



Crystal Engineering of Lansoprazole for Solubility and Bioavailability Enhancement.

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Abstract: The existing work deals with the purposes of synthesis and characterization of lansoprazole co-crystals with various conformers. Nine conformers were selected under the study to prepare co-crystals of lansoprazole for enhancing its solubility, dissolution, and bioavailability. The formulated co-crystals were characterized by FTIR, DSC, PXRD, saturation solubility study, in vitro dissolution studies, and stability study. The conclusion of the study shows a major improvement in solubility with piperazine co-former. Lansoprazole and piperazine co-crystal 1:1M were formulated as tablets. The results show that solubility and dissolution of lansoprazole were enhanced by co-crystallization and it shows pharmaceutical stability.

Keywords: lansoprazole, Co-crystal, Solubility, Dissolution.

INTRODUCTION

Co-crystallization is the ability to convey the drug to the patient safely, effectively, and economically, depending largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state. This provides an important force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties. Co-crystallisation has gained increased importance in enhancing the physical properties and/or stability of solid dosage forms. The co-crystal formation involves a combination of a given active pharmaceutical ingredient with another pharmaceutically acceptable molecule in the crystal lattice. The resultant crystalline phase will maintain the intrinsic activity of the parent drug while possessing a different physicochemical profile. The benefits related to the co-crystallization approach are that it alters the properties of all types of drug molecules, including weakly ionizable and non-ionizable, to form co-crystals, and the being of numerous prospective counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis. Further esteemed advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity for intellectual property (IP) protection and the possibility of extending the life cycles of old APIs.¹

Lansoprazole is a BCS class 2 drug .that inhibits gastric acid secretion. This is the treatment of active gastric ulcers and duodenal ulcers. It is also approved for the long-term treatment of healed reflux esophagitis, healed duodenal ulcers, and the treatment of hyper secretory conditions such as Zollinger-Ellison syndrome. Its mechanism of action is to selectively inhibit the membrane enzyme H⁺/K⁺ ATPase in gastric parietal cells. In clinical trials, lansoprazole is more effective than placebo or histamine (H₂)-receptor antagonists in the treatment of reflux esophagitis.² Lansoprazole was selected as it has poor solubility, compressibility, and flow properties which might be set with the help of co-crystallization.³ The objective of this present study was to check crystal stars with maximum solubility were selected and evaluated by DSC, FTIR, and PXRD.

MATERIALS AND METHODS

Materials

Lansoprazole was provided by senior Lab., Hyderabad as a gift sample for the study. Calcium gluconate, sodium bicarbonate, croscarmellose sodium, and piperazine from the pharmaceuticals lab of Bhagwan College of Pharmacy

Methods

Preparation of co-crystals

By using the neat grinding method lansoprazole is co-crystallised with 9 co-crystals cofomer. The grinding was done for 20 min for every batch. After that from Carr's index, Hausner's ratio and angle of repose flow properties of co-crystal were determined.⁴

Melting point determination

By using the Digital melting point apparatus the melting point of lansoprazole, CCFs, and co-crystal was determined in triplicate.⁵

Differential Scanning Calorimetry (DSC)

Thermal analysis of lansoprazole and co-crystals was performed by using differential scanning calorimetry. The placed samples were in aluminium pans, which are hermetically sealed and then these aluminium pans were heated at a rate of 20°C/min from 50° to 350°C under constant purging dry nitrogen flow (20mL/min). For reference purposes, an empty aluminium pan was used.⁶

Fourier Transfer-Infrared Spectroscopy (FTIR)

Shimadzu FTIR spectrometer Prestige 21 with DRS assembly was used in attenuated total reflectance (ATR) mode for collecting FT-IR spectra of samples.

Powder X-Ray diffraction Study (PXRD)

In PXRD sample of co-crystal and lansoprazole was exposed to a beam of the monochromator. X-ray radiation using a Bruker D8 Determine, which was diffracted and recorded by an X-ray detector. The diffracted data was processed and an X-ray diffraction pattern of powder was plotted.

Solubility Study

As per Higuchi and Connors's method saturation solubility studies of lansoprazole and its co-crystal were done. For this study take vials and then add an excess quantity of co-crystal and 10 ml of different solvents in these vials. The vials are then shaken on rotary shaking for 24hr. then the solution was filtered through filter paper no 41(Whatman) and then at 280 nm with correct dilution, the filtrate was analysed by UV spectrophotometer.⁷

Preparation of Immediate release tablets of lansoprazole Co-crystals

The powder mixture of Lansoprazole cocrystal (API), Calcium hydroxide (as a flocculant), croscarmellose sodium (super disintigrent) and was dry blended first for 20 minutes followed by the addition of calcium lactate (antacid) and Calcium gluconate (Anti hypo calcemic agent). The powder mixture was further blended for 10 minutes. The resulting powder mixtures were then compressed into tablets (average tablet weight 500 mg) using a rotary tablet machine equipped with a 13 mm flat-faced punch. The tablets (LT) were evaluated for thickness, hardness, weight variation, friability, and drug content. The compositions for one tablet are reported in the table.

Formulation of Lansoprazole Tablet**Table 1 formulation of lansoprazole tablet**

Ingredients	Quantity (mg)
Lansoprazole cocrystal	37.035
Calcium hydroxide	0.375
Croscarmellose sodium	45
Calcium lactate	150
Sodium bicarbonate	275.9

Dissolution study of co-crystals and their formulation

The In vitro dissolution study was carried out using a USP type 2 apparatus (USP tablet Dissolution apparatus Veego VDA-6DR USP standards) at a rotation speed of 100 rpm. The dissolution medium chosen was PBS pH 7.4 (volume 1000ml, temperature 37°C) as it is official for USP. A 5ml of sample at each sampling interval was withdrawn. After each sampling, the sample withdrawn was replaced by the same dissolution media kept in the control flask. The sample withdrawn was then immediately filtered and analysed for sample content by UV spectrophotometer at 285 nm after suitable dilutions. This test provides an evaluation of the physiological drug candidate.⁸

Stability Study

In this study, the tablet of lansoprazole and piperazine co-crystal was packed in aluminium foil and for the period of one month it is stored under the following environmental condition as prescribed by ICH conditions at 5°C ± 30°C and 25° ± 2°C/ RH 60% ± 5%. The tablets were evaluated at end of the 15th and 30th day for parameters like physical changes, drug content, disintegration time, and dissolution study of the formulation.

RESULT AND DISCUSSION

The per cent solubility and melting point of lansoprazole and co-crystals were reported in Table 2. It was observed that the Solubility of lansoprazole is 25% was pointedly improved by co-crystal formation with piperazine as compared to other CCF under study.

Table 2 solubility and melting point of lansoprazole and co-crystals

Sr. no	Coding of co-crystal	LSP+ Co-former	MP	Solubility%
	F	LSP	170-175	25
1	F1	LSP+Urea	150-155°C	36.38
2	F2	LSP+Mannose	158-163°C	18.6
3	F3	LSP+Piperazine	125-130°C	79.41
4	F4	LSP+Dextrose	165-170°C	32.03
5	F5	LSP+a-naphthol	85-90°C	20.63
6	F6	LSP+B-naphthol	78-82°C	12.67
7	F7	LSP+Caffeine	230-235°C	20.42
8	F8	LSP+Mannitol	142-147°C	33.5
9	F9	LSP+Maltose	148-152°C	43.96

The micromeritics characterization of lansoprazole and its various co-crystals were as represented in Table. Co-crystal of lansoprazole and piperazine shows improvement in flow property

Micromeritic characterization of lansoprazole and Different co-crystals

Table 3 micromeritics of lansoprazole

Micromeritic characterization / Co-crystals	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner's ratio	Angle of repose (°)
Lansoprazole	0.49	0.87	43.63	1.77	30.93
F1	0.27	0.62	30.85	1.35	36.5
F2	0.30	0.64	30.55	1.41	32.63
F3	0.36	0.70	29.81	1.46	27.30
F4	0.31	0.58	30.69	1.40	35.77
F5	0.58	0.84	32	1.32	30.52
F6	0.42	0.65	31.22	1.62	32.22
F7	0.31	0.68	32.36	1.32	36.85
F8	0.37	0.74	31.85	1.55	29.33
F9	0.40	0.82	32.96	1.46	33.21

FTIR of Lansoprazole

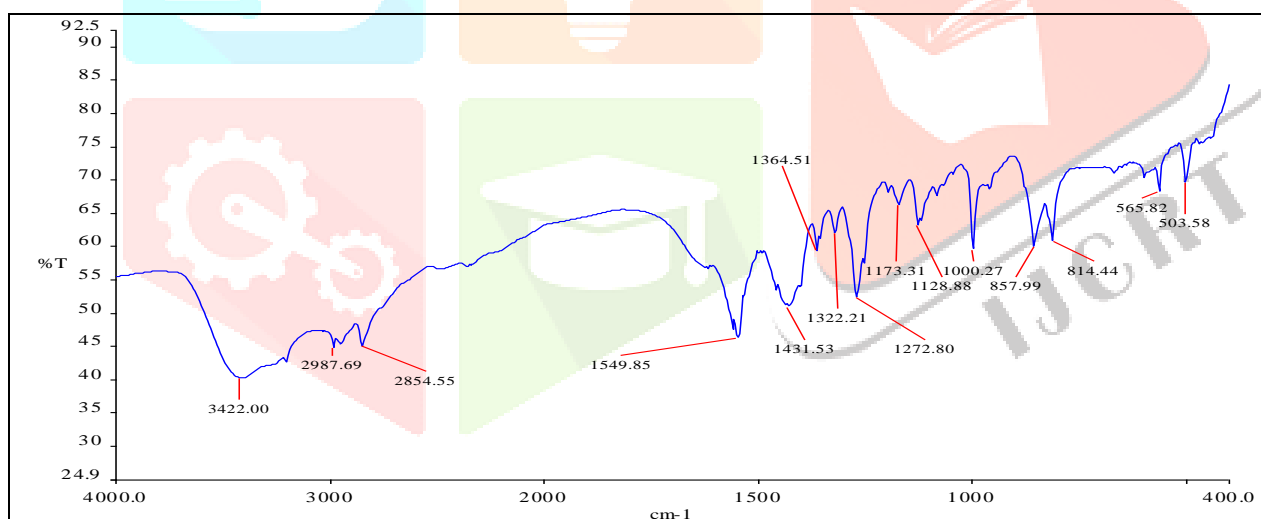


Figure 1 FTIR of Lansoprazole

FTIR of Lansoprazole

Table 4 FTIR of Lansoprazole

Functional group	Observed frequency(cm-1)	Reported frequency(cm-1)
Stretching of Amine	3233	3500-3300
Stretching of aromatic ring	1437.73	1401.66
Stretching of C-H bond	2854.55	2960-2800

By co-relating the stretching of IR spectrum and the structure of lansoprazole it can be concluded that the given structure follows the same functional group that is mentioned in the table.

PXRD of Lansoprazole

The diffraction pattern of lansoprazole showed that it is highly crystalline as indicated by its numerous distinctive peaks (9.62°, 16.26°, 16.86°, 17.27°, 18.97°, 20.40°, 21.59°, 23.10°, and 27.61°) with major characteristic diffraction patterns.

