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Development And *In-Vitro* Evaluation of Pantoprazole Sodium cocrystals

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ABSTRACT

Pantoprazole is extensively metabolized in the liver and has a total serum clearance of 0.1 l/h/kg, a serum elimination half-life of about 1.1 h, and an apparent volume of distribution of 0.15 L/kg. 98% of pantoprazole is bound to serum proteins. Elimination half-life, clearance, and volume of distribution are independent of the dose. Almost 80% of an oral or intravenous dose is excreted as metabolites in urine; the remainder is found in feces and originates from biliary secretion. The clearance of pantoprazole is only slightly affected by age, with its half-life being approximately 1.25 h in the elderly. Pantoprazole is an acid labile drug that requires protection from degradation in acidic media. Hence, co-crystallization of pantoprazole sodium with appropriate co-formers will inhibit its degradation in acidic medium ensuring fast release in the stomach. The acid-labile drugs for oral administration may also be protected from gastric acidity by inhibiting its degradation upon entering into acidic environment. So, the current approach includes co-crystallization of the provided drug with appropriate co-former which prevents degradation of drug by quick absorption and protects the drug from low pH. Apart from that, the formulations also modulate or control the drug release for an immediate action.

Keywords: Pantoprazole sodium, Co-crystal, solvent drop method, Co-former.

Introduction

Co-crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. Co- crystallisation is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers [1]. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state [2].

Pharmaceutical co-crystals:

Pharmaceutical co-crystals offer an alternative method to alter the dissolution rate and solubility of BCS Class II drugs [3]. Co-crystals consist of an API and a generally regarded as safe (GRAS) molecule, with specific stoichiometric compositions. However, there is no single definition as to what a pharmaceutical co-crystal. Multiple definitions appear in the literature, but a common definition is "a stoichiometric multi- component system connected by non-covalent interactions where all the components present are solid under ambient conditions" [4-6]. As both the API and co-former in a co-crystal must be solid on their own under ambient conditions, solvates and hydrates are not classed as co-crystals.

Application:

A key question concerning the practical application of a co-crystal of a commercial API is whether the co-crystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the co-crystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require. The USA Food and Drug Administration (FDA) have released draft guidance on the regulatory classification of pharmaceutical co-crystals for applicants for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). The FDA defines cocrystals as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" -

the implication is that it is two or more types of molecules that are referred to here [7].

The FDA also regards co-crystals as dissociable "API-excipient" complexes, blurring the boundary between co-crystals and physical mixtures. This guidance has generated a strong response from some researchers in the co-crystal field who propose alternative, yet also potentially controversial definitions that distinguish multicomponent APIs and their co-crystals from solvates [8] and hydrates.

Materials and Methods:

Materials:

Pantoprazole Sodium procured from Marksan Pharmaceutical Ltd., Goa, Sodium Benzoate from Central Drug House, New Delhi, Sodium Hydrogen Carbonate from Loba Chemie Pvt Ltd, Mumbai, Gallic Acid from Labogens Fine Chem Ind. New Delhi, Iso propyl alcohol, Methanol from Fisher Scientific India Pvt. Ltd. New Delhi, Potassium Dihydrogen orthophosphate and Disodium hydrogen orthophosphate from Thomas Baker, New Delhi were obtained.

Methods:

Estimation of Pantoprazole Sodium by UV-visible spectrophotometer:

The standard stock solution of Pantoprazole Sodium (1mg/ml) was prepared in methanol. This solution was diluted with methanol, to obtain various dilutions from 5-40 µg/ml. Absorbance of these solutions was recorded at 290 nm [9] against methanol as blank using UV-visible spectrophotometer and standard curve was plotted against concentration.

Solubility Studies:

The spontaneous interaction of two or more substances to form a homogenous molecular dispersion is called solubility. For quantitative solubility study, excess amount of drug was taken in thoroughly cleaned test tubes containing 1 ml of different solvents (Methanol, Ethanol, Acetone, Chloroform, 0.1N HCl, water, PBS pH 6.8 and 7.4) and test tubes were tightly closed. These test tubes were shaked on water bath shaker for 24 h at room temperature. After 24 h each sample was centrifuged 15,000 rpm and supernatant was withdrawal. After that supernatant was filtered and filtrates was suitably diluted and determined spectrophotometrically [10].

Partition Coefficient of Drug:

Partition coefficient (oil/water) is a measure of a drug's lipophilicity/hydrophilicity and an indication of drug's ability to cross cell membranes. It is defined as the ratio of unionized drug distributed between the organic and aqueous phases at equilibrium. Partition coefficient provides a means of characterizing the lipophilic/hydrophilic nature of the drug. Drugs having values of P much greater than 1 are classified as lipophilic, where as those with values much less than 1 are indicative of a hydrophilic drug. The partition coefficient [11] is commonly determined using an oil phase of n-octanol and water. In the case n-octanol and water:

$$P_{o/w} = \frac{C\,(n-octanol)}{C\,(water)}$$

The partition coefficient ($P_{o/w}$) therefore is the quotient of two concentrations of drug in n-octanol ($C_{n\text{-}octanol}$) and water (C_{water}) respectively and is usually given in the form of its logarithm to base 10 (log P).

FTIR of Pantoprazole Sodium and Excipients:

FT-IR Spectroscopy was used for structure analysis. The potassium bromide (KBr) disc technique was employed. Since the KBr has no absorption in the fundamental region of IR spectrum, only the spectrum of sample is obtained. An FT-IR spectrum of Pantoprazole Sodium and drug plus excipients mixture was recorded for the determination of drug interaction with excipients [12].

Preparations of Co-crystals of Pantoprazole Sodium:

The co-crystals of Pantoprazole sodium were prepared by solvent evaporation method. