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Preformulation Studies of Pantoprazole: Fundamental Part of Formulation Design

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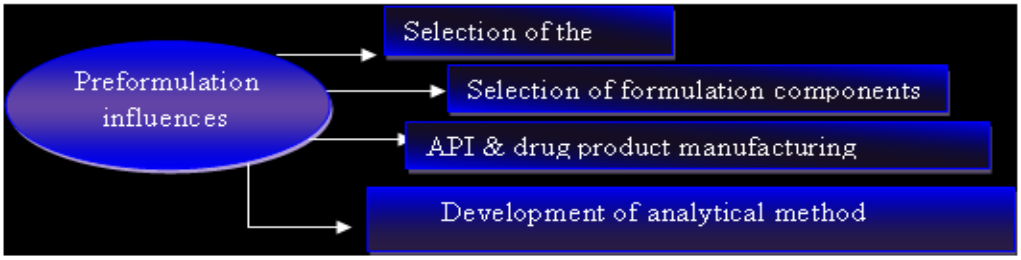
Abstract

Once the novel molecule is planted, preformulation study is one of the fractions that is started. In a larger sense, it covers with research on a molecule's physical, chemical, analytical, and medicinal properties and offers suggestions for effective modifications that could be made to improve performance. The study of preformulation factors can contribute to the development of pharmaceutical formulations that are dependable, safe, stable, and efficacious. Pantoprazole is an irreversible proton pump inhibitor (PPI) that reduces gastric acid secretion. PPIs, pantoprazole binds to the proton pump (H+,K+ -adenosine triphosphatase) in the parietal cells to exercise its pharmacodynamic effects; however, in comparison to other PPIs, its binding may be more specific for the proton pump. When given as an enteric-coated, delayed-release tablet, pantoprazole is well absorbed and has a 77 % oral bioavailability. It is metabolized by the liver's cytochrome P2C19 into the inactive metabolite hydroxypantoprazole, which is then subjected to sulphate conjugation. Independent of dose, the elimination half-life ranges from 0.9 to 1.9 hours. Similar to other PPIs, pantoprazole is effective in promoting the healing of gastric and duodenal ulcers. In the present works overall objective of preformulation studies of Pantoprazole is to engender information useful in developing stable and Bioavailable dosage forms.

Keywords: Preformulation study, Pantoprazole, Solubility & Analytical methods.

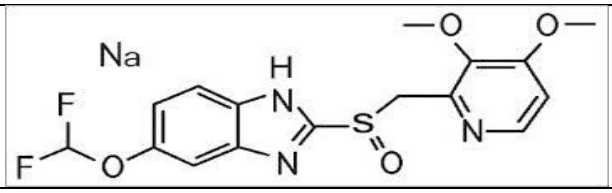
INTRODUCTION

The primary step in the logical development of dosage forms for a medicinal substance is preformulation research. The study includes an analysis of the physical and chemical characteristics of a drug material both on its own and when mixed with an excepient. Preformulation testing generally aims to produce data that will be useful to the formulator in creating stable and bioavailable dosage forms that can be mass manufactured. Preformulation studies are made to provide the relevant information, particularly on the physicochemical, physico-mechanical, and biopharmaceutical properties of medicinal ingredients, excipients, and packaging materials [1]. The physicochemical characteristics of the new molecule that may have an impact on therapeutic performance and the creation of an effective dosage form should be the focus of these investigations. A rationale for formulation design could someday be provided by a systematic study of these features [2, 3].



A substituted benzimidazole derivative called pantoprazole is a PPI that reduces the amount of acid that the stomach parietal cells secrete. More than 80 nations throughout the world currently have access to IV pantoprazole, which is intended for the treatment of Zollinger-Ellison syndrome, gastric and duodenal ulcers, and gastroesophageal reflux disease (GERD). In numerous nations, IV pantoprazole is now recommended for the prophylaxis of acute bleeding stress ulcers as well as the treatment of bleeding peptic ulcers and the prevention of rebleeding. In this study, the evidence for the use of IV pantoprazole in the treatment of PUB, prophylaxis against acute bleeding stress ulcers, and prevention of rebleeding is rigorously analyzed [4].

DRUG PROFILE- PANTOPRAZOLE [5]

IUPAC	-5(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3H-benzoimidazole.
MOLECULAR FORMULA	$C_{16}H_{14}F_2N_3NaO_4S$.
MOLECULAR WEIGHT	383.371
BIOAVAILABILITY	77%
METABOLISM	Hepatic (CYP2C19, CYP3A4)
ELIMINATION HALF LIFE	1hours
T_{max}	2.5 hours
EXCRETION RENAL	71% as metabolites
PROPRIETARY NAME	PROTONIX
ROUTE OF ADMINISTRATION	Oral, IV
CHEMICAL STRUCTURE	

Pantoprazole sodium sesquihydrate is a white to off- white crystalline powder and is racemic.

Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium is freely soluble in phosphate buffer at pH 6.8 and partially soluble in water and practically soluble in n-hexane. The stability of the compound in aqueous solution is pH dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8 [6].

In the present works an attempt was made to study preformulation parameters of Pantoprazole which helps to engender information useful in developing stable and Bioavailable dosage forms.

MATERIAL AND METHODOLOGY

Drug: Jubilant Life Sciences, Noida, Uttar Pradesh. (India).

PREFORMULATION STUDIES

Identification of drug

Drug characterization: The drug was observed for the organoleptic properties Pantoprazole was physically characterized on the basis of appearance and taste.

Melting point determination: The measurement of the melting point is a major concern in preformulation studies. The most important reason to determine the melting point during preformulation is the crystalline solubility. The melting point of the drug was determined by the capillary melting technique.

Solubility Study

Solubility of pantoprazole was determined in distilled water, ethanol, and phosphate buffer. For this purpose, saturated solution of drug was prepared. Sample of 1ml each were withdrawn in triplicate from the saturated solution and after proper dilution of these samples with respective solvents. The absorbance was taken at λmax of 289nm with the help of calibration curve. The concentrations of dilutions were determined.

Partition Coefficient

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 289 nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous}}$$

Loss on drying

An empty weighing bottle was cleaned, dried and weighed accurately. About 1gm of drug was placed in the weighing bottle and weighed again. The accurate weight was noted. Now this weighing bottle with drug was kept at 60℃ temperature in vacuum for 3 hours. It was again weighed and the loss on drying was determined according to following formula:

$$\%\ \textbf{Loss on drying} = \frac{\text{Weight of drug before drying} - \text{Weight of drug after drying}}{\text{Weight of drug before drying}} \times 100$$

Drug-excipient Interaction study by Fourier Transforms Infrared Spectroscopy (FTIR)

FT-IR spectra of pure drug: HPMC (1:1), drug: pantoprazole (1:1) mixtures were recorded on Shimadzu FT-IR- 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide (KBr) pellet method was employed and back ground spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400-4000 cm^{-1} at spectral resolution 2 cm^{-2} and ratio against background interferogram.

UV- VISIBLE SPECTROPHOTOMETRIC STUDY

Using the U.V spectrum of the drug, it is possible to choose an analytical wavelength suitable to quantity the amount of drug in a particular solution. The greater the number of molecules that absorb light of a given wavelength, the greater the extent of light absorption and higher the peak intensity in absorption spectrum. If there are only a few molecules that absorb radiation, the total absorption of energy is less and consequently lower intensity peak is observed. This makes the basis of Beer-Lambert Law which states that the fraction of incident radiation absorbed is proportional to the number of absorbing molecules in its path [7].

When the radiation passes through a solution, the amount of light absorbed or transmitted is an exponential function of the molecular concentration of the solute and also a function of length of the path of radiation through the sample. Therefore,

$\text{Log } I_o / I = \varepsilon\ c\ l$……. (2.1)

Where,

I_o = Intensity of the incident light (or the light intensity passing through a reference cell)

I = Intensity of light transmitted through the sample solution

c = Concentration of the solute in mol L^{-1}

l = Path length of the sample in cm

ε = Molar absorptivity or the molar extinction coefficient of the substance whose light absorption is under investigation.

The λ_{max} of Pantoprazole in different solvent was found to be-

- **a.** Distilled water (λ_{max}- 289nm)
- **b.** P^H 6.8 Phosphate buffer (λ_{max}-289nm)

Preparation of standard stock solution (distilled water)

The standard stock solution of pantoprazole was prepared by dissolving 10 mg of drug In 100 ml of distilled water in volumetric flask to produce standard stock solution 100 µg/ml. the aliquots at range from 0.5 to 5 µgm/ml of standard stock solution were taken in 25 ml of volumetric flask separately to get the concentration range 2 to 20 µgm/ml the absorbance of each sample was measure at 289 nm then the calibration curve was prepared by plotting the graph between concentration and absorbance.

Preparation of calibration curve in distilled water

A stock solution of 100µgm/ml was prepared in Distilled water. Different dilutions 2,4,6,8,10,12,14,16,18,20 µgm/ml was prepared from the stock solution. The absorbance of these aliquots was taken at previously determined λmax i.e.289 nm. The graph was plotted taking absorbance at Y-axis and concentration at X-axis. The graph obeyed the Beer-Lambert's law in the selected concentrations range.

Preparation of standard stock solution (buffer solution pH 6.8)

The standard stock solution of pantoprazole was prepared by dissolving 10 mg of drugIn 100 ml of phosphate buffer (pH 6.8) in volumetric flask to produce standard stock solution 100 µg/ml. the aliquots at range from 0.5 to 5 µgm/ml of standard stock solution were taken in 25 ml of volumetric flask separately to get the concentration range 2 to 20 µgm/ml the absorbance of each sample was measure at 289 nm then the calibration curve was prepared by plotting the graph between concentration and absorbance.

Preparation of calibration curve in phosphate buffer (pH 6.8)

A stock solution of 100 µgm/ml was prepared in phosphate buffered 6.8. Different dilutions of 2,4,6,8,10,12,14,16,18, 20µgm/ml were prepared from the stock solution. The absorbance of these aliquots was taken at previously determined λ_{max} i.e. 289nm. A graph was plotted taking absorbance at Y-axis and concentration at X-axis. The graph obeyed the Beer-Lambert's law in the selected concentration range.

RESULTS AND DISCUSSION

The generally goal of the present work was to investigate preformulation studies of pantoprazole is to generate information useful in developing stable and Bioavailable dosage forms. Various Preformulation Characteristics were tabulated in Table 1. The partition coefficient of rutin was found 2.05, which confirms the lipophilicity of the drug.

FTIR is the most important analytical technique, to determine the structure of the compound, by predicting the presence of certain functional groups in the compound which can be observed at definite frequency and to study the drug polymer interaction. The spectra were recorded for pantoprazole, hydroxyl propyl methylcellulose (HPMC), Eudragit RS 100. Eudragit S 100 loaded pantoprazole tablets, obtained in KBr pellets using a Perkin-Elimer FT-IR spectrometer and at mid IR region (wavelength 25-2.5, wave number from $400cm^{-1}$ to $4000cm^{-1}$), in order to identify the possibility of any interaction between the drug and polymer material. IR spectroscopy is among the most important analytical techniques to determine the structure of the compound by predicting the presence of certain functional groups which are observed at a definite frequency and to study the drug-polymer interaction. A peak-by-peak correlation is excellent evidence for identity. The FTIR spectrum, there was no variation in the pantoprazole peaks from the standard spectrum of IP 2014(fig 1-7).The result was tabulated in table 4-10 .The analytical method for determination of drug was UV spectroscopy. The absorption spectral analysis showed the λ_{max} of pantoprazole at 289 nm. The calibration curve was obtained for a series of concentration in the range of 2-20 µ g/mL. It was found to be linear and hence, suitable for the estimation of the drug, as shown in the Table 12 & 13, Fig 9 & 10. The Linearity was established across the range and the absorbance of standard stock solution in distilled water and phosphate buffer in the range of 2-20 µg/ml (Table 12 and 13) measured at 289 nm. The Regression equation in distilled water was found to be Y = 0.081x – 0.149 and R2 = 0.999 respectively. While the regression equation r2 in phosphate buffer was found to be Y = 0.0396x – 0.0165 and R2 = 0.999 (Figure 9 & 10).

Table 1: Preformulation Characteristics

S. No	Characteristics	Results
1.	Appearance	White to off-white crystalline powder.
2.	Melting Point	139-140^{0}C
3.	Solubility	Freely soluble in phosphate buffer at P^H 6.8, very slightly soluble in water.
4.	Partition coefficient	2.05

Table 2: Solubility data of drug in different solvents

SOLVENT	CONCENTRATION	SOLUBILITY
distilled water	5mg/ml	slightly soluble
phosphate buffer at pH 6.8	5mg/ml	free soluble
Ethanol	5mg/ml	Slightly soluble
N-Hexane	5mg/ml	Insoluble

Table 3: Percentage loss on drying of pantoprazole

S. no.	Weight of drug before drying (gm)	Weight of drug after drying (gm)	% loss on drying (%w/w)	% average lod (%w/w)	Limits of % lod
1	1	0.9985	0.15		
2	1	0.9990	0.10	0.12	0.1-0.7
3	1	0.9989	0.11		

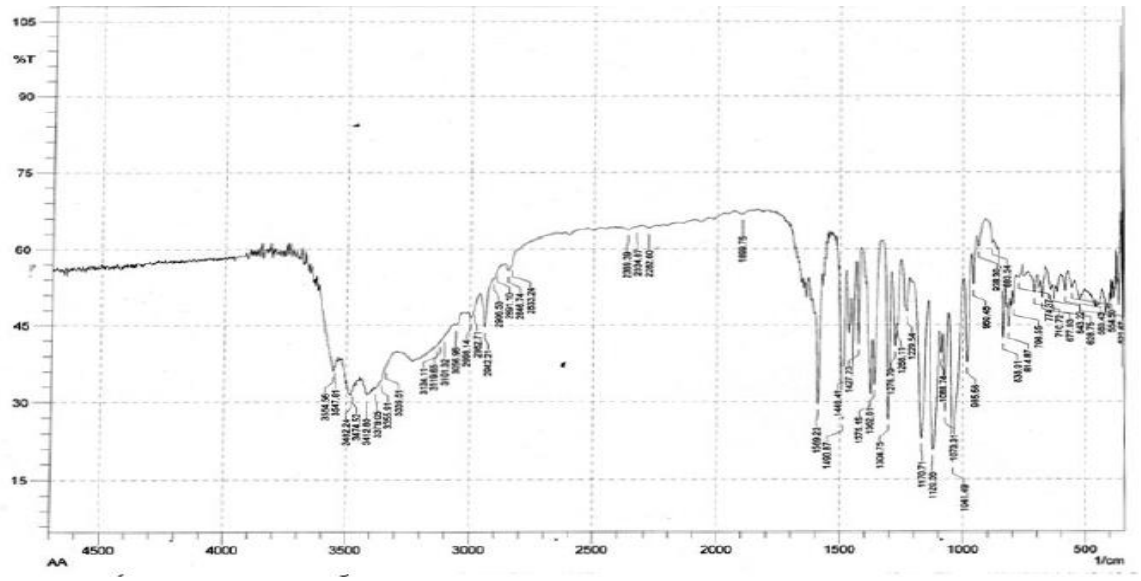


Figure 1: FTIR Spectra of pure drug pantoprazole

Table 4: Peaks of pantoprazole

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1589.23	N-H bending vibration
1304.75	(C-N vibrations) Aromatic primary
1170.71	Sulpher compound (sulfonyl chloride)
1120.56	(O-H bending and C-O stretching vibration primary alcohols

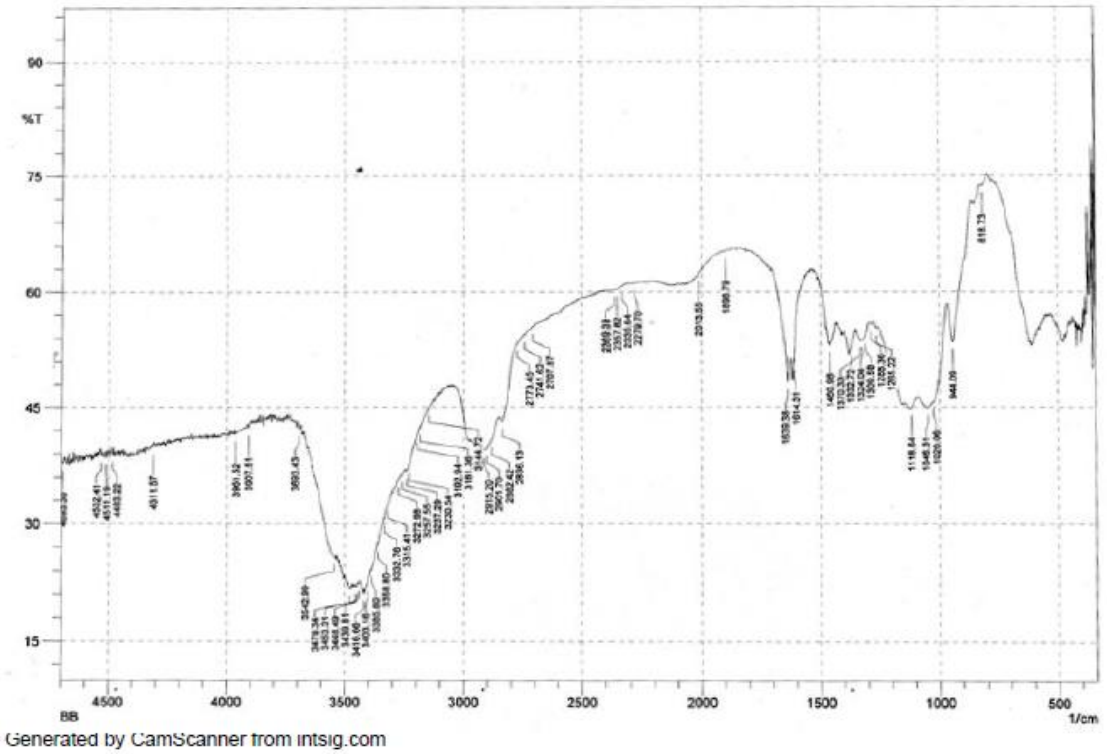


Figure 2: FTIR Spectra of polymer (HPMC)

Table 5: Peaks of polymer (HPMC)

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1639.38	(N-H bending vibrations)
1614.31	(N-H bending vibrations) primary amides, dilute solutions
3416.66	(N-H stretching vibrations) secondary free one bond
1332.72	(C-N vibrations) aromatic primary

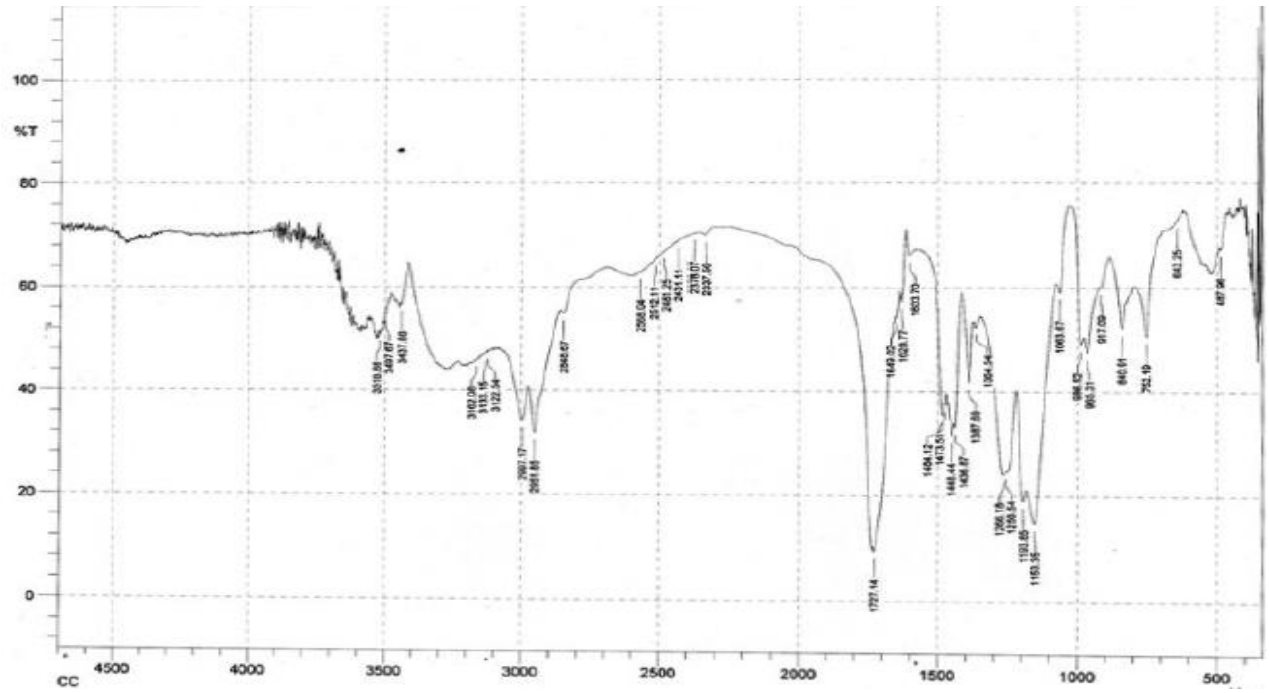


Figure 3: FTIR spectra of polymer (Eudragit RS 100)

Table 6: Peaks of polymer (Eudragit RS 100)

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1721.35	Aldehydes (carbonyl stretching vibrations saturated aliphatic)
1629.74	Unsaturated nitrogen compounds C-NO, nitroso compounds
848.62	(C-H bending two adjacent hydrogen atoms
751.52	(C-H bending) Aromatic, substitution type

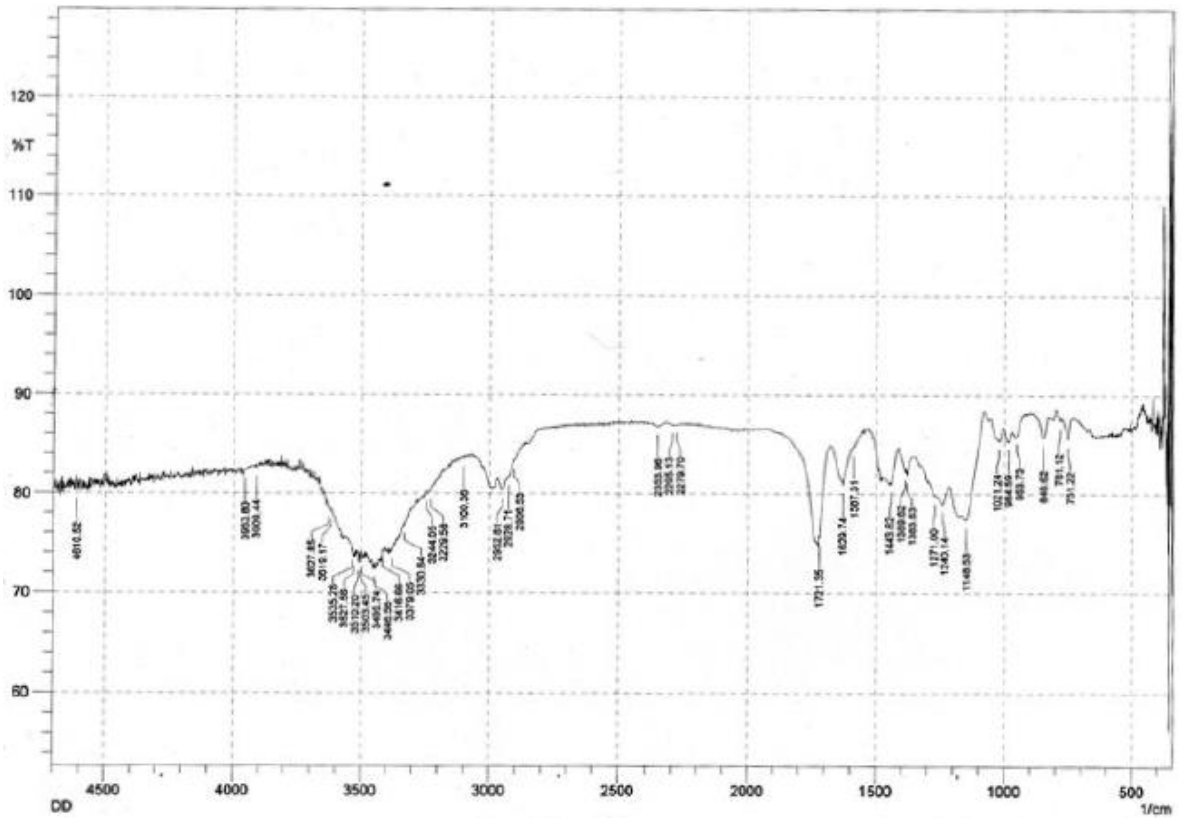


Figure 4: FTIR spectra of polymer (Eudragit S 100)

Table 7: Peaks of polymer (Eudragit S 100)

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
2997.17	Miscellaneous chromophonic groups Alcohol and phenols (O-H stretching vibrations) chelate compounds
2951.85	Hydrocarbon chromophore (C-H stretching, Alkane
1727.14	Carbonyl chromophore (ketone stretching vibrations α di ketones
1448.44	Alkane, $-CH_2-$ (C-H bending)
1153.35	Tertiary alcohol (O-H bending and C-O stretching vibrations)
840.91	Alkene, trisubstituted (C-H bending)
752.19	Aromatic, substitution type (four adjacent hydrogen atoms)

