IJAPB International Journal of Advances in Pharmacy and Biotechnology

Journal homepage: http://ijapbjournal.com/

Research Article

Preparation and Characterization of Rabeprazole Cocrystals

Raju Thenge[1*], Pritesh Chaware[1], Vaibhao Adhao[1], Nilesh Mahajan[2]

[1]*Dr. Rajendra Gode College of Pharmacy, Malkapur, Buldana, Maharashtra, India.*
[2]*C Dadasaheb Balpande College of Pharmacy, Besa-Nagpur, Maharashtra, India..*

ARTICLE INFO

Article history:
Received 02 Sep 2020
Received in revised form 20 Sep 2020
Accepted 23 Sep 2020
doi.org/10.38111/ijapb.20200603007

Keywords:
Rabeprazole, SEM, DSC, FTIR, XRD, Acid stability, dissolution rate

ABSTRACT

Rabeprazole (RBZ), a PPIs are used in the treatment of acid-related gastro-duodenal disorders by reducing gastric acid secretion. The stability of RBZ in aqueous media is a function of pH with an increased rate of degradation as the pH decreases. Degradation of RBZ leads to a yellow or purple discoloration of the pellets, film layer or dissolution medium. Stability of PPI also decreases under moisture conditions. Exposure of RBZ to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability. Hence an attempt has been made to prepare the Cocrystals of RBZ to increase the acid stability by solvent evaporation method using coformer sodium bicarbonate. The RBZ Cocrystals were characterized by SEM, FTIR, DSC and XRD. The prepared RBZ Cocrystals were evaluated for dissolution rate and acid stability study. The RBZ sodium bicarbonate Cocrystals showed improved in the stability in the acidic medium and thus the drug may protect compared to pure RBZ. The scanning electron microscopy clearly showed the formation and confirmation of new solid phase with the coformer. The FTIR spectra indicated the shifting of characteristic peak in the Cocrystals but does not showed any interaction between the coformer used. DSC data showed the change in the endotherm with the MPs of Cocrystals. XRD spectra indicated the significant difference in the 2θ and the intensity of the peaks. Hence the Cocrystal formation could be helpful to acid stability of RBZ.

1. Introduction

Cocrystals incorporate pharmaceutically acceptable guest molecules like coformer into a crystal lattice along with the API. Cocrystals have regained attention as attractive alternate solid forms for drug development. Physiochemical properties of pharmaceuticals may be improved by obtaining cocrystals using cocrystallization. Cocrystallization techniques with pharmaceutically acceptable compounds do not affect pharmacological activity of API however will improve physical properties, like solubility, hygroscopicity, compaction behavior. New opportunities for producing a larger diversity of solid forms of drug substances exhibiting the proper balance of important properties for development into a viable and effective drug product may be met by cocrystals.[1,2]

Developing novel strategies to extend the stability of medication are a good challenge to prepare solid dosage form. Various ways have been used for improving the stability of drugs including emulsifications and use polymer drug vehicles for delivery of drug. These techniques have been shown to be effective at enhancing oral bioavailability. To overcome this problem, we are using cocrystallization technique that led to improving acid stability of drug by incorporating suitable co-former.[3,4]

Rabeprazole isused in the treatment of acid-related gastro-duodenal disorders by reducing gastric acid secretion. The steadiness of PPIs in aqueous media is a function of pH with an enhanced degradation as the pH decreases. Degradation of rabeprazole leads to a yellow or purple discoloration of the pellets, film layer or dissolution medium. Stability of proton pump inhibitor also decreases under moisture conditions. Exposure of PPIs to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability[5,6].

* *Corresponding author.* Tel.: +918275556283.
E-mail address: rajuthenge11@gmail.com

2. Material and Methods

Rabeprazole is obtained as gift sample from Leben Pharmaceutical, Akola. Sodium bicarbonate is used as coformer and obtained from Molychem, Mumbai. The solvents used are of analytical grade.

Preparation of Rabeprazole Cocrystal

Cocrsytals of rabeprazole were prepared by following solvent evaporation method. Rabeprazole sodium and sodium carbonate were added into water upto saturation level. The equimolar ratio of drug and coformer were used to form the Cocrystals. The solution was agitated, and covered with aluminium foil with hole and left to evaporate under ambient temperature for 24 hr. Then the solution was filtered and dried to obtain the crystals. The crystals were stored in desiccators for further study[7].

***Characterization* of *Rabeprazole Cocrystal*[8]**

X-ray diffractometry

X-ray powder diffraction (XRPD) measurements of the crystal forms were analyzed on a powder diffractometer. Samples were filled into 0.7 mm glass capillaries and mounted on a goniometer head. These data were collected using CuK-α radiation (=1.5418A°) and tube voltage and current of 30kV and 30mA, respectively. Scanning parameter range was 2-40° at continuous scanning rate of 3deg/min. The monochromater slit was set to 2 mm.

Scanning electron microscopy (SEM)

Rabeprazole along with cocrystal were analysed at different magnifications to obtain closer views of particles, to study texture, morphology and physical appearance. Samples were placed on an electron microscope brass stub, and pictures were taken by random scanning at different magnifications.

Differential scanning calorimetry (DSC)

Thermal analysis of rabeprazole crystals was performed using DSC instrument, which was calibrated for temperature and cell constants using indium. Sample of rabeprazole cocrystals and CCA (1-3 mg) crimped in aluminum pan were analyzed from 20 to 200°C with heating rate of 10°C/min. An inert atmosphere was maintained by purging nitrogen at flow rate of 50ml/min.

FTIR Study

The study was conducted with an intention to check the compatibility of coformers like nicotinamide, with rabeprazole. Also, it helps to check the suitability of coformers for crystallization by investigating the hydrogen bond interaction. FTIR spectra were obtained using a FTIR spectrometer. The dispersion of samples (pure drug and nicotinamide) was prepared into KBr and compressing into disk. The pellet was placed in the light path and spectrum was recorded in the scanning range 4000 to 500 cm^{-1}.

***Acid stability study*[9]**

Procedure for standard drug solution

About 200 ppm of rabeprazole was accurately prepared in distill water. The maximum wavelength (λ_{max}) was observed at 284 nm and this wavelength was adopted for absorbance measurement.

Preparation of 0.1 N hydrochloric acid

8.36 ml of analytical grade hydrochloric acid was taken in a 1000 ml volumetric flask and de-mineralized water was added to make up the volume.

Standard stock solution

Accurately weighed equivalent amount of Cocrystal containing 20 mg of drug, (25.9 mg co-crystal) and introduced in 100 ml volumetric flasks. Distilled water was added and shaken vigorously and volume was made up to 100ml to make the strength of the solution 200ppm in 100 ml.

Procedure for acid stability using UV- spectrophotometer

To determine the effect of acidic pH, 5 ml of 200 ppm solution was prepared and taken in test tube, then 5ml of 0.1N HCl was added in test tube. They were then left for a period of 1 hour. Upon completion of time period, solutions were transferred to a cuvette separately and then absorbance of the solutions was recorded at the wavelength of 284 nm.

Formulation of Cocrystals into tablet

Different tablets were prepared for drug and cocrystals. Accurately weighed the quantities of ingredients as shown in formulation table 1, mixed well and passed through sieve #40 and compressed by direct compression method to have tablets. Since, further acid stability test of tablet to be carried out, these prepared tablets are not coated[10].

Table 1. Formulation of tablet containing cocrystals

Ingredients	F1	F2
Rabeprazole sodium	20.00	-----
Cocrystals of Rabeprazole	------	25.9
HPMC	5.00	5.00
Crosscarmellose sodium	1.50	1.50
Mannitol	87.50	87.50
Talc	3.00	3.00
Magnesium stearate	7.50	7.50

Evaluation of Tablets

Hardness

Three tablets were selected randomly and hardness of the tablet was determined by using hardness tester. The tablet was keep along its oblong axis in between two anvils of hardness tester. At this point, reading should be zero kg/cm^2.Constant force was applied until the tablet fractured. The value at this point was noted in kg/cm^2. The mean value was calculated from the readings of three tablets.

Friability

10 tablets were accurately weighed and placed in the friabilator (Electrolab friabilator) and operated for 4 minutes (100 revolutions). The tablets were removed, dedusted and reweighed. The tablets should not loose more than 1% weight to pass this test. Percent friability (%F) was calculated as follows

$$\% F = [(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100$$

Weight variation

Twenty tablets were weighed individually and the mean value calculated to check for weight variation.

Disintegration time

The disintegration time was determined by using tablet disintegration apparatus. Disintegration of tablet was observed in 0.1N HCl at 37°C.The

time taken for all the tablets to disintegrate was noted. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

Dissolution studies

The *in-vitro* dissolution study was carried out in the dissolution apparatus (Electro lab) paddle type. 900ml of the dissolution medium (0.1 N HCl) was used and the temperature was maintained at 37±0.5° C. The speed of paddle was set at 100 rpm. Sample of 5 ml was withdrawn at regular intervals of 10, 20, 30, 45, and 60 minutes. For each sample, 5ml of the fresh dissolution medium replaced. The sample was filtered and diluted with dissolution medium and then analyzed in UV-spectrophotometer. The absorbance was measured at 284 nm and percent drug release was calculated.

3. Results and Discussion:

Cocrystallization by slow evaporation method

At the saturated solution, nuclei formation occurred as a result of cocrystallization. After the evaporation of solvent, dry solid powder was obtained that was scratched from the walls of beaker and then dried. The cocrystal solid mass thus obtained was used for characterization.

Powder X-ray diffraction

The X-ray diffraction pattern of co-crystal was studied by X-ray diffractometer. The X-ray diffraction pattern of pure drug has more number of peaks when compared to cocrystal. Also, rabeprazole cocrystals shows decrease in intensity of peaks. However, the differences in the relative intensities of the IR peaks may be attributed to

differences in the crystal size and habits of the cocrystals, which may be attributed to the different physicochemical property of drug in cocrystallization.

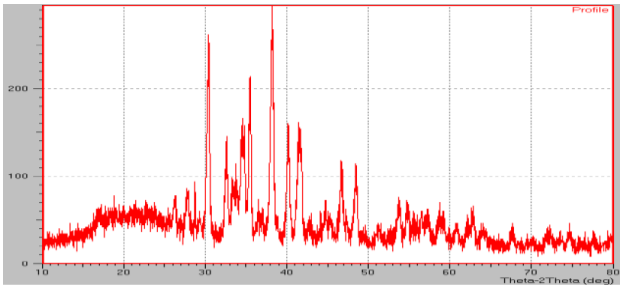

Figure 1: XRD spectra of pure rabeprazole

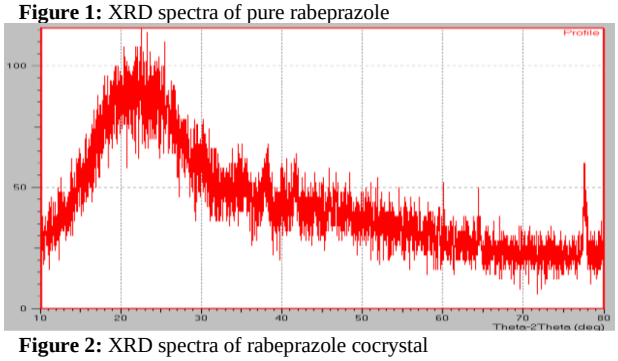

Figure 2: XRD spectra of rabeprazole cocrystal

SEM study (Surface morphology)

Rabeprazole along with cocrystal were analyzed at different magnifications to obtain closer views of particles, to study texture, morphology and physical appearance. Cocrystals having irregular shape as compared with pure rabeprazole. Also size of cocrystal is larger than pure drug.

Differential scanning Calorimetry (DSC)

Cocrystals prepared by solvent evaporation method showed characteristic endothermic peak of rabeprazole drug. The thermal behaviour of pure rabeprazole and its cocrystals are shown below. The differential scanning calorimetry thermogram showed that Rabeprazole appeared on sharp endothermic peak at about 136°C corresponding to its melting point. However, the cocrystals obtained showed the shift of endothermic peak towards lower temperature.

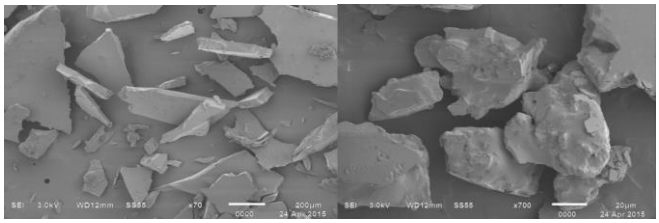

Figure 3: SEM of pure rabeprazole and rabeprazole Cocrystal

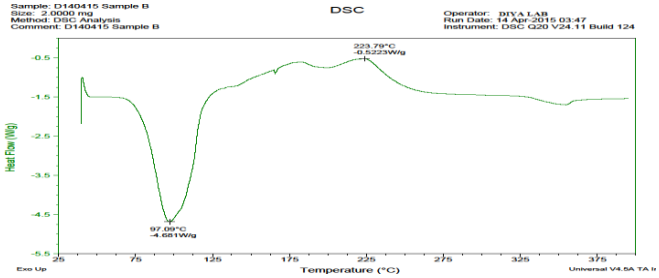

Figure 4: DSC thermogram of pure rabeprazole

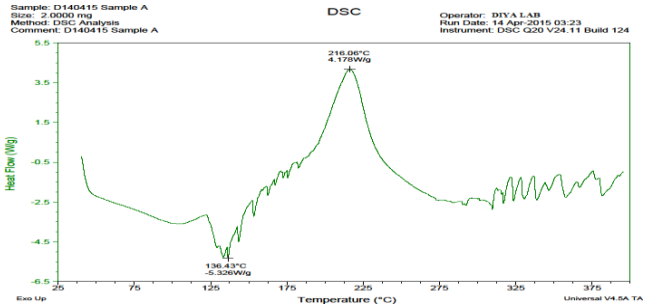

Figure 5: DSC thermogram of rabeprazole cocrystals

Table 2: Interpretation of IR spectra of pure RBZ & its cocrystals

Interpretation	Drug	Cocrystal
$-CH_2$ -	781	781
C-O-C stretch	1247	1248
C-H bend	1456	1456
C=C stretch	1683	1697
C-C stretch (in ring)	1521	1527
S=O	1076	1076
C-N stretch (aromatic)	3452	3450
N-C-N	3379	3379
$C-CH_3$ stretch	2968	2966

Hardness, friability and weight variation study

The aesthetic nature of the tablet, its physical identity and overall tableting properties are essential for acceptability. The shape and size of all the formulations is smooth, flat and free from any cracks.. The rabeprazole cocrystals tablets showed good tableting properties and have disintegrated within 65 seconds compared to pure rabeprazole tablet.

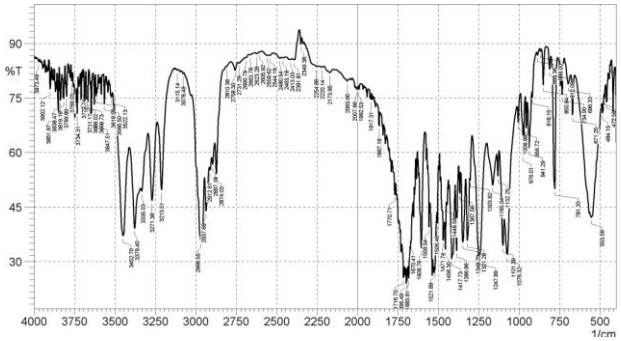

Figure 6: FTIR spectra of pure rabeprazole

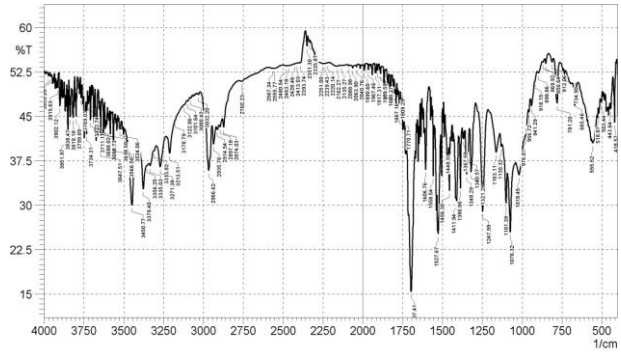

Figure 7: FTIR spectra of rabeprazole cocrystals

Dissolution studies

The rabeprazole cocrystals showed higher drug release that that of pure rabeprazole. Tablets containing pure rabeprazole showed lower drug concentration as compared with tablets containing rabeprazole cocrystals. This was because drug undergoes degradation in acidic medium, but rabeprazole cocrystals survived because of basic nature of coformer.

Acid stability study of tablets

The acid degradation study of pure rabeprazole was studied by HPLC method. Proposed HPLC method was used for the determination of acid stability of rabeprazole for about 90min. The acid stability of rabeprazole cocrystals was found to be about 80.18% for sodium bicarbonate as coformer.

Table 4: Evaluation of tablets of rabeprazole and its cocrystals

Formulation	Hardness (Kg/cm2)	Friability (%)	Weight Variation (mg)	Disintegration (Seconds)
Pure RBZ tablets	4.2±0.5	0.557±0.2	128.4±0.5	787±5
RBZ Cocrystals based tablets	4.7±0.4	0.621±0.1	130.8±0.6	65 ±4

4. Conclusion

Acid stability of rabeprazole was enhanced by formulating it as cocrystals using the conformer sodium bicarbonate by following solvent evaporation method. The characterization of rabeprazole Cocrystals using SEM, FTIR, DSC and XRD confirms the formation of new crystalline phase. The acid stability profile by using UV method indicated the improvement of acid stability of rabeprazole by cocrystallization technique.

Table 5: Dissolution studies of pure rabeprazole and cocrystals of rabeprazole

Time (min)	% drug release	
	Pure rabeprazole	Cocrystals of rabeprazole
0	0	0
10	13.12±1.12	18.75±1.05
20	20.62±1.36	26.25±1.42
30	26.87±1.75	38.75±2.75
40	36.25±0.52	58.12±1.17
50	44.37±2.21	72.50±0.36
60	48.75±1.32	85.62±2.58

Acknowledgements

The authors are thankful to Leben laboratories, Akola for providing the gift sample of drug and AICTE for financial assistance for the project.

Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

References

1. Shan N, Zaworotko MJ. The role of co-crystals in pharmaceutical science. Drug Discovery Today 2008; 13:440-446.
2. Trask AV, Motherwell WDS, Jones W. Physical stability enhancement of theophylline via co-crystallization. Int J Pharm 2006; 320:114-123.
3. Shan N, Zaworotko MJ. The role of co-crystals in pharmaceutical science. Drug Discovery Today 2008; 13:440-446.
4. Jones W, Motherwell WDS, Trask AV. Pharmaceutical co-crystals: An Emerging approach to physical property enhancement. MRS Bull 2006; 31:875-879.
5. Raffin RP, Guterres SS, Pohlmann AR, Re MI. Powder Characteristics of Lansoprazole. Delivery system produced in different spray-dryer scales. Drying Tech 2006; 24: 339-48.
6. Schultheiss N, Newman A. Pharmaceutical co-crystals and their physicochemical properties. Cryst Growth Des.2009; 9: 2950–2967.
7. Chadha R, Sani A. Arora P, Jain D. Cocrystal of efavirenz with selectedCo-formers: Preparation and characterization. Int J Pharm Pharm Sci 2012;4(2):244-50.
8. Nanjwade VK, Manvi FV, Shamrez AM, Meenaxi MM, Nanjwade BK. Development andcharacterization of novel pharmaceutical crystalline complex of lomefloxacin. Int J Drug Dev & Res 20l2;4:227-33.
9. He W., Tiana Z., Yang M., Junhong F., Zhang S., Guana P., Wang J., Wua W. A comparative study of the effect of different alkaline stabilizers on physicochemical properties of lansoprazole in formulation. Asian J of Pharm Sci.2011; 6 :89-100.
10. Ralph E. Advances in Proton Pump Inhibitor Therapy: An Immediate-Release Formulation of Omeprazole. Drug forecast. 2005; 30(12):698-713.