteric polymer. The medication was chosen based on a review of the literature, which showed that pantoprazole is unstable in the stomach's acidic environment. Eudragit L100 was chosen as the polymer of choice to coat the tablet. Preformulation characteristics for the medication, such as its melting point, IR, DSC, solubility, and partition coefficient, were assessed for identification and characterisation. The F5 batch of tablets was chosen for enteric coating based on the evaluation results of the core tablets. Enteric polymer Eudragit L100 was applied to the F5 batch at 6% and 8% with 1.5% PEG serving as a plasticizer. The drug content, weight fluctuation, hardness, and in vitro drug release of the coated F5 Batch containing 6% and 8% Eudragit L100 were assessed. It was discovered that the F5 batch coated with 8% polymer outperformed the F5 batch coated with 6% polymer. As a result, F5 (8%) was chosen as the best formulation.

Keywords: Pantoprazole, UV, Coated tablet, IR, DSC, solubility.

Introduction

Drug delivery has metamorphosed from the concept of Pill to Molecular medicine in the past 100 years. Better appreciation and integration of pharmacokinetic and pharmacodynamics principles in design of drug delivery system has been developed a lead to improve therapeutic efficacy. Drug research has evolved and matured through several phases beginning from pill to pharmaceutical dosage form.

During the past few years, conventional dosage forms are rapidly being replaced by the new and novel drug delivery systems. Amongst these, the modified release dosageforms have become extremely popular in modern therapeutics because of their advantages over conventional dosage forms. The term drug delivery can be defined as technique that is used to get the therapeutic agent inside the human body conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug

administration are effective but some drugs are unstable or toxic and have narrow therapeutic ranges and also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels.

The oral route of drug administration is the most important method of administrating drugs for systemic effects. At least 90% of all the drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. It is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in themouth and stomach. Usually most of the drugs are absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before it is transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching thebloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect. When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

Limitation of conventional dosage form

- Poor patient compliance-increased chances of missing the dose of a drug with short halflife for which frequent administration is necessary.
- A typical peak valley plasma concentration-time profile is obtained which makes attainment of steady- state condition difficult.
- The unavoidable fluctuations in the drug concentration may lead to under- medication or over-medication as the CSS values fall or rise beyond the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especiallyof a drug with small therapeutic index whenever over- medication occurs.

Modified release dosage form

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injection of suspensions of insoluble drugcomplexes, e.g. Procaine penicillin, protamine zinc insulin, insulin zinc suspension or injections of the drug in oil, e.g. Fluphenazine decanoate. Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug. Drug release only occurs sometime after theadministration or for a prolonged period of time or to a specific target in the body. Dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish

therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate-release dosage form. Modified-release systems are designed to influence the release profile of a drug from its delivery system. The modified-release systems can be further divided into

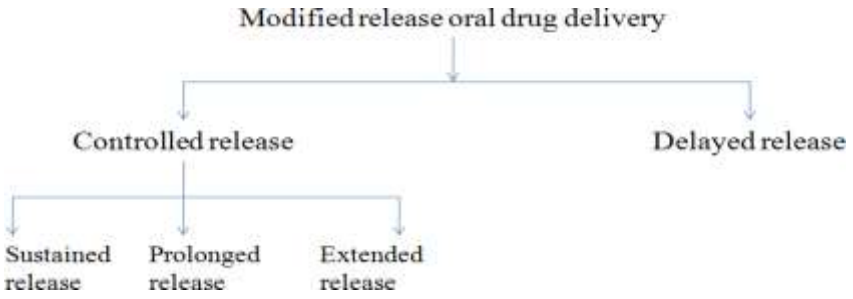


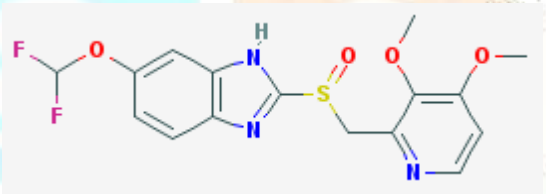
Figure 1: Classification of modified release drug delivery

Pantoprazole sodium

Category: Anti-Ulcer Agents, Proton-pump Inhibitors

Chemical IUPAC Name: Sodium 5-(difluoromethoxy)-2[[(3, 4, dimethoxy-2-pyridinyl) methyl] sulfinyl]-1H benzimidazole sesquihydrate.

Chemical structure:



Molecular formula: C16H15F2N3O4S x1.5 H2O

Molecular Weight: 383.37 gm/mol

Description: White to off- white crystalline powder and is racemic has a weakly basicand acidic property.

Solubility:

- Pantoprazole sodium sesquihydrate is freely soluble in water,
- Very slightly soluble in phosphate buffer at pH 7.4, and
- Practically insoluble in n- hexane

Mechanism of action:

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 h for all doses tested.

Pharmacokinetics

Pantoprazole sodium is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (Cmax) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg.

pH: Between 9.0 & 11.5 (2% w/v solution in water)

Bioavailability: 77%

Peak plasma concentration: 2.52 mg/l **Tmax:** 2.5 hours (under fasting conditions) **T1/2:** The mean elimination half-life is 1 hour.**Volume of distribution:** 0.15 l/kg **Excretion:** Through renal excretion

Absorption: The absorption of pantoprazole is rapid, with a Cmax of 2.5 μg/ml that occurs approximately 2.5 h after administration of a single or multiple oral 40 mg doses of pantoprazole sodium delayed release tablets. Pantoprazole is well absorbed;it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Administration of pantoprazole with food may delay its absorption up to 2 h or longer; however, the C max and the extent of pantoprazole absorption (AUC) are not altered.

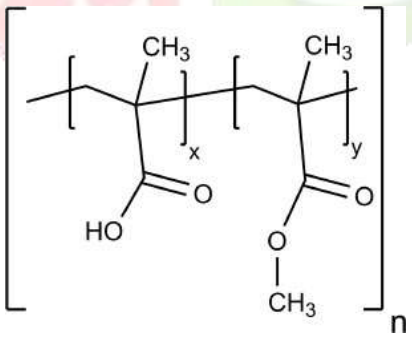
Distribution: The apparent volume of distribution of pantoprazole is approximately
11.0 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding ofpantoprazole is about 98%, primarily to albumin.

Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the routeof administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 h, they still have minimal accumulation (23%) with once daily dosing.

Excretion: After a single oral or intravenous dose of pantoprazole to healthy, normal metabolize volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Polymer profile EUDRAGIT® L 100Chemical structure

EUDRAGIT® L 100 is anionic copolymer based on methacrylic acid and methylmethacrylate. The ratio of the free \ carboxyl groups to the ester groups is approx. 1:1.



The monomers are randomly distributed along the copolymer chain.

Description

White powder with a faint characteristic odour.

Solubility

1 g of EUDRAGIT® L 100 dissolves in 7 g methanol, ethanol, in aqueous isopropyl alcohol and acetone (containing approx. 3 % water), as well as in 1 N sodiumhydroxide to give clear to cloudy solutions.

EUDRAGIT® L 100 is practically insoluble in ethyl acetate, methylene chloride, petroleum ether and water.

Particle size

At least 95 % less than 0.25 mm

Viscosity / Apparent viscosity

EUDRAGIT® L 100: 60 - 120 mPa . s

Storage

Store at controlled room temperatures (USP, General Notices). Protect againstmoisture. Any storage between 8 °C and 25 °C fulfils this requirement.

EXPERIMENTAL WORK

Selection of drug and excipients

On the basis of literature survey, drug and various excipients were selected in thepresent investigation.

Preformulation study

Identification and characterization of drug

Melting Point

The melting point of API was determined by Digital melting point apparatus (LAB TRONICS Ltd). The capillaries filled with powder were placed in Melting point apparatus containing liquid paraffin. The melting point of the drug was noted.

Saturation Solubility of drug

Saturation solubility studies were conducted according to method given by Higuchi and Connors in triplicate. In order to determine saturation solubility, an excess amount of drug was added to vials contaning 5 ml of water. The vials were subjected to rotary shaking and sonication and allowed to stand to equilibration for 24 hrs, after that samples were filtered through Whatman filter paper and filtrate was analyzed by UV Spectrophotometer at 292 nm after appropriate dilutions.

FT-IR Spectroscopy

Shimadzu FTIR spectrometer Prestige 21 with DRS assembly was used in Attenuated total reflectance (ATR) mode for collecting FT-IR spectra of samples. The spectra's were collected over the range of 4000-400 cm^{-1} in 45 scans, with a resolution of 5 cm^{-1} for each sample.

Differential Scanning Calorimetry (DSC)

Thermal analysis of the API and polymers were performed using a differential scanning calorimeter DSC-60A Shimadzu calorimeter. The sample powders (2mg) were placed in aluminium pans, sealed hermetically and then these hermeticallysealed aluminium pans were heated at a scanning rate of 20°C/min from 50° to 300°C under constant purging dry nitrogen flow (20 mL/min). Empty aluminium pan was used as a reference.

Analytical method development and validation

UV spectrophotometer is widely employed for routine drug analysis. Therefore one ofthe objectives of the present study was to develop and validate an UV Spectrophotometric method for analysis of Pantoprazole sodium sesquihydrate.

Formulation of pantoprazole core tablets

Preparation of powder blend

Required quantity of pantoprazole, croscarmellos sodium, manitol, calcium phosphate, and microcrystalline

cellulose were weighed (Table 1), transferred in a mortar and pestle and mixed thoroughly. The above prepared blend was passed through sieve no 80 and finally, specified quantity of magnesium stearate and talc were added and mixed for the formulation of tablets.

Table 1: Composition of tablets

Ingredients (mg)	**Batch Code**				
	F1	**F2**	**F3**	**F4**	**F5**
Pantoprazole sodium	40	40	40	40	40
Croscarmellose sodium	2	4	6	8	10
Microcrystalline cellulose	27	25	23	21	19
Mannitol	50	75	100	75	75
Dicalcium phosphate	75	50	25	50	50
Talc	2	2	2	2	2
Magnesium stearate	4	4	4	4	4
Total weight	**200**	**200**	**200**	**200**	**200**

Evaluation of enteric coated tablet

***In vitro* drug release study of coated tablets**

USP dissolution apparatus type II (Electrolab TDT-08L, Mumbai, India) was used to determine the *in vitro* release of pantoprazole from the prepared formulations. The dissolution medium was 900 mL of 0.1N HCl for 2 hr and phosphate buffer (pH 6.8) for 1 hr. The tablet was kept in to the basket at 37 ± 0.5 °C and 100 rpm. Samples (5 mL) were withdrawn at regular time intervals and the dissolution medium was replaced with equal volume fresh dissolution medium. The samples were measured byUV spectrophotometer against blank.

The coated tablets were evaluated for weight variation, hardness and drug contentaccording procedures described previously.

RESULTS AND DISCUSSION

Selection of drug and polymer

Pantoprazole was selected as literature revealed that it degrades in the low pH of stomach and possess serious bioavailability problems. Other polymers were selected on the basis of literature survey.

Preformulation study

Identification and characterization of drug

Melting point

Melting point of pantoprazole was determined by digital melting point apparatus andwas obtained 138-140 ^{0}C which is in accordance with reference that is 139-140 ^{0}C.

Saturation solubility study

The solubility of pantoprazole in water was estimated by adding excess amount ofdrug and it was found as given in Table 2

Table 2: Saturation solubility of drug

Sr. No.	Solubility (mg/ml)	Mean solubility (mg/ml)
1	41.93	41.41
2	40.89	

Partition coefficient

The partition coefficient was determined and calculated value was in agreement withreference value. The result is given in Table 3

Table 3: Partition coefficient

Sr. No.	Partition coefficient	Mean
1	2.00	2.09
2	2.18	

Infrared spectroscopy

IR spectrum is used as effective tool for the identification and characterization of drug. IR spectrum of the pantoprazole shows principle peaks corresponding to thefunctional groups present in the drug. The result is depicted in Table 4

Sr. No.	Functional group	IR absorption band (cm^{-1})
1	N-H	3483.56
2	O-H	3358.18
3	CH2	3176.87
4	CH3	2960.83
5	C-O	1591.33
6	C-F	1373.36
7	S=O	1049.31

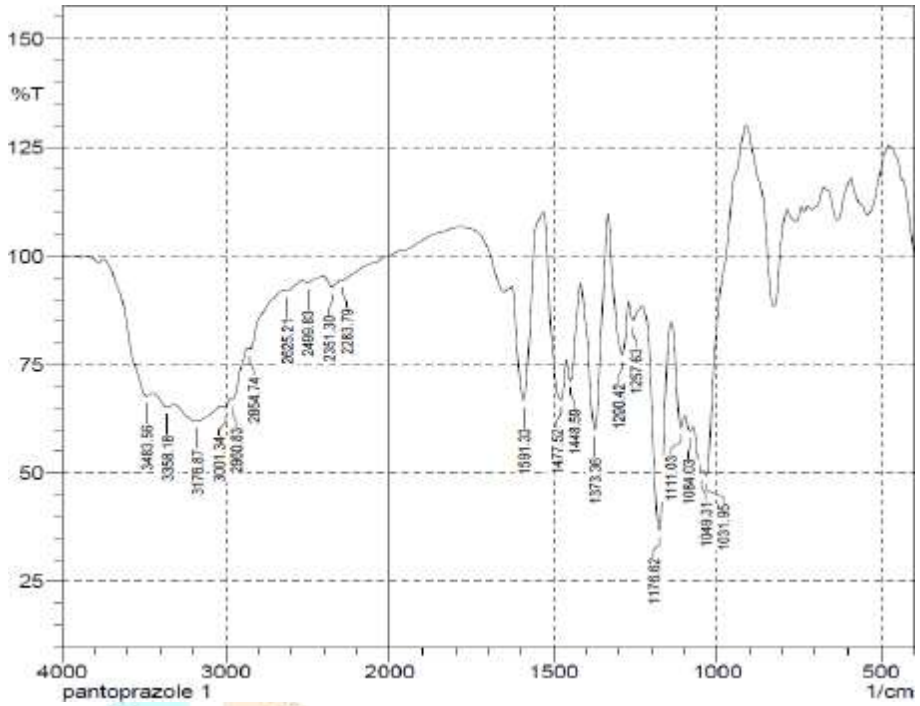


Figure 2: IR spectrum of pantoprazole

Differential scanning calorimetry (DSC)

Thermal behavior of the drug can be determined by DSC. Melting point of thepantoprazole was found 136.31 °C which is near to reference melting point. The DSC thermogram of pantoprazole is shown in figure 9.

Drug polymer Compatibility study

The results of drug and excipient compatibility study are shown in Table 10. From theresults it was found that the colour, odour and assay of drug and excipients were not changed, hence they are compatible with each other.

Analytical method development and validation

The pure drug pantoprazole was scanned over a range of 200-400 nm to determine its λmax. The maximum absorption was found at 292 nm in water, 283.8 nm in 0.1 N Hydrochloric acid and 288 nm in pH 6.8 phosphate buffer which corresponds to the literature value.

