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Improvement of Acid Stability of Lansoprazole by Co crystallization Techniques

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ABSTRACT

The proton pump inhibitor are rapidly degraded in the acidic medium Thus it has less bioavailability since it is acid labile , mostly available in the enteric coated tablet to prevent acids degradation .But the onset of action is delayed. It is a great challenge to formulate simple compression solid dosage form of these drugs with considerable stability and efficacy. The Cocrystals of Lansoprazole was prepared by solvent evaporation using nicotinamide as a cofomer. The prepared cocrystals were characterized by FTIR, SEM, DSC and XRD study. The cocrystals also evaluated for solubility and acid stability studies. The formation of Lansoprazole cocrystals were confirmed using FTIR, DSC showed the decreased in the melting point of cocrystals corresponds to melting point of pure Lansoprazole. The SEM also confirmed the changes in the habit of crystals. The acid stability study performed using HPLC and confirmed that the Cocrystals of Lansoprazole stable upto 75 % than the pure lansoprazole in 0.1 N HCL.

Keywords: Cocrystals, Lansoprazole, Acid stability, FTIR, Differential Scanning Calorimetry

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INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. This is especially true for Class II (low solubility and high permeability) substances according to the BCS. The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. As for BCS Class II drugs the rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS Class II drugs.^{1,2} In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds eventually appear into the marketplace³⁻⁵. Among these biopharmaceutical properties, solubility remains a key issue⁴, with drugs often discarded during commercial production due to their low solubility. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Many approaches have been adopted for improving the aqueous solubility of drugs including micronisation^{6,7}, salt formation⁸, emulsification⁹, solubilisations using co-solvents¹⁰, and the use of polymer drug vehicles for delivery of poorly soluble drugs¹¹. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of these approaches is dependent on the specific physicochemical nature of the molecules being studied^{4, 12,13}. Over the last decade, there has been growing interests in the design of pharmaceutical co-crystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility. To start with, it is necessary to know two important definitions: co-crystal and pharmaceutical co-crystal. Co-crystals can be defined in a number of ways^{14,15}. A restrictive definition utilized is that Co-crystals are structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts. The cocrystal components are discrete neutral molecular reactants which are solids at ambient temperature. Based on this definition of Co-crystals, a pharmaceutical cocrystals means a cocrystals with one of the cocrystal components as an active pharmaceutical ingredient (API) and the other components are called cofomers. From the definition, it is clearly shown that an API hydrate is not a cocrystal, however a solid-state API hydrate can Cocrystallised with a solid cofomers to form a cocrystal. Currently cocrystal approach is a method of great interest for the pharmaceutical industry. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical Co-crystals can enhance other essential properties of the APIs such as flowability, chemical stability, compressibility and hygroscopicity. The proton pump inhibitor widely prescribed by the physician and available in the

tablet or capsule. The proton pump inhibitor are rapidly degraded in the acidic medium Thus it has less bioavailability since it is acid labile , mostly available in the enteric coated tablet to prevent acids degradation .But the onset of action is delayed. It is a great challenge to formulate simple compression solid dosage form of these drugs with considerable stability and efficacy. Therefore the cocrystals of lansoprazole was prepared and evaluated for acid stability study. Therefore Cocrystals of lansoprazole are prepared using alkaline coformer to improve the stability in acidic medium. Use of alkaline coformer makes the acidic environment alkaline and helps to improve the stability of proton pump inhibitor thereby enhancing its therapeutic efficacy.

MATERIALS AND METHOD

Lansoprazole is obtained as gift sample from Dr. Reddys Laboratories, Hyderabad. Nicotinamide is used as coformer and obtained from Merk Mumbai. The solvents used are of analytical grade.

