IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Selection of Different Excipients for Controlled Release Formulations of Pantoprazole Through Drug–Excipient Compatibility Testing

Sheikh Sofiur Rahman*[1], Hrishikesh Sarma[1], Shatabdi Ghose[2]

[1] **Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical science, Hatkhowapara, Azara, Guwahati-781017, Assam, India**

[2] **Department of Pharmacology, Girijananda Chowdhury Institute of Pharmaceutical science, Hatkhowapara, Azara, Guwahati-781017, Assam, India**

ABSTRACT

Objective: The present study was undertaken to determine the compatibility of Pantoprazole (PPZ) with some commonly used tablet excipients to develop a controlled release-mucoadhesive tablet for PPZ.

Methods: Differential scanning calorimetry (DSC), Isothermal stress testing (IST) and with the support of Fourier transform infrared spectroscopy (FT-IR) were used to evaluate the compatibility of the drug-excipients mixture. The developed prototype formulations were evaluated for 3 months of stability studies at 2-8 and 25 ºC/60% RH using compatible excipients.

Results: The results of DSC, IST and FT-IR studies confirmed the absence of incompatibility of PPZ with the excipients used in the formulations. The result of stability studies show that the formulations were more stable at refrigerator (2-8 ºC) than stored at 25 ºC/60%RH.

Conclusion: Overall, the study concludes no concrete evidence of interaction between PPZ and the excipients used in the formulation. Besides, the selection of proper excipients, storage condition will also play an important role in the development of stable dosage form for PPZ.

Keywords: Pantoprazole, Differential Scanning calorimetry, Isothermal stress testing, controlled release, Incompatibility.

INTRODUCTION

Pantoprazole sodium sesquihydrate, is a sodium 5-(diflurомethoxy)- 2-[[3,4,dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H benzimidazole sesquihydrate. (fig.1). The molecular formula is C_{16} $H_{15}F_2N_3O_4$ X 1.5 H_2O and the molecular weight is 432.4 gm/mol. Because of the gradual degradation of PPZ sodium during heating, the melting point cannot be determined. It is a white to off-white powder.

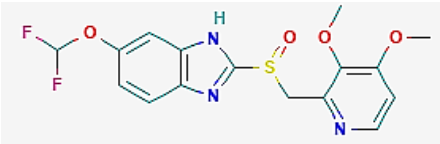

Fig.1: Structural Formula of PPZ

PPZ 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 the 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 hr for all doses tested [1-3].

Incompatibility between drugs and excipients can alter the stability and bioavailability of drugs, thereby, affecting their safety and/or efficacy. Studies of the drug–excipient compatibility process is an important parameter in the development of a stable solid dosage form. Preliminary drug-excipient compatibility testing aids in selecting excipients that increase the probability of developing a stable dosage form. [4-5].

Despite the importance of drug–excipients compatibility testing, there is no universally accepted protocol for this purpose. DSC has been extensively reported in the literature for testing the compatibility of excipients with some drugs [5, 7-11]. Another method that is commonly employed for evaluating the drug–excipients compatibility is IST. The method involves storing the drug–excipients blend with or without moisture at high temperatures and determining the drug content [9, 12-13].DSC can be used in combination with IST to evaluate the compatibility of drugs with the selected excipients.

In the present study, techniques of DSC, IST and support of FT-IR were used to assess the compatibility of PPZ with selected excipients as a part of preformulation studies for the development of controlled-release mucoadhesive tablets of PPZ. Excipients found to be compatible were used for different trials formulation. Finally, the optimized formulation was developed using the compatible excipients that were evaluated for 3 months of stability studies at 2-8 ºC and 25ºC/60% RH.

MATERIALS AND METHODS

Materials

PPZ was purchased from Yarrow Chem. Products, Mumbai-37, India. Sodium alginate was received as gift samples from Colorcon Asia Pvt Ltd. Goa, India. Chitosan was purchased from Meggle GmbH, Wasserburg, Germany. Sodium CMC, Carbopol 934 were collected from Balaji, Drugs, India; and all other ingredients were procured from the local supplier and were of analytical grade.

Differential scanning calorimetry

A differential scanning calorimeter (Jade DSC, Perkin Elmer, and the USA) was performed for thermal analysis of drugs and mixtures of drugs and excipients. Individual samples (drugs and excipients), as well as physical mixtures of drug and selected excipients (all passed through a 60-mesh sieve), were weighed directly in the pierced DSC aluminum pan (table 1) and scanned in the temperature range of 25–300 ºC under an atmosphere of dry nitrogen. The heating rate of 10 ºC/min was used and thermograms obtained were observed for any interaction.

Table 1: Peak temperature and enthalpy values of PPZ in various drug–excipient mixtures drug–excipient

Sample	**Ratio (drug–excipient)**	**T_{peak} (ºC)**	**ΔH_{fcorr} (J/g)[a]**
PPZ	1:1	158.11	192.43
PPZ + Chitosan	1:3	156.16	30.45
PPZ + PVP K 30	1:1	118.63	68.60
PPZ + Lactose	1:2	144.95	149.30
PPZ + Magnesium Stearate	1:3	129.24	94.84
PPZ + Sodium Alginate	1:2	122.19	294.35

IR spectroscopy

IR spectra of drug and drug–excipient blends were recorded on a Bruker spectrophotometer (Model-220, Germany) in the range of 4000–500 cm^{-1} by using potassium bromide discs.

Isothermal stress testing

Isothermal stress testing for IST studies, PPZ and different excipients (table 2) were weighed directly in 4 ml glass vials (n=3) and mixed on a vortex mixer for 2 min. In each of the vials, 10% w/w water was added and the PPZ–excipients blend was further mixed with a glass capillary (both the ends of which were heat-sealed).

To prevent any loss of material, the capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 50 ºC. These samples were periodically examined for any unusual colour change. After 3 weeks of storage under the above conditions, samples were quantitatively analyzed using a UV spectrophotometer (UV- 1800-Double beam spectrophotometer, Shimadzu, Japan).

Table 2: Results of analysis of IST samples after 3 weeks of storage at stressed conditions (stored at 50 ºC)

Sample	Ratio (drug–excipient)	% Remaining (±SD, n = 3)	
		Control conditions @ 2-8 ºC	Stressed conditions @ 50 ºC
PPZ	1:1	102.13 ± 0.11	97.73 ± 0.06
PPZ + Chitosan	1:3	101.51 ± 0.22	96.24 ± 0.10
PPZ + PVP K 30	1:1	100.92 ± 0.09	98.16 ± 0.14
PPZ+ Lactose	1:2	101.41 ± 0.23	97.21` ± 0.21
PPZ + Magnesium Stearate	1:3	99.13 ± 0.11	98.10 ± 0.31
PPZ + Sodium Alginate	1:2	102.50 ± 0.18	97.26 ± 0.13

Formulation development and stability studies

Mucoadhesive tablets of PPZ were prepared using various tablet excipients selected from compatibility studies. The concentrations of polymers used for the formulation development were 15-35%. For the production of tablets, the excipients sodium alginate, chitosan, lactose, and magnesium stearate were chosen and weighed in accordance with the formula, transferred to a mortar and pestle, and mixed thoroughly. The above excipients were dried and mixed with the 40 mg drug and passed through sieve no 120 and were directly compressed in a tablet compression machine using 6 mm round punches. The core tablets were then coated in an automated perforated coating pan (GAC-250, Gans coater, India) with a coating solution shown in table 4. A sufficient coating solution was applied until desired weight gain (12± 0.5 %) was obtained. The tablets were dried in an oven for 16 h at 50 ºC before being stored or evaluated. The PPZ tablets were collected and stored in air-tight containers. The tablets of 150 mg were prepared as shown in table 3.

The optimized formulation of PPZ was packed in strips of 0.04mm thick aluminum foil laminated with PVC coating and stored in ICH-certified stability chambers (WTC Binder, Germany) maintained at 40 ºĊ and 75% RH. The samples were withdrawn periodically and subjected to assay and dissolution studies.

For the assay, one accurately weighed tablet (n = 5) was dissolved in 100 ml of phosphate buffer pH 6.8. The samples were sonicated (Ultrasonic water bath, 3510, Branson, USA) for 30 mins, after which they were filtered through a 0.45 µm nylon membrane filter. The filtered solutions, after appropriate dilution with phosphate buffer pH 6.8, were analyzed by a validated UV spectroscopic method [14] at 289 nm (Shimadju, Model no: UV 1800 240V)

Drug release testing of the formulations (n = 6) was carried out using the USP-I dissolution apparatus (Libinda, DS 8000 India) at 100 rpm. Simulated Intestinal Fluid, pH 6.8 (100 ml) maintained at 37± 0.5 ºC was used as dissolution medium. The samples (5 ml) were withdrawn at the predetermined time and replaced with an equivalent amount of fresh medium. The samples were filtered through a 0.45-µm nylon membrane filter and analyzed spectrophotometrically at 289 nm. The cumulative percent drug release was plotted against time to determine the release profile.

Table 3: Composition of optimized mucoadhesive tablets of PPZ

Ingredients	Quantity (mg)
PPZ	40
Sodium alginate	26.5
Chitosan	26.5
Lactose	54.5
Magnesium stearate	3

Total weight of tablet = 300 mg

Table 4: Composition of coating solution

Ingredients	Quantity
Eudragit L 100	10%(w/v)
Triethyl citrate	25% (w/w)
Acetone	Vol. in ml
Isopropyl alcohol	Vol. in ml

Assessment of difference factor and similarity factor

Release profiles of formulation stored at different storage conditions were compared using a model-independent pair-wise approach, which included the calculation of "difference factor", f_1 and "similarity factor", f_2. These fit factors directly compare the difference between the percent drug released for a reference and a test product [15]. The difference factor (f_1) measures the percent error between the two curves over all time points and is calculated as follows:

$$F_1 = \frac{\sum_{j=1}^{n} |R_j - T_j|}{\sum_{j=1}^{n} R_j} X\ 100 \qquad (1)$$

Where n is the number of sampling points, R_j and T_j are the percents dissolved of the reference and test products at each time point j. The two release profiles are considered to be similar if f_1 value is lower than 15 (between 0 and 15). The similarity factor (f_2) is a logarithmic

transformation of the sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated using the following equation:

$$F_2 = 50log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n} W_j|R_j - T_j|^2\right]^{-0.5} X\ 100\right\} \quad (2)$$

The two dissolution profiles are considered similar, if f_2 value is more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, all data points of release study were taken into consideration.

RESULTS AND DISCUSSION:

DSC scans of PPZ and PPZ–excipient mixtures are shown in (fig.2). The thermal behavior of pure PPZ, respective excipient, and the combination of PPZ and excipients is compared in the DSC thermograms. Peak transition temperature (T_{peak}) and heat of fusion or enthalpy (ΔH_f) of PPZ in various excipients mixtures is summarized in table 1.

The DSC curve of PPZ showed a first endothermic event between 125 ºC and 135 ºC (ΔH_{fusion}= 192.45 Jg^{-1}), with a melting temperature of T_{onset}=158.11ºC. This endothermic peak was also retained in all the mixture of drug-excipients with a little shifting of the peaks which may be due to the presence of moisture or impurity of the excipient.

The thermogram of PPZ–chitosan mixture showed an endothermic peak of the drug at 89.2 ºC indicating that there was no interaction. The DSC scan of PPZ– PVK30 mixture showed an endothermic peak of the drug at 118.63 ºC, indicating that there was no interaction. The DSC the thermogram of PPZ–spray-dried lactose mixture showed an endothermic peak of drug at 97.35 ºC indicating the absence of chemical incompatibility between PPZ and spray dried lactose .

The endothermic peak of PPZ was found at 129.24 ºC and 122.19 ºC in the mixture of PPZ- magnesium stearate and PPZ-sodium alginate respectively indicating the absence of interaction.

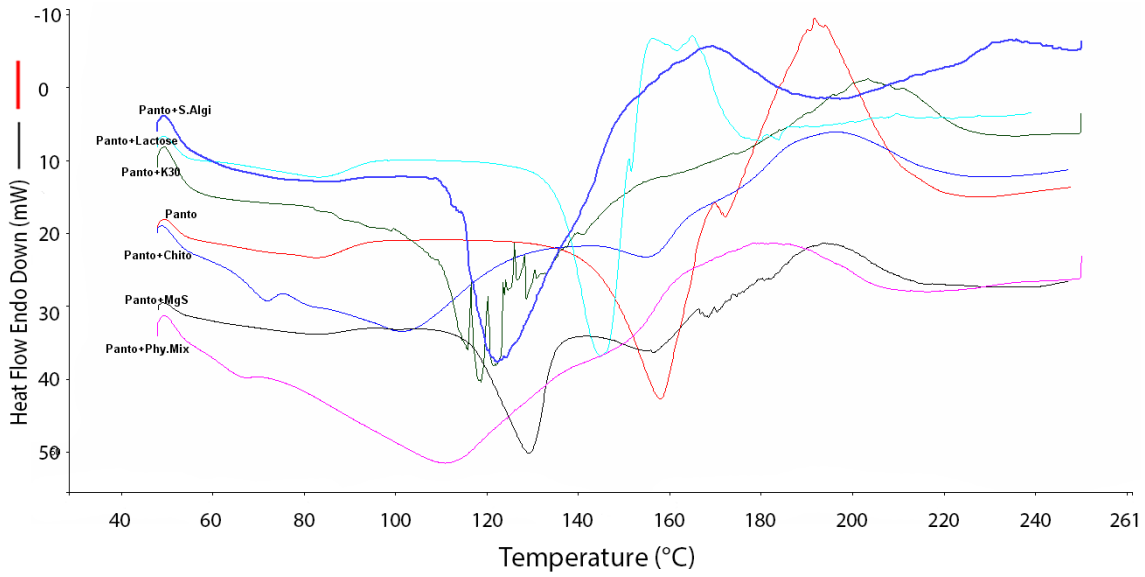

Fig. 2: DSC thermogram of PPZ with excipients mixture

In the majority of the cases, the melting endotherm of PPZ was well preserved with slight changes in terms of broadening or shifting towards the lower/higher temperature. It has been reported that the quantity of material used, especially in drug–excipient mixtures, affects the peak shape and enthalpy [9-10]. Thus, these minor changes in the melting endotherm of the drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility [11, 16-18]. The results of DSC studies were further correlated with FT-IR and IST results.