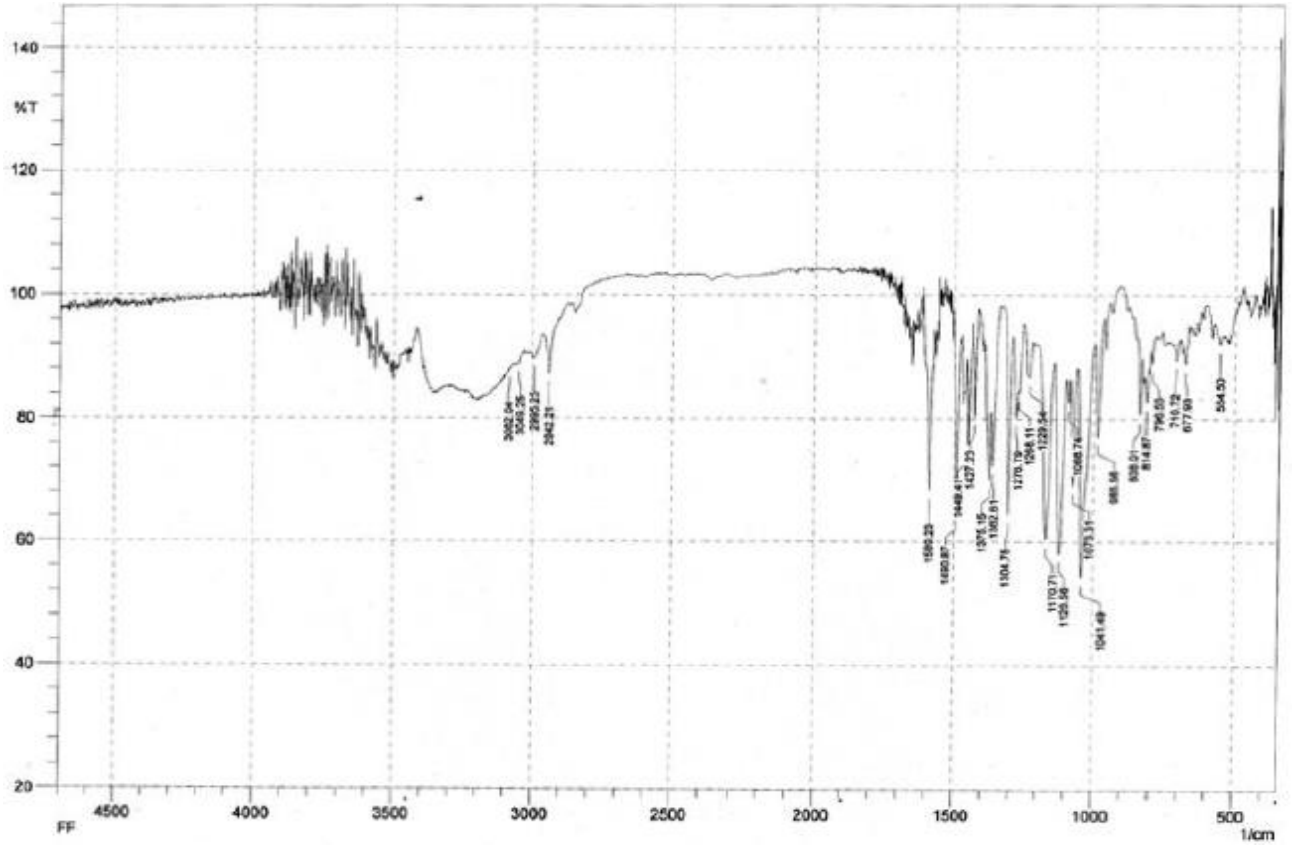


Figure 5: FTIR spectra of combination of drug, magnesium stearate and talc

Table 8: Peaks of combination drug, magnesium stearate and talc

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
2941.41	Alkane (C-H Stretching)
2849.63	Aldehyde (C-H stretching vibrations, two bonds)
1589.23	(N-H bending vibrations) primary
1449.41	(C-H bending) Alkane, $-CH_3$
1427.23	(C-C multiple bond stretching) aromatic
1375.15	(C-H) bending, alkane, gem dimethyl
1169.75	Sulphur compounds (S=O stretching vibrations sulphites
1119.60	O-H bending and C-O stretching vibration (secondary alcohol)
1041.49	O-H bending and C-O stretching vibrations (primary alcohols)

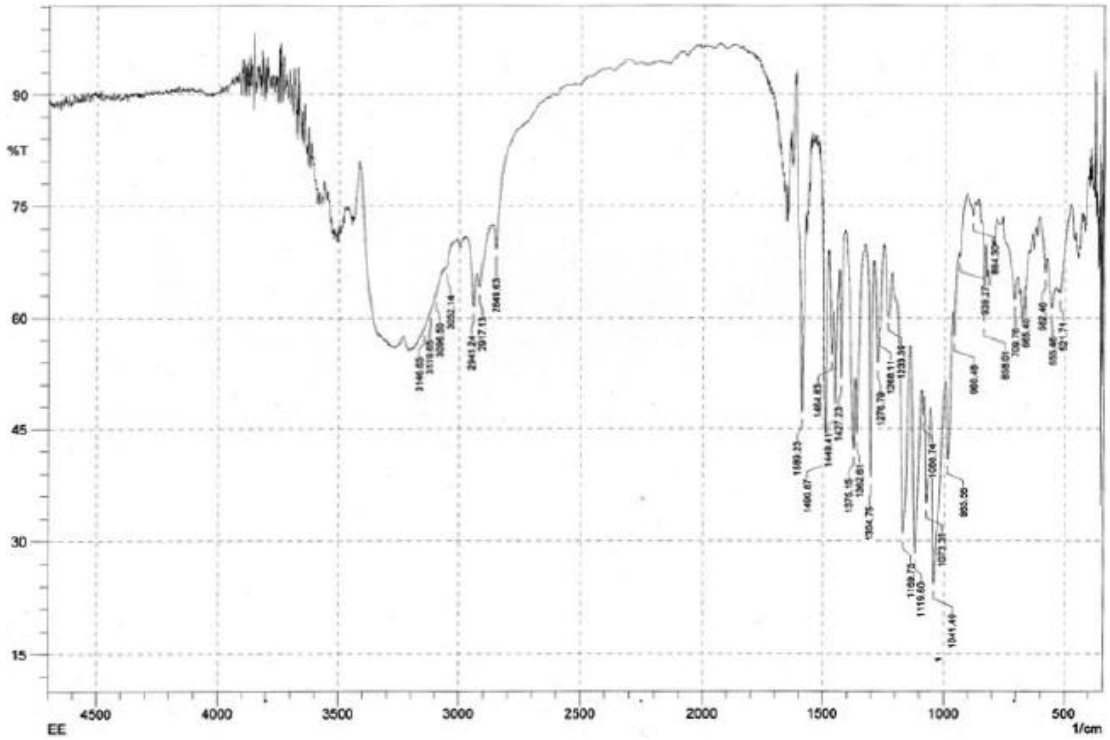


Figure 6: FTIR spectra of combination of drug and HPMC

Table 9: Peaks of combination drug and HPMC

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1589.23	(C-C multiple bond stretching) Aromatic
1490.87	(N-H bending vibrations) Amine salts
1304.75	(C-H bending) Alkene, distributed, gem
1170.71	Sulpher compounds (S=O stretching vibrations) sulfonamides.
1120.56	(O-H b bending and C-O stretching vibrations primary alcohols)
985.56	(C-H bending) Alkene, monosubstituted
1041.49	O-H bending and C-O stretching vibrations (primary alcohols)

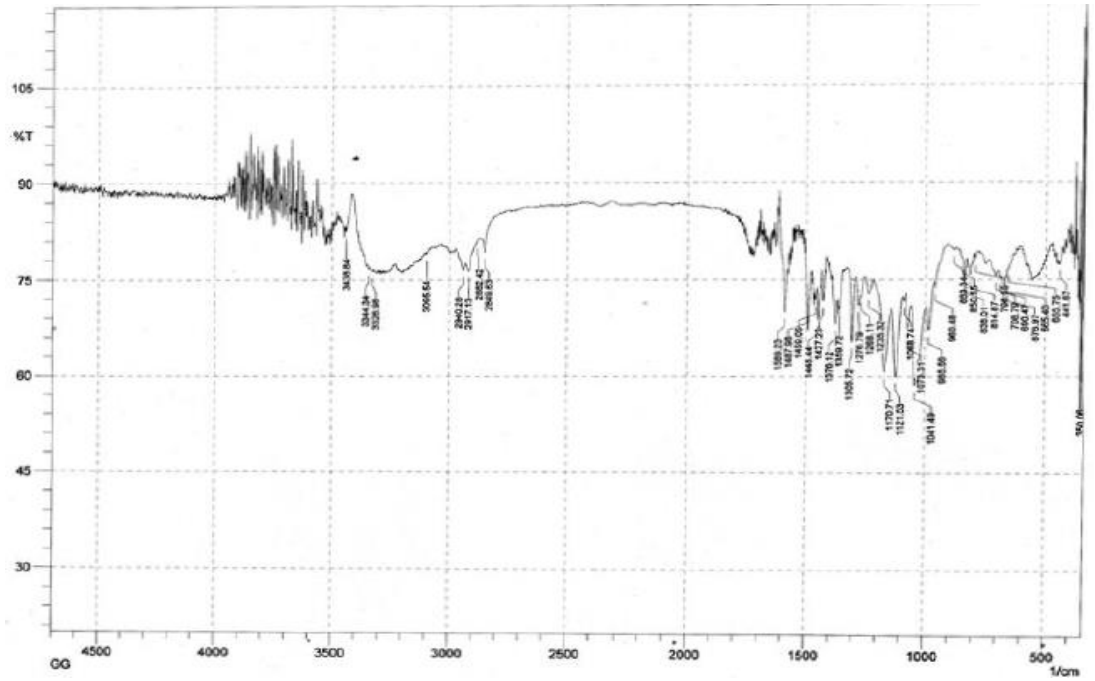


Figure 7: FTIR spectra of combination of drug and RS 100

Table 10: Peaks of combination drug and RS 100

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1589.23	Unsaturated nitrogen compound C-NO, Nitroso compound)
1170.71	Sulpher compounds (S=O stretching vibrations) sulfonamides.
2121.53	(C-C multiple bond stretching) Alkyne, monosubstituted.
2849.63	Aldehydes (carbonyl stretching vibration saturated, aliphatic) (C-H stretching vibrations two bond).

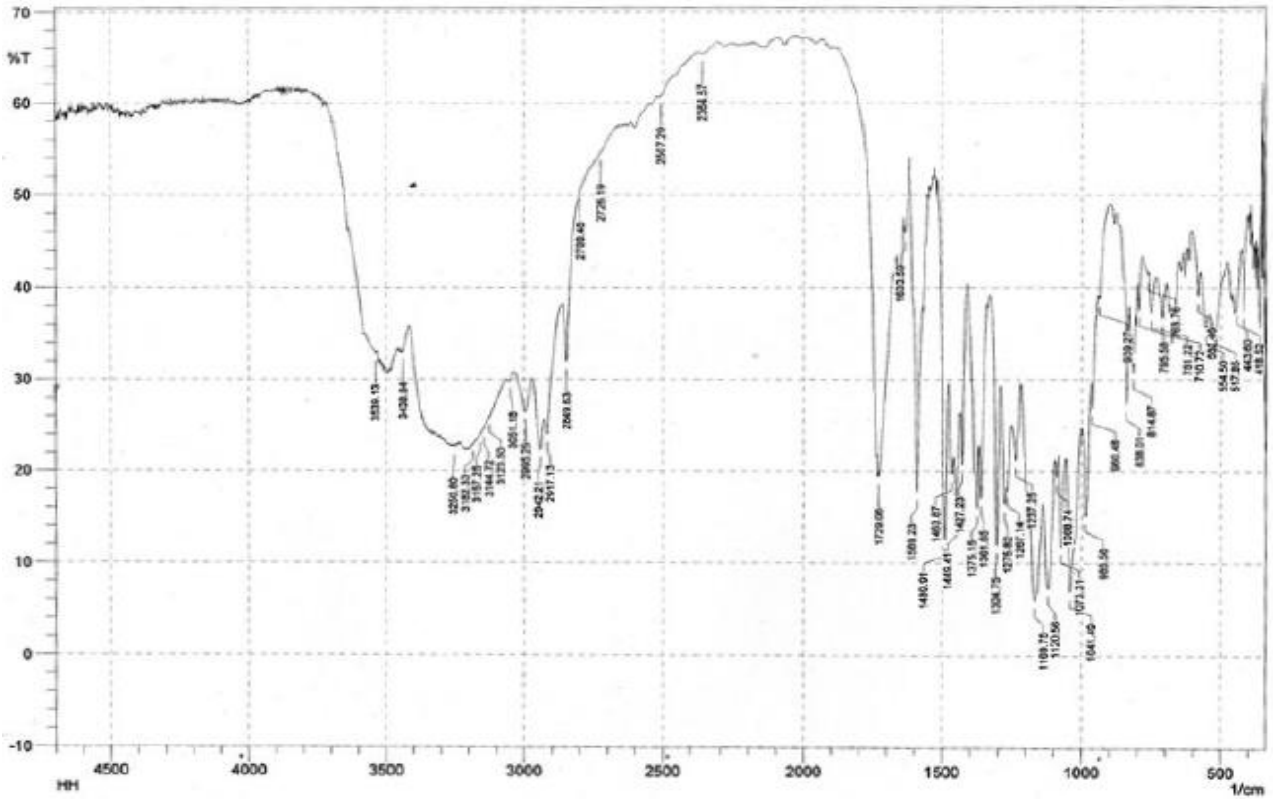


Figure 8: FTIR spectra of combination of drug and S 100

Table 11: Peaks of combination drug and S 100

PEAKS RANGE (cm^{-1})	FUNCTIONAL GROUPS
1729.06	Carbonyl chromophore (Ketone stretching vibrations) α ketones.
1589.23	(C-C multiple bond stretching) Alkene
1449.41	C-C multiple bond stretching) Aromatic.
1304.75	Unsaturated nitrogen compounds C-NO_2 nitro compounds.
1120.56	(O-H bending and C-O stretching vibrations) primary alcohols.
1041.49	Sulpher compounds (S=O stretching) sulfoxides
985.56	(C-H) bending) Alkene, mono substituted (vinyl).