Preparation of Cocrystals of Lansoprazole

The co-crystals of lansoprazole was prepared by slow solvent evaporation method. The equimolar mixture of lansoprazole and nicotinamide (conformer) was dissolved in ethanol. The solution is warm to obtained clear solution. The solution is then filter through whatmann filter paper. The solution is then covered with aluminium foil having small hole to evaporate the solvent. The solution is kept for 24 hrs to obtained co-crystals¹⁶

Characterization of Lansoprazole Cocrystals

Solubility studies

Equilibrium solubility studies of drug and its co-crystal were performed by introducing excess amount of sample (100mg) in water, which was stirred by using magnetic stirrer at ambient condition. The aliquots were withdraw from the slurry after 48 hour with the help of graduated pipette then filtered through a 0.45 μm membrane filter, diluted suitably and absorbance was measured spectrophotometrically using UV visible spectrophotometer (SHIMADZU, UV-1800, Japan.) at 284 nm. ¹⁷

FTIR study

Compatibility of pure drug and its co-crystal of were studied by using FTIR (Brooker, Alfa-T, Germany).The. samples were triturated with dried potassium bromide using mortar and pestle. The mixture after grinding into fine powder was kept uniformly in suitable die and compressed into a pellet form by using hydraulic press.¹⁰⁰, The resultant pellet was mounted in a suitable holder in the IR spectrophotometer. Pure drug and its co-crystal was scanned and recorded in the range of 4000-400 cm^{-1} by using Infrared spectrophotometer¹⁷

Scanning electron microscopy

The morphology of pure drug and its co-crystal were studied by SEM (JEOL 5400. Japan). The sample were scanned under the required magnification at voltage of 20 kv¹⁷

Differential scanning calorimetry

The melting point determination by using DSC method. Thermograms were obtained by heating all the samples (5 mg) of pure drug and its co-crystals grown in presence of additives at a constant heating rate of 10°C/min with chart speed of 40 ml/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion were automatically calculated. The temperature range for the scan was 30°C to 300°C for all the samples.¹⁷

Powder X-ray diffraction spectroscopy

X-ray diffraction pattern of pure drug and its co-crystal were studied by using the X-ray diffractometer (BRUKER D8 ADVANCE, Germany). The sample were screened at an angle between 2-40° and scanning rate is 3°/min.^{17,18}

Stability testing

To compare the stability of pure drug and its co-crystal, samples of both were evaluated at 75% RH for time period of 1, 3, 7 and 30 days condition. Open glass vials contained 100 mg of pure drug and its co-crystal was stored in the stability chamber (Remi Elektro Technik Ltd, India). A vial was removed for each sample at each time point. Upon removal from the chamber, the samples were promptly evaluated for any change in the physical state and its weight. These results indicated the hygroscopicity and physical stability of drug and its co-crystal.¹⁹

Acid stability study using HPLC²⁰

Chromatographic condition

The column used was C₁₈, 5 µm, 4.6 x 250 mm HPLC cartilage column. The mobile phase was a mixture of 5:3:2 (v/v/vi) 0.05 M potassium di-hydrogen phosphate, methanol and acetonitrile (pH adjusted to 3 by o-phosphoric acid) filtered through a 0.45 µm membrane filter. The flow rate was 1 ml/min. injection volume was 20µl. The separation was monitored at a wavelength of 284 nm.

Preparation of 0.1 N Hydrochloric Acid

Acid degradation study was carried out in 0.1 N HCl which provide the acidic environment of stomach. For this 8.5 ml conc. HCl was diluted up to 1000 ml volume with distilled water in 1000 ml volumetric flask to get 0.1 N HCl .

Preparation of the acid degradation product

Standard preparation for pure drug

40 mg of the drug were transferred into a 100 ml volumetric flask; make up the volume 100 ml with 0.1 M HCl. The solution was set aside at room temperature.

Standard preparation for cocrystal

80 mg of co-crystal (equivalent to 40mg of drug) was transferred into a 100ml) volumetric flask make up the volume 100 ml with 0.1 M HCl. The solution was set aside at room temperature.

Test solution for pure drug

Withdraw first sample from the above standard solution of pure drug after 2 minutes and second sample after 30 minutes. Neutralized it with 0.1M sodium hydroxide and properly diluted up to 20 ppm. 20 ppm solution was passed through a suitable 0.45 μm membrane filter.

Test solution for co-crystal

Withdraw first sample from the above standard solution of co-crystal after 2 minutes and second solution after 30 minutes. Neutralized it with 0.1M sodium hydroxide and properly diluted up to 20 ppm. The solution was passed through a suitable 0.45 μm membrane filter.

RESULTS AND DISCUSSION:

Lansoprazole was obtained as a crystalline pure drug from the supplier; hence it was used as such for the preparation of co-crystal forms. It showed good solubility in ethanol, methanol, It was practically insoluble in water and other organic solvent. Nicotinamide showed good solubility only in ethanol. Hence ethanol was selected as a solvent for the preparation of co-crystal. Other organic solvent and method are tried to obtained the co-crystals, but it was failed to recrystallized thus equimolar Lansoprazole and Nicotinamide mixtures was dissolved in ethanol. The solution was then agitated to form a clear solution The solution was covered with aluminium foil and left to evaporate under ambient laboratory condition. At the saturated solution, nuclei formations occur for co- crystallization. After the evaporation of solvent, dry solid powder was obtained that was scratched from the walls of beaker then dried at 50° C for 15 min and stored in desiccators for further studies.

Equilibrium solubility studies:

The solubility study of drug and its co-crystal were carried out by shaking method in water for 24 hours. It reveals that the pure drug solubility was 1.36 mg/ml and solubility of co-crystals was 4.65mg/ml. This indicates the increase in solubility due to the formation of complex of drug and conformer.

Table 1. Solubility data of Lansoprazole and its cocrystals

Sample	Solubility (mg/ml)
Lansoprazole	1.36
Cocrystals of Lansoprazole	4.65

FTIR Study:

The FTIR of pure Lansoprazole and its cocrystals compared with each other showed slight difference in their peaks this may due to the formation of hydrogen bonding between the pure drug and co-crystals. But the functional group and characteristic peaks of the pure drug is not change shown in Figure 1. This indicates no interaction between the drug and cofomer. The characteristic peaks of drug and co-crystals are shown in Table 2.

Table 2: Interpretation Infrared spectroscopy peaks of drug and its co-crystal

Sr. No.	Characteristic peaks of pure drug and co-crystal (cm ⁻¹) Functional group	Pure Drug	Co-crystal
1	C-C	1558	1589
2	C-F	1506	1460
3	C-O-C	1205	1219
4	C-N	1159	1159
6	N-H	3275	3385
7	C=C	1734	1716
8	C-H	2899	2958
9	S=O	1373	1292
10	S-C	665	599
11	C-O-C	1205	1219
12	N=C	1635	1589
13	O-H	3265	3298
14	N-O	1558	1604

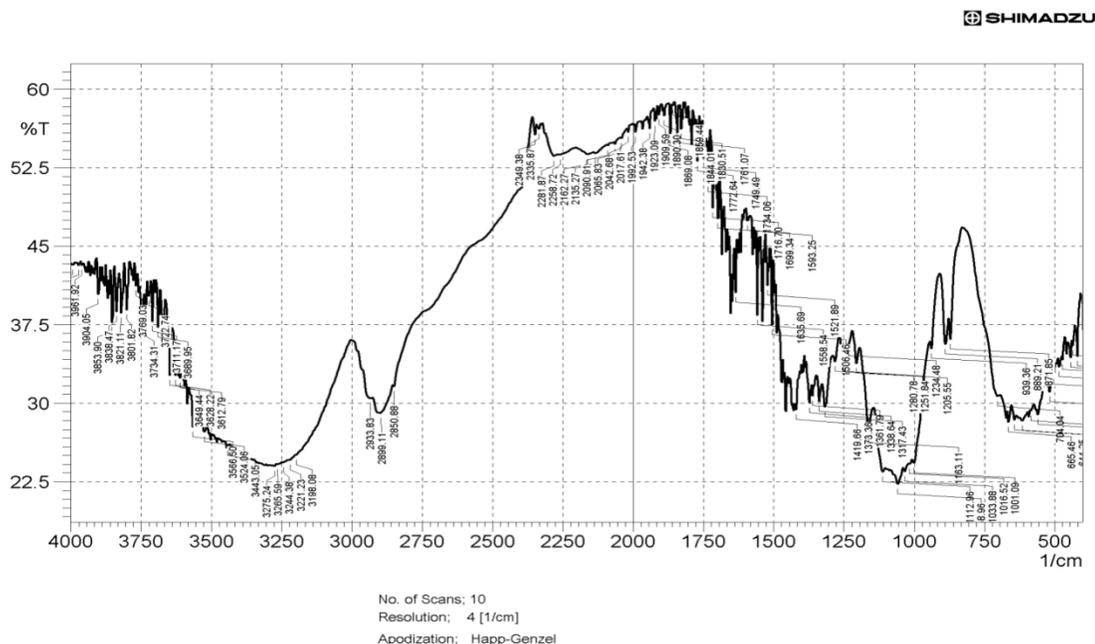


Figure 1: FTIR Spectra of pure Lansoprazole

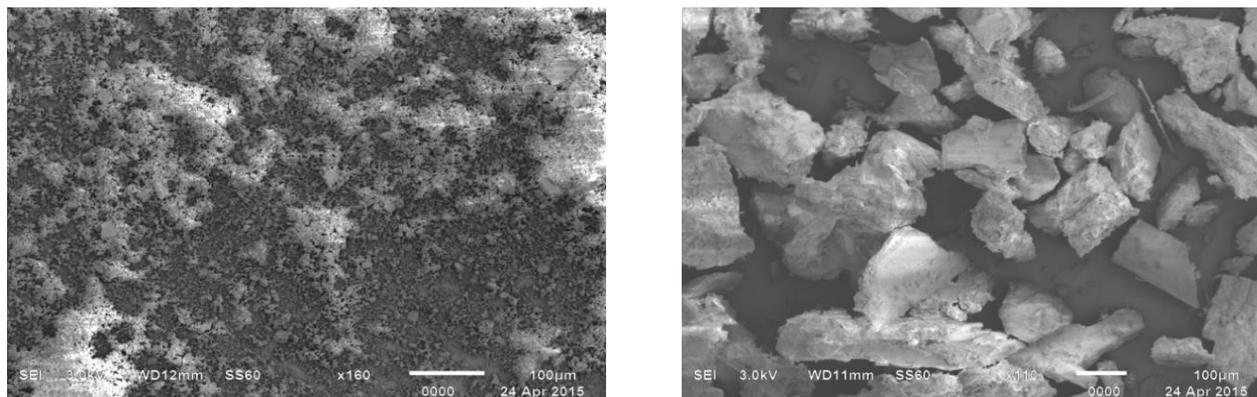


Figure 2 (c): SEM of pure Lansoprazole at 100um Figure 2 (d): SEM of co-crystals at 100um

Differential scanning calorimetry:

The melting point of a solid is the temperature at which the vapor pressure of the solid and the liquid are equal. The melting point was determined by DSC method. The DSC thermogram shown that Lansoprazole appeared on sharp endothermic peak at about 180.53^oC corresponding to its melting point. The melting point Lansoprazole cocrystals is shifted to lower at 156.75 ^oC. The nicotinamide also appeared at 121.51^oC. From this it reveals that co-crystal of Lansoprazole yield was not 100% due to which lansoprazole peak interference shown in Figure 3 and 4.

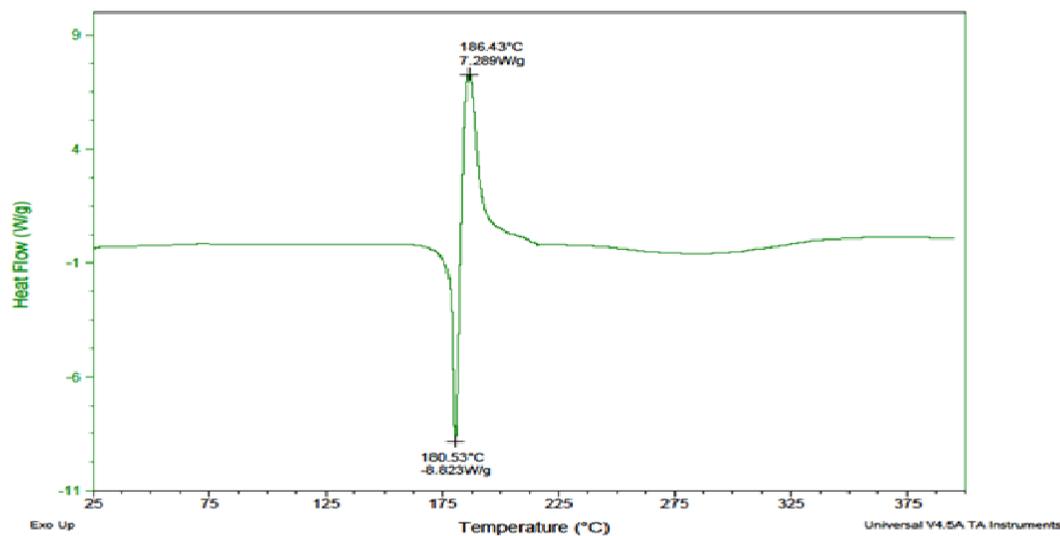


Figure 3: DSC thermogram for pure Lansoprazole

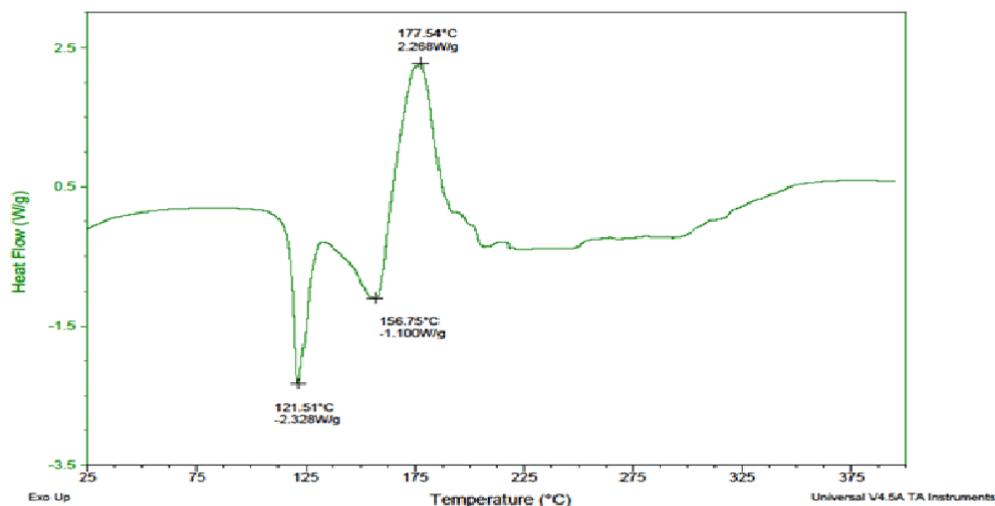


Figure 4: DSC Thermogram for Lansoprazole Cocrytals

X-ray Diffraction Spectroscopy

The X-ray diffraction pattern of various crystal forms were studied by X-ray diffractometer. The X-ray diffraction pattern of pure drug has more number of peaks when compared to its co-crystal form. Co-crystal has decreased number of peaks as well as intensity as compared to pure drug as shown below. However, the differences in the relative intensities of their peaks may be attributed to differences in the size and habits of the crystal, which may be attributed to the different physicochemical property of the drug in the co-crystallization

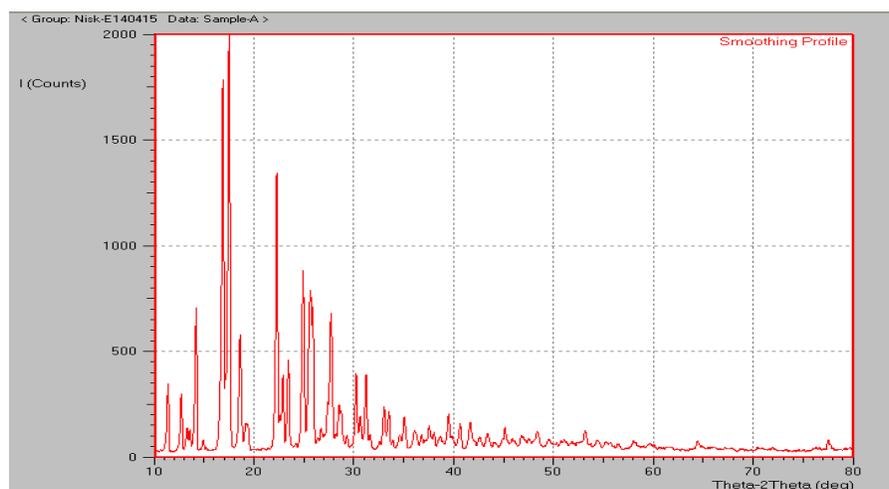


Figure 5: DSC Thermogram of pure Lansoprazole

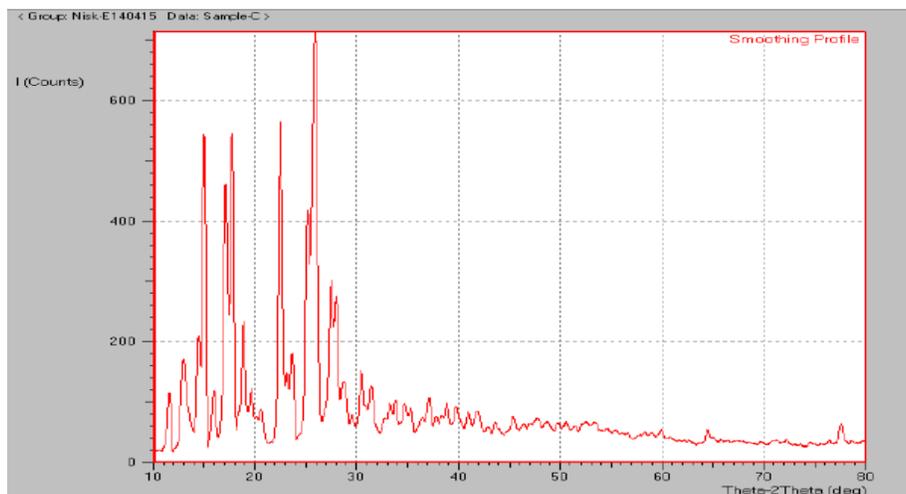


Figure 6: XRD pattern of Lansoprazole cocrystals

Stability study:

Each open glass vials contained 100 mg of pure drug and co-crystal was stored in the stability chamber for one month. At the specific intervals, samples were withdrawn to check its physical appearance and weight, respectively. There were no change in the physical appearance and its weight samples on 1, 3 and 7 day but on 30m day it shown increase the weight in drug (0.5%) and its co-crystal (0.2%), respectively. These results indicated that lansoprazole and its co-crystal are not hygroscopic, so it should be stored properly and protected from humidity.

Acid stability study using HPLC:

HPLC was chosen as stability indicating method. The degradation rate of drug and its co-crystal had a direct relationship with H^+ ion, as the pH value increases, the rate of degradation decreased. The instability of these samples was studied in the acidic medium 0.1 N HCL.

Lansoprazole test sample:

First sample of lansoprazole withdrawal after 2 min in 0.1 N HCL was recorded on HPLC and chromatogram shown in Figure 7. It was found that there was no degradation of drug and single peak of lansoprazole was observed at 8.187 min showing 100% peak area.

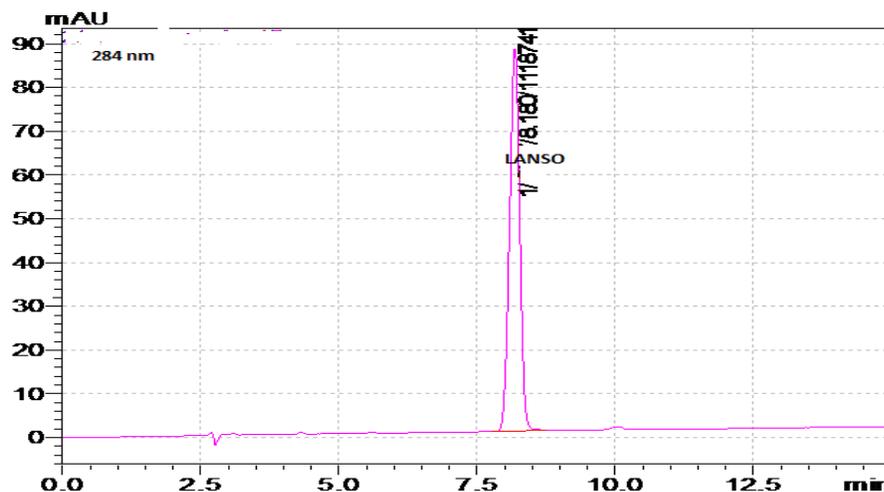


Figure 7: HPLC chromatogram of lansoprazole after 2 min in 0.1 N HCL

But when sample withdrawn after 30 min from 0.1 N HCL the percentage area of lansoprazole was found 04.244% at its retention time 8.187 min which reveals that lansoprazole was degraded upto 96 % as shown chromatogram Figure.8.