FT-IR spectrum of PPZ is shown in fig. 3 and the following characteristics bands were observed 2977.33 cm^{-1} for (C-H aromatic); 2943 cm^{-1} for (C-H); 1070 cm^{-1} for (S=O) and 1380 cm^{-1} for (C-O), 1455 (C-N), 1357 (C-C) .The above characteristics band is also found in various PPZ-excipients mixture. FT-IR spectra of Chitosan and PPZ– Chitosan were shown in fig. 4 and fig. 5 respectively. The comparative FT-IR spectra of Sodium alginate and PPZ-sodium alginate shown in fig. 6 and fig. 7 indicating the absence of interaction.

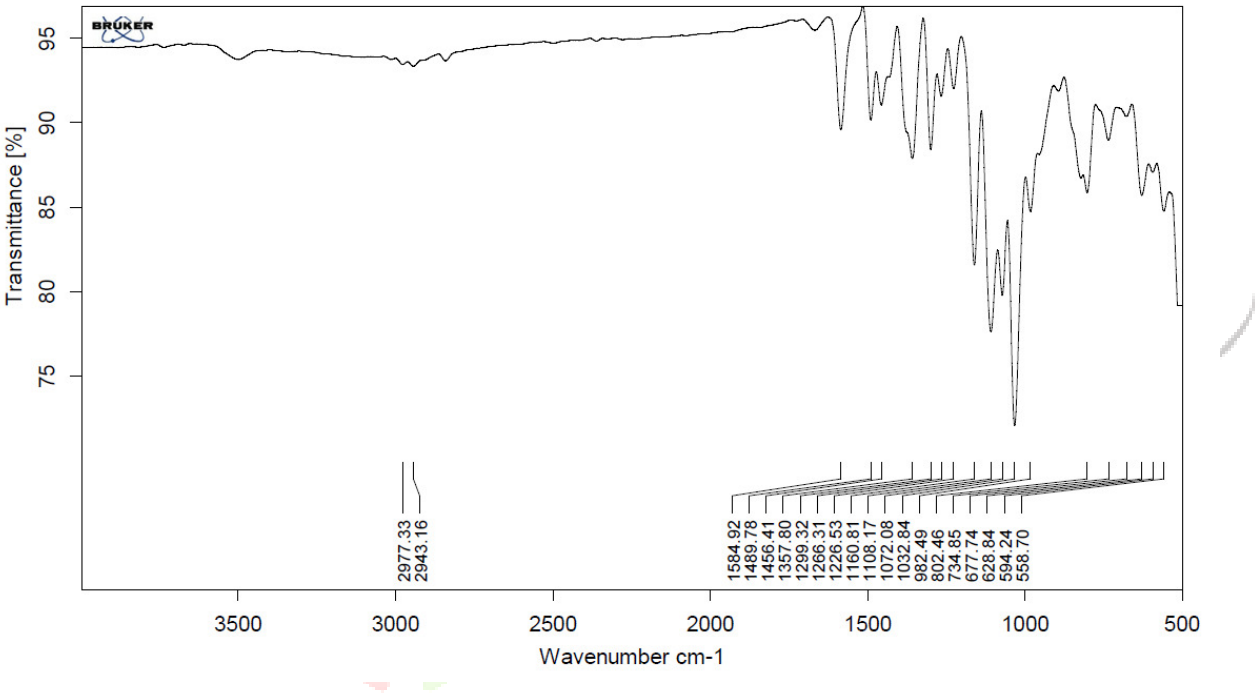

Fig. 3: FT-IR spectra of PPZ

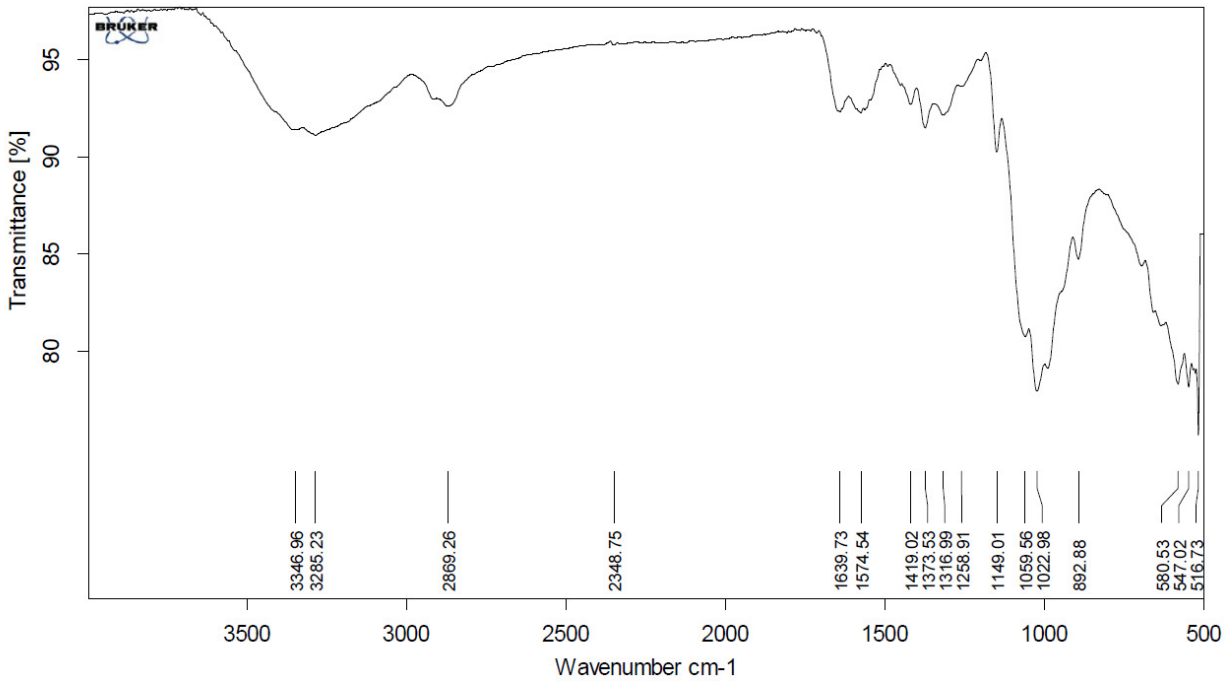

Fig.4:FT-IR spectra of Chitosan

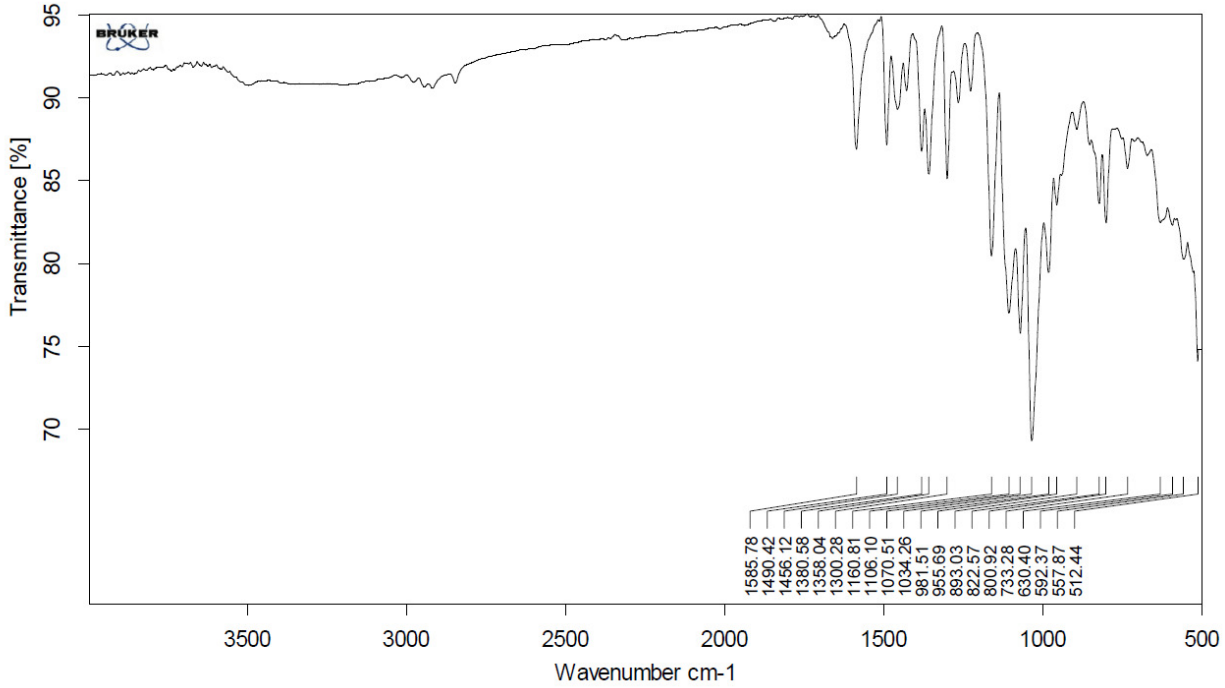

Fig. 5:FT-IR spectra of PPZ + Chitosan

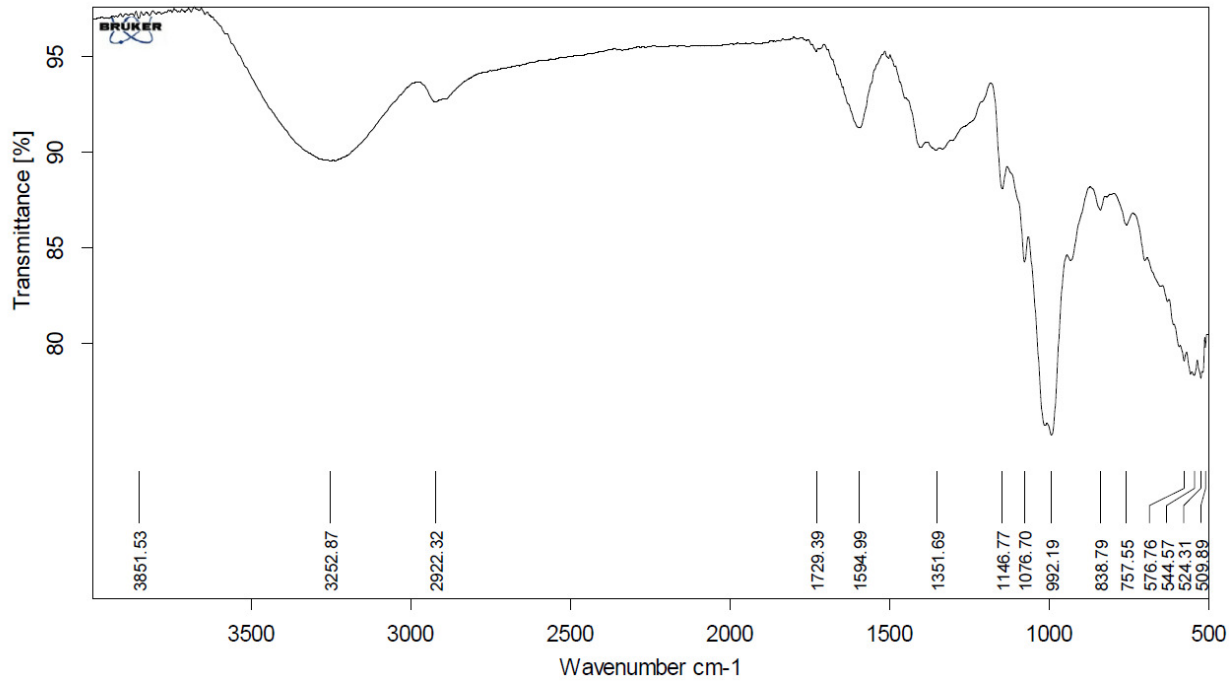

Fig. 6: FT-IR spectra of Sodium alginate

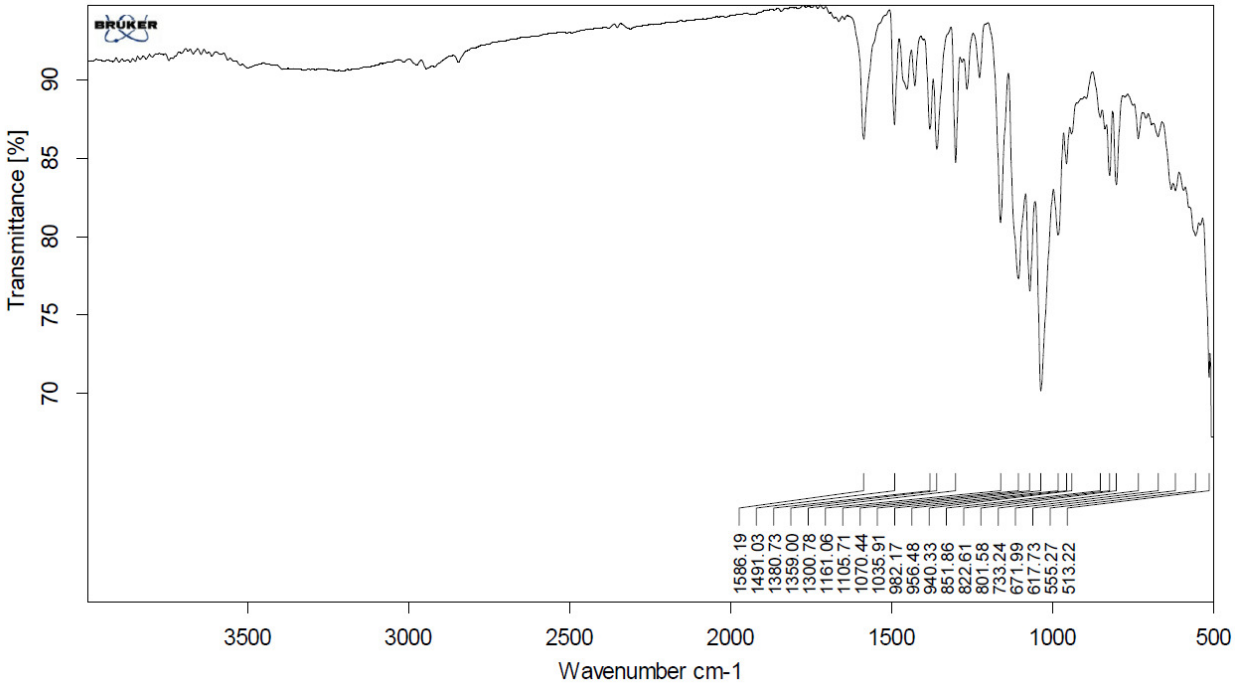

Fig.7: FT-IR spectra of PPZ + Sodium alginate

The results of IST studies showed the content of the drug in all the PPZ-excipients mixtures were found in the range of 99.13±0.11% to 102.50±0.18% in controlled condition (Refrigerator, 2-8 ºC) and in stressed condition (stored at 50 ºC) was 96.21±0.24 % to 98.16 ± 0.14 % (table 2). The results showed 3-5% variations in stressed conditions with respect to the controlled condition and the difference in

drug content in the mentioned conditions was found statistically significant p=0.0032 ($p<0.05$), indicating the decomposition of PPZ at the stressed conditions.

Thus, this result does not necessarily indicate the incompatibility of PPZ with the excipients used at the mentioned PPZ-excipients mixtures, because the DSC and FT-IR studies showed the presence of PPZ peak in all PPZ-excipient mixtures. The changes in drug content in the stressed condition may be due to the thermodynamic instability of PPZ at 50 ºC.

Formulation development and stability studies

The optimized formulation showed hardness of 25.45 ± 1.32 Kg/cm^2, drug content of 102.13 ± 0.14 %, and drug release of 22.14± 0.74%, 38.92±1.86%, 65.13±3.21%, 90.93± 1.05% at 2, 4, 8, 12 hours respectively.

The optimized formulation, packed in strips of 0.04 mm thick aluminum foil coated inside with polyethylene, was evaluated after 3 months of storage at stability conditions (25 ºC/60%RH) and at refrigerator (2-8 ºC) results of which are shown in table 4 and fig. 8. It is evident that the formulation is having good stability in terms of both drug content and dissolution stability stored at the refrigerator (2-8 ºC).

There was little change in the drug content (table 4) after 3 months of storage at stability conditions (25 ºC/60%RH), but the change in drug content was not statistically significant as $p>0.10$ (Paired t-test).

The release profile can be considered similar after 3 months of stability studies as shown by the different factor and similarity factor values $f1$ =10.70 (less than 15) and $f2$=50.48 (more than 50) respectively. Based on the results, it can be concluded that the formulations are more stable storage at refrigerator (2-8 ºC) than the storage at 25 ºC/60% RH.

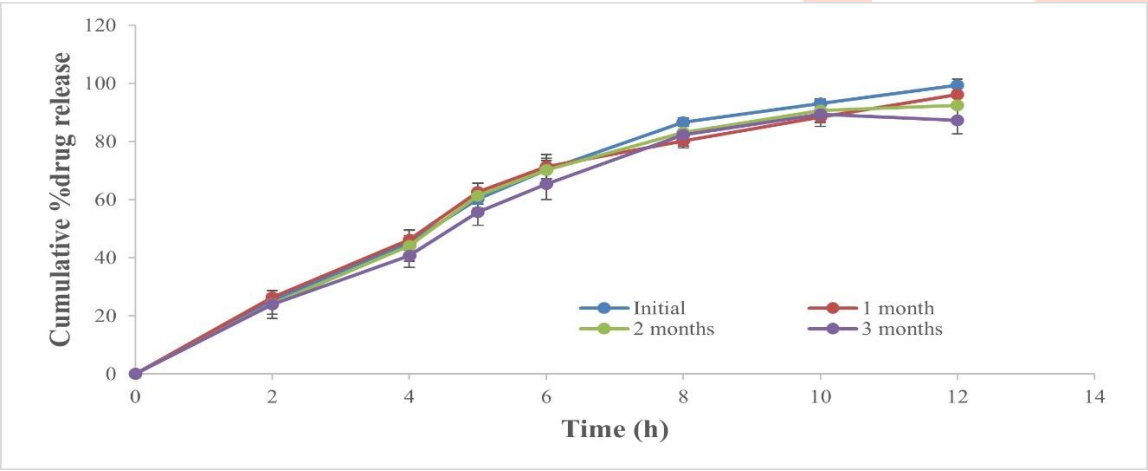

Fig.8: Dissolution stability of optimized PPZ formulations after 3 months of storage @25 ℃/ 60% RH stability conditions

Table 5: Stability studies results of the optimized formulation after 3 months of storage @25 ºC/ 60% RH and refrigerator @ 2-8 ºC.