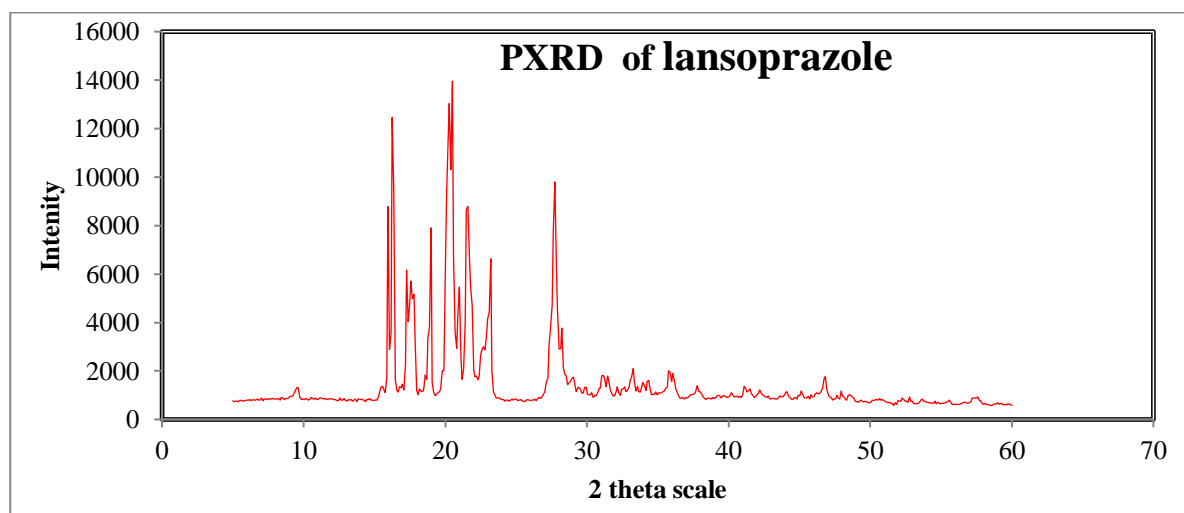


Figure 2: X-ray crystallography of lansoprazole

IR of co-crystal

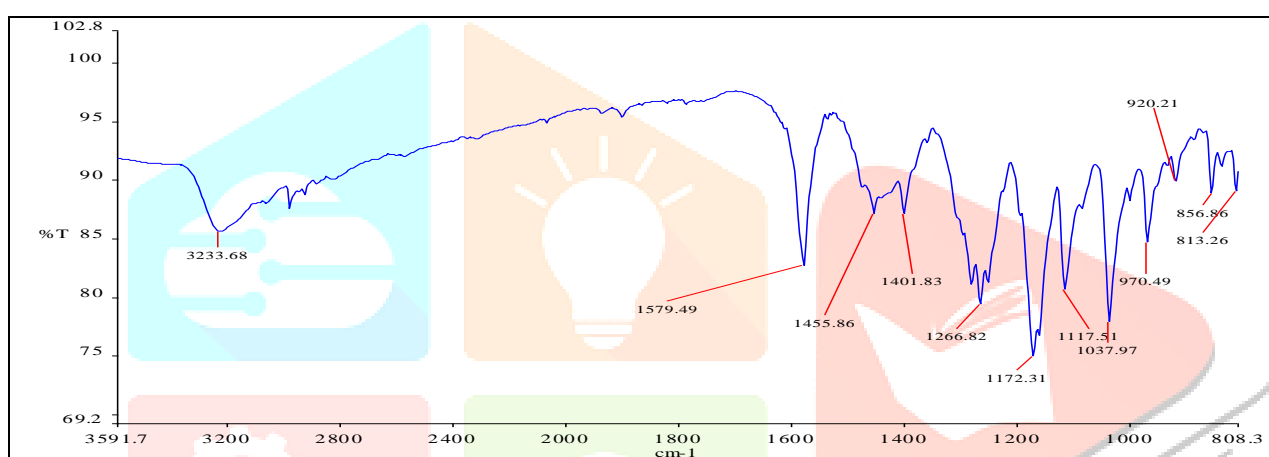


Figure 3: IR of co-crystal

IR of Lansoprazole and piperazine co-crystal

Table 5 FTIR frequency data correlate with the reported frequency of co-crystal

Functional group	Observed frequency(cm-1)	Reported frequency(cm-1)
Stretching of Amine	3422	3500-3300
Stretching of the aromatic ring	1431.53,1322.21	1401.66
Stretching of Phenyl ether	1117	1250-1040
Stretching of Sulphoxide	1038	1050
Stretching of Fluoride	1253,1282,1267	Multiple bands between 1350-1100
Stretching of Amine	3233	3500-3300

By comparing the IR of LSP: Piperazine (Table 5) with pure drug and CCF (Piperazine) it is observed that the IR Spectrum of LSP: Piperazine Co-crystal is having different Stretching than Pure drug and CCF which means that the new crystal lattice structure has formed.