Table 12: Calibration curve data of pantoprazole in distilled water

S. NO	CONCENTRATION (µgm/ml)	ABSORBANCE
1	2	0.041
2	4	0.156
3	6	0.343
4	8	0.494
5	10	0.662
6	12	0.831
7	14	0.981
8	16	1.15
9	18	1.322
10	20	1.494

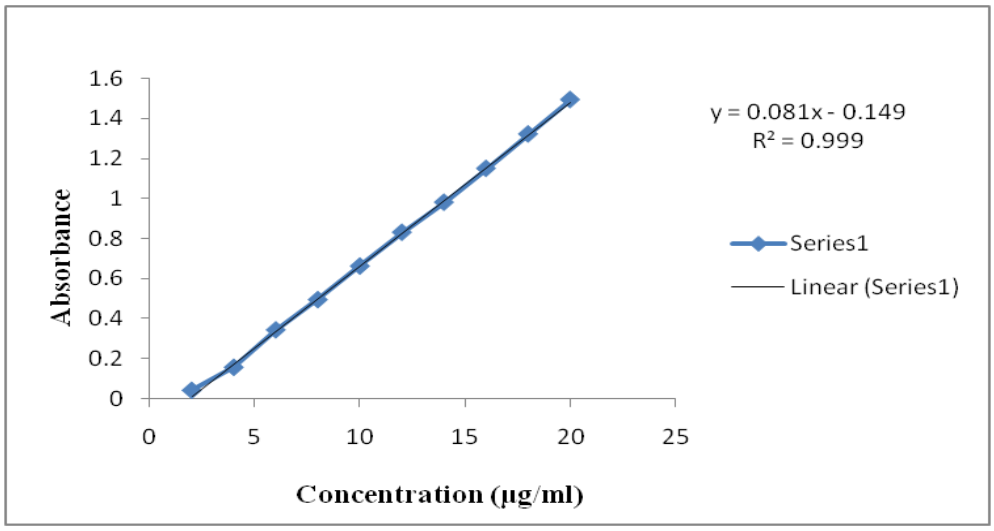


Figure 9: Standard curve of Pantoprazole in distilled water

Table 13: Calibration curve data of pantoprazole in phosphate buffer (6.8)

S. NO	CONCENTRATION (µgm/ml)	ABSORBANCE
1	2	0.072
2	4	0.139
3	6	0.223
4	8	0.299
5	10	0.362
6	12	0.462
7	14	0.539
8	16	0.620
9	18	0.692
10	20	0.782

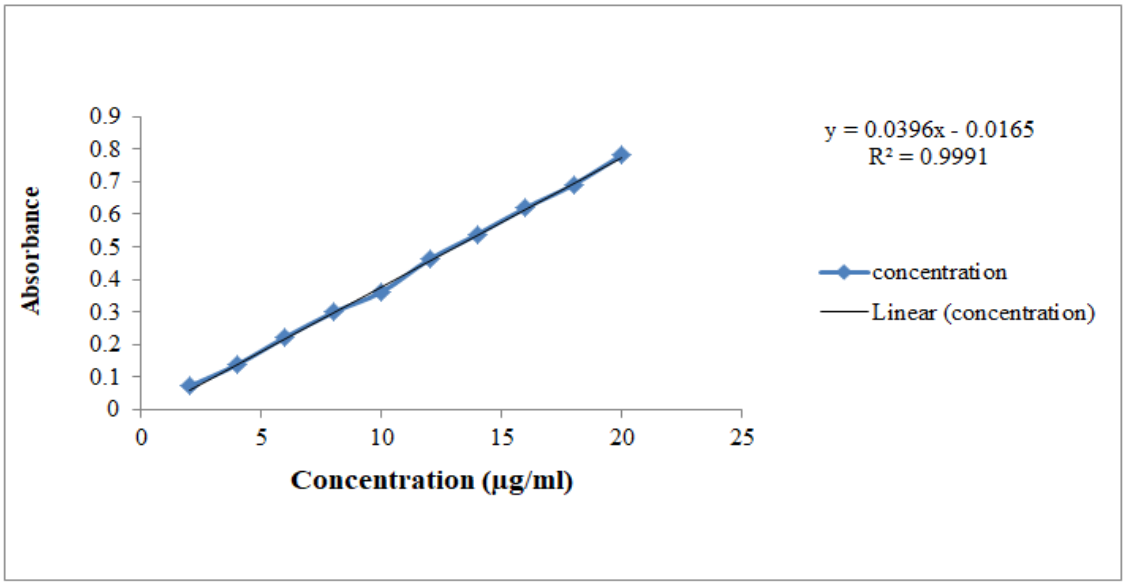


Figure 10: Standard curve of Pantoprazole in phosphate buffer

CONCLUSION

The preformulation stage is a fundamental part in establishing the properties of drug that will consent to suitable risk assessment for development. Usually it begins throughout the lead optimization phase, continues through predomination, and on into the early phases of development. Hence, it is essential that preformulation should be performed as carefully as possible to facilitate rational decisions to be made. The preformulation study of pantoprazole is to generate

information useful in developing stable and Bioavailable dosage forms.

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