Parameter	Refrigerator @ 2-8 ºC				Storage @ 25 ºC/60% RH		
	Initial	One month	Two months	Three months	One month	Two months	Three months
% Drug content (±SD,n=5)	102.14±0.11	101.83±0.22	101.16±0.02	101.51± 0.13	101.31±0.11	100.73± 0.14	98.82± 0.22
Hardness (kp)[a]	25.73±1.92	28.71±1.92	28.82± 2.13	28.81 ± 1.96	25.13 ± 1.72	28.63± 1.96	28.43 ± 1
f_1	-----	-----	-----	-----	3.36	6.8	10.72
f_2	-----	------	-----	-----	75.01	60.42	50.48

[a]Initial sample (0-month) of refrigerator @ 2-8 ºC condition was taken as reference to calculate *f*1 and *f*2 values

CONCLUSIONS

Overall, this study concludes no concrete evidence of interaction between PPZ and all the excipients used in the development of the mucoadhesive tablet of PPZ. The result of DSC revealed the absence of incompatibility indicating the presence of PPZ in all PPZ-excipients mixtures with slight broadening and shifting of endothermic peaks with some excipients which may be due to the presence of moisture or physical interaction or impurities. Furthermore, to rule out any interaction, IST and FT-IR studies were conducted and the results of IST and FT-IR studies confirmed the compatibility of the drug with the excipients used in the formulations. The result of stability studies showed that the formulations were more stable storage at refrigerator (2-8 ºC) than stored at 25 ºC/60 % RH. Thus, besides the selection of proper excipients storage conditions will also play an important role in the development of a stable dosage form for PPZ.

REFERENCES

1. Tripathi. KD. “Essential of Medical Pharmacology”, New Delhi, India. Jaypee brother’s medical Publisher Ltd, 2008:PP. 639.
2. Gupta M.K, Sharma N, Agarwal D, Chichi M.P, Jain M, Srivastava S.; “Enteric Coated Preparation of Pantaprazole’’. *Asian J Bio Pharm Res*2012;2(3):14-25.
3. Sujit K. D., Sibaji S, Chakraborty S., “Formulation Development and Evaluation of Pantoprazole Enteric Coated Tablets”. Int J Chem Tech Res 2012; 1: 663-666.
4. Jackson K, Young D, Pant S. Drug/excipient interactions and their affect on absorption: PharmaceutSci Tech Today. 2000; 3: 336-45.
5. Mura P, Faucci MT, Manderioli A, Bramanti G, Ceccarelli L. Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy. J Pharm Biomed Anal 1998; 18: 151-63.
6. Mura P, Faucci MT, Manderioli A, Bramanti G, Ceccarelli L. Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy. J Pharm Biomed Anal 1998; 18: 151-63.

7. Tonder ECV, Lotter AP, Botha S.A. Compatibility study between doxylamine succinate with other drugs and excipients using differential scanning Calorimetry. Drug Dev Ind Pharm 1990; 16: 2125-33.
8. Venkataram S, Khohlokwane M, Wallis S.H. Differential scanning calorimetry as a quick scanning technique for solid state stability studies. Drug Dev Ind Pharm 1995; 21: 847-55.
9. Kandarapu R, Grover V, Chawla HPS, Garg S. Evaluation of compatibility of ketorolac tromethamine with selected polymers and common tablet excipients by thermal and isothermal stress testing. STP PharmaSci2001; 11: 449-57.
10. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int J Pharm 1995; 119: 71-79.
11. Botha SA, Lotter AP. Compatibility study between naproxen and tablet excipients using differential scanning Calorimetry. Drug Dev Ind Pharm 1990; 16: 673-83.
12. Serajuddin AT, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, Varia SA. Selection of solid dosage form composition through drug-excipient compatibility testing: J Pharm Sci. 1999; 88: 696-04.
13. Gu L, Strickley RG, Chi LH, Chowhan ZT. Drug-excipient incompatibility studies of the dipeptide angiotensin-converting enzyme inhibitor, moexipril hydrochloride: dry powder vs wet granulation: Pharm Res 1990; 7: 379-83.
14. R.K. Verma, Development and evaluation of novel osmotically controlled oral drug delivery systems for glipizide and isosorbide mononitrate, Ph.D. thesis, Department of Pharmaceutics, NIPER, SAS Nagar, India, 2002.
15. X. Moore JW, Flanner HH. Mathematical Comparison of curves with an emphasis on in vitro dissolution profiles: Pharm Tech 1996; 20: 64-74.
16. Kandarapu R, Grover V, Chawla HPS, Garg S. Evaluation of compatibility of ketorolac tromethamine with selected polymers and common tablet excipients by thermal and isothermal stress testing: STP Pharma Sci. 2001; 11: 449-57.
17. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients: Int J Pharm1995; 119: 71-79.
18. Botha SA, Lotter AP. Compatibility study between naproxen and tablet excipients using differential scanning Calorimetry: Drug Dev Ind Pharm 1990; 16: 673-83.
19. Smith A. Use of thermal analysis in predicting drug-excipient interactions: AnalProc 1982; 19: 559-61.
20. Durig T, Fassihi AR. Identification of stabilizing and destabilizing effects of excipient--drug interactions in solid dosage form design: Int J Pharm 1993; 97: 161-70.
21. Malan CEP, Villers MM, Lotter AP. Application of differential scanning calorimetry and high performance liquid chromatography to determine the effects of mixture composition and preparation during the evaluation of niclosamide-excipient compatibility: J Pharm Biomed Anal 1997; 1: 549-57.