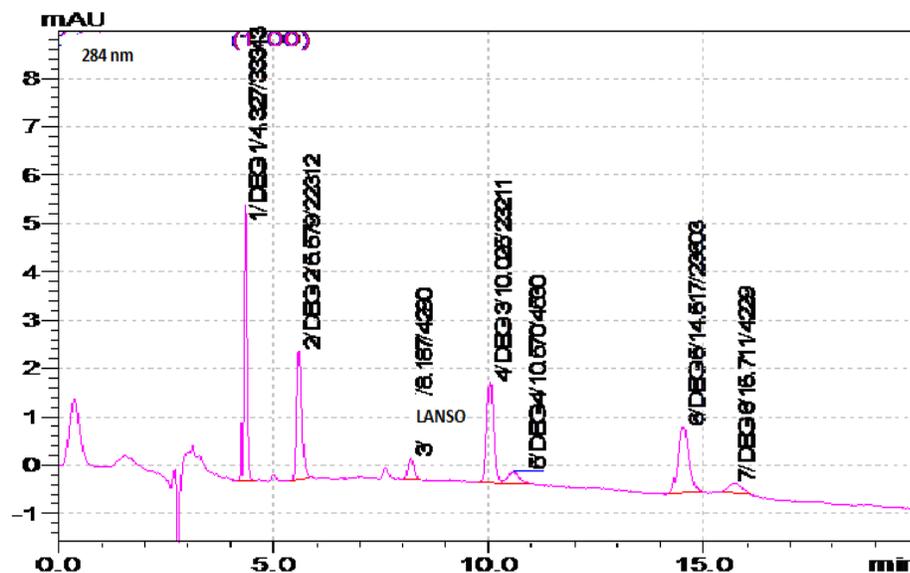


Figure 8 HPLC chromatogram of Lansoprazole after 30 min in 0.1 N HCL

Table 3. Peak table of HPLC chromatogram of after 30 min in 0.1 N HCL

Peak	Name	RT	Area	% Area	Tailing F.	T. Plate	Resolution
1	DEG 1	4.327	34386	27.2787	1.226	9900.288	--
2	DEG 2	5.579	24982	19.8187	1.386	9205.655	6.158
3	LANSO STD	8.187	5350	4.2441	1.113	13681.743	10.179
4	DEG 3	10.025	25797	20.4650	1.142	17234.790	6.275
5	DEG 4	10.570	4168	3.3069	--	9230.147	1.457
6	DEG 5	14.517	27187	21.5676	1.127	15435.094	8.710
7	DEG 6	15.711	4184	3.3191	1.183	12604.239	2.333

Lansoprazole Cocrystal test sample:

The sample of co-crystals of lansoprazole was taken after 30 min from 0.1 N HCL and injected in HPLC. It was observed that the drug was found to be stable upto 75.00% from peak area table as compared to pure lansoprazole.

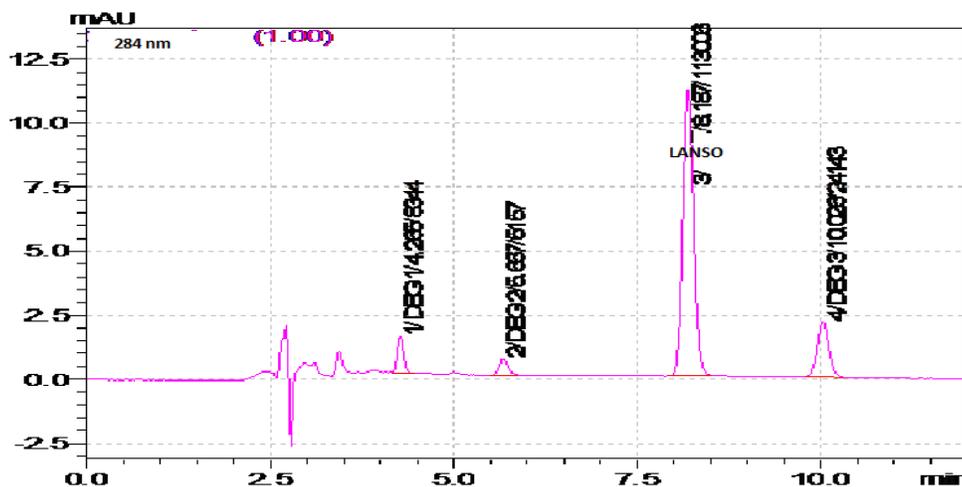


Figure 9: HPLC chromatogram of co-crystal after 30 min in 0.1 N HCL

Table 8. Peak table of HPLC chromatogram of co-crystal after 30 min in 0.1 N HCL

Peak	Name	RT	Area	% Area	Tailing F.	T. Plate	Resolution
1	DEG 1	4.265	8344	5.5384	1.237	9745.468	--
2	DEG 2	5.667	5157	3.4233	1.298	10216.558	7.064
3	LANSOCC	8.187	113006	75.0121	1.108	13824.559	10.023
4	DEG 3	10.026	24143	16.0262	1.100	17629.896	6.335

CONCLUSION:

To improve the acid stability of Lansoprazole, its cocrystals was prepared with the cofomer Nicotinamide by using slow evaporation method. Its characterization by using SEM, FTIR, DSC and XRD revealed the formation of new crystalline phase. The acid stability profile by using HPLC method strongly suggested the improvement of acid stability of Lansoprazole by Co crystallization techniques.

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