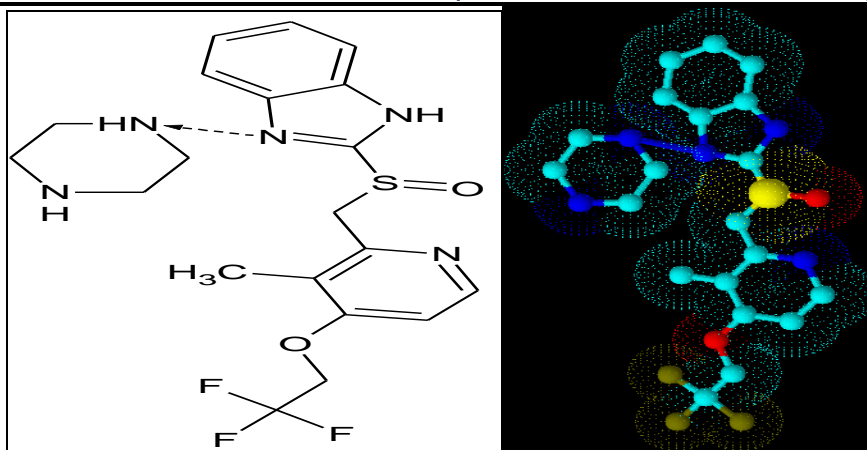


Figure 4: Probable structure of LSP: Piperazine Co-Crystal with Hydrogen bonding

The possible structure showing the co-crystal arrangement with hydrogen bonding is shown in figure 4. Benzimidazole nitrogen may act as a hydrogen acceptor. Thus, it produces co-crystals with greater solubility and stability than other co-crystals.

XRD of Co-crystal

The diffraction pattern of lansoprazole showed that it is highly crystalline in nature as indicated by its numerous distinctive peaks (5.60° , 14.52° , 16.86° , 17.47° , 22.29° , 23.40° , and 25.61°) with major characteristic diffraction patterns (Figure .5).

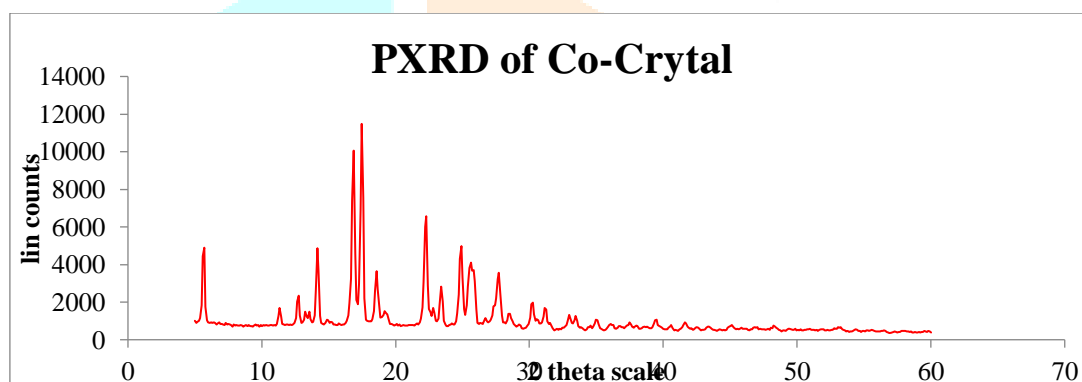


Figure 5: Crystallography of Co-crystal

Formulation and Evaluation parameter of lansoprazole tablet

Table 6 Evaluation of lansoprazole tablet

Drug Parameter	Observed values
Hardness	5.5 ± 0.10 kg/cm ²
Thickness	3.6 ± 0.04 mm
Wt. variation	550 ± 0.05
Friability	$1.08 \pm 0.05\%$
Content uniformity	$99.72 \pm 0.10\%$
Disintegration test time	18.83 (sec) ± 0.01

CONCLUSION

Co-crystals are new aspect for pharmaceutical industries and provides new ideas to deal with poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical product than solvates or hydrates. The synthesized lansoprazole shows improvement in solubility by neat grinding method with piperazine as it is used as a co-crystal former. It is a green method for improving the solubility and bioavailability of lansoprazole.

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