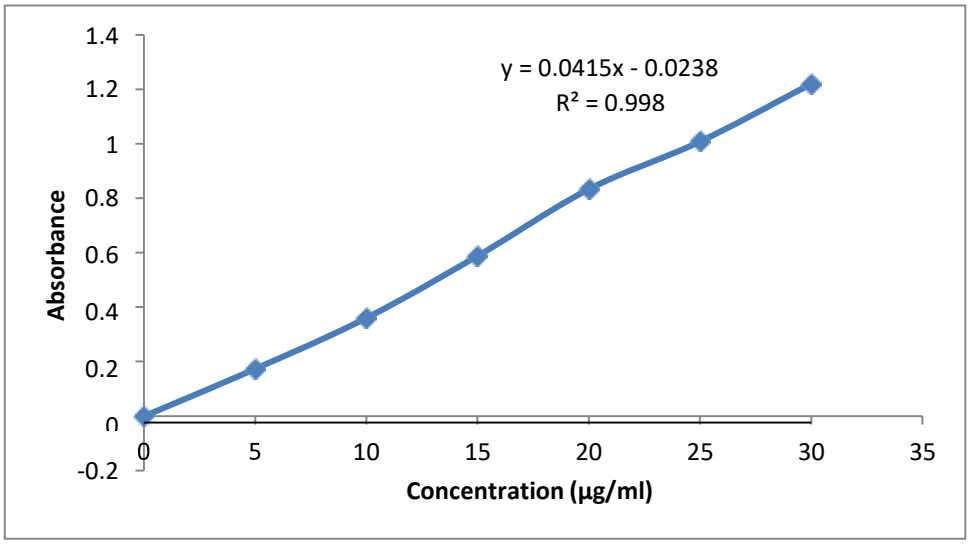


Figure 3: Calibration curve in water

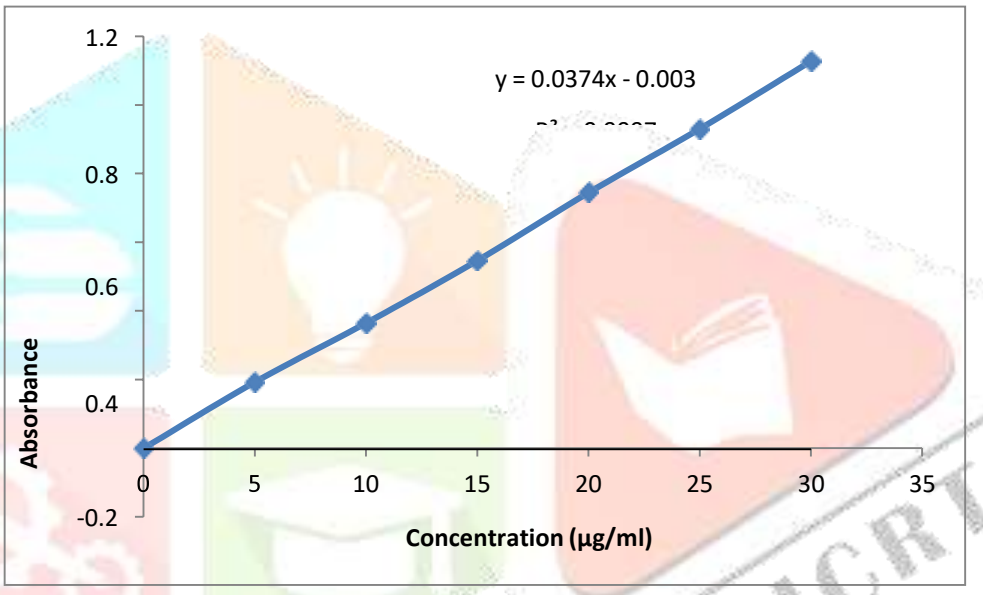


Figure 4: Calibration curve in 0.1 N HCl

Formulation of pantoprazole core tablets

Evaluation of powder blend

The powder blend prepared for the formulation of tablets was evaluated for thevarious pre-compression parameters. The various pre-compression parameters arepresented in Table 17

Table 5: Pre-compression parameters of powder blend

Formulatiocode	Parameters				
	Bulk density (gm/mL)	Tapped density (gm/mL)	r's Index(%)	Hausner's ratio	Angle of repose (Ɵ)
F1	0.357±0.03	0.384±0.05	7.03±0.09	1.075±0.04	28.31±0.26
F2	0.312±0.04	0.335±0.02	6.86±0.15	1.073±0.05	27.20±0.14
F3	0.306±0.03	0.326±0.03	6.13±0.12	1.065±0.02	29.13±0.34
F4	0.312±0.03	0.334±0.06	6.58±0.14	1.070±0.06	26.23±0.26
F5	0.348±0.08	0.328±0.05	5.74±0.13	1.06±0.08	26.13±0.26

Tablet Post compression parameters

The pantoprazole core tablets were prepared by direct compression method and evaluated for their hardness, weight variation, content uniformity, friability and in vitro drug release (Table 18). The hardness of the core tablets varied from 4.93 ± 0.15 and 5.80 ± 0.12 Kg/cm^2. Hardness has to be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard thatthe disintegration time is unduly prolonged. The friability of the prepared tablets was found less than 1% w/w which indicates that friability was within the range and this might also be affected by the hardness of the tablets. The drug content of pantoprazolesodium present in tablets formulation ranged from 96.28 ± 0.15 and 99.08 ± 0.35%. The mass uniformity was found between 198 ± 0.15 and 208 ± 0.20 mg and disintegration time varied between 6.02 ± 0.21 and 11.48 ± 0.15 and all showsfavorable results.

Table 6: Post compression parameters of pantoprazole tablet

mulationcode	**Parameters**				
	ardness (Kg/cm2)	**Friability (%)**	**Weight variation (mg)**	**g content(%**	**isintegration time(min)**
F1	5.80 ± 0.12	0.69 ± 0.015	199 ± 0.12	96.28 ± 0.15	10.6± 0.62
F2	5.56 ± 0.24	0.51 ± 0.017	206 ± 0.24	97.62 ± 0.27	8.26± 0.56
F3	5.73 ± 0.25	0.71 ± 0.016	203 ± 0.16	98.92 ± 0.42	9.32± 0.18
F4	4.93 ± 0.15	0.64 ± 0.015	208 ± 0.20	98.17 ± 0.16	11.48± 0.15
F5	**5.60 ± 0.24**	**0.42 ± 0.018**	**198 ± 0.15**	**99.08 ± 0.35**	**6.02± 0.21**

From the above five formulations, Batch F5 was selected for the further coating with enteric polymer Eudragit L100 based on the results of post compression parameters. The tablets (F5 batch) were coated with 6% and 8% solution of Eudragit L100 and subjected to physicochemical evaluation.

Evaluation of enteric coated tablet

Physicochemical evaluation of coating film

Physicochemical evaluation of Eudragit L100 was studied for different parameters such as film thickness, and film solubility. The thickness of the films was 0.24 ± 0.08 mm. The enteric polymer Eudragit L100 was found completely soluble in phosphate buffer (pH 6.8) and insoluble in 0.1 N HCl.

The enteric coated tablets were evaluated for drug content, hardness and weightvariation and results are reported in table 7.

Table 7: Evaluation parameters of enteric coated tablet

Formulation code	ardness (Kg/cm2)	Weight variation (mg)	ꝛ content(%
F5 (6%)	6.3 ± 0.14	219 ± 0.24	97.54 ± 0.12
F5 (8%)	6.5 ± 0.31	220 ± 0.15	99.27 ± 0.45

Results are mean ± SD n=3

After evaluation it is clear that batch F5 coated with 8% Eudragit L100 showed better results than F5 batch coated with 6% Eudragit L100. The drug content for F5 (8%) batch was 99.27% and other parameters were also better than F5 (6%) batch.

***In vitro* drug release of pantoprazole enteric coated tablet**

In vitro drug release of F5 batch was studied after coating with Eudragit L100 6% and8%. The results are given in table 20 and represented by figure

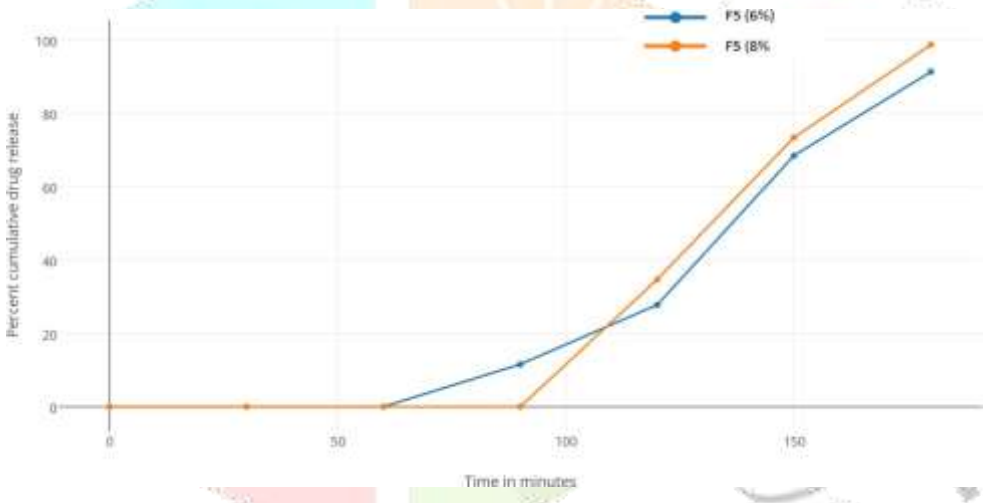


Figure 5: In vitro drug release of enteric coated pantoprazole tablet

The graph clearly indicates F5 (8%) batch was superior in drug release than F5 (6%). The F5 (6%) batch started drug release at 90 min and released 97.54% in 3 hours whereas F5 (8%) started drug release at 120 min and released 99.27% in 3 hours. The less drug release in case of F5 (6%) may be attributed to the insufficient coating with Eudragit L100 and drug release was started at 90 min . From all the evaluation parameters F5 (8%) batch was selected optimized because drug was not released in

0.1 N HCl for 2 hours and showed maximum drug release, good hardness and less weight variation as compared to F5 (6%) batch.

Table 8: In vitro drug release from enteric coated tablet

Time (min)	Percent cumulative drug release	
	F5 (6%)	F5 (8%)

0	0	0
30	0	0
60	0	0
90	11.53	0
120	27.74	34.64
150	68.43	73.37
180	91.34	98.65

CONCLUSION

The objective of the present investigation was to formulate and evaluate enteric coated tablets of pantoprazole using eudragit L100 as enteric polymer. The drug was selected on the basis of literature survey which revealed that pantoprazole is not stablein the acidic conditions of the stomach. From the variety of polymers Eudragit L100 was selected for coating the tablet. The drug was evaluated for preformulation parameters like melting point, IR, DSC, solubility and partition coefficient for the identification characterization. All the parameters were close to the reference values. The next important step was analytical method development and validation in various media like water, 0.1 N HCl and phosphate buffer pH 6.8 according to ICH Q2R1 guidelines. The various validation parameters were found within the prescribed range.In the next phase five batches of core tablets were designed by varying the concentration of superdisintegrant crosscarmellose sodium. The powder blend for the preparation of core tablets was evaluated for preformulation parameters and compressed into tablets by direct compression method. The five batches of developed core tablets were evaluated for the hardness, friability and drug content and weight variation. Form the results of evaluation of core tablets, F5 batch was selected for the enteric coating. The F5 batch was coated with enteric polymer eudragit L100 at 6% and 8% using 1.5% PEG as plasticizer. The coated F5 Batch with 6% and 8%Eudragit L100 was evaluated for drug content, weight variation, hardness and *in vitro*drug release. It was found that F5 batch coated with 8% polymer showed better resultsthan F5 (6%) coated batch. Hence F5 (8%) was selected as optimum formulation.

Enteric coated tablet of pantoprazole coated with Eudragit L100 polymer were successfully developed and evaluated. The enteric coated tablet showed good performance *in vitro*, drug was not released in 0.1 N HCl upto 2 hrs and startedrelease after 2 hrs as desired.

Further studies will be required to evaluate the performance of dosage form in vivo and *In Vitro In vivo* Correlation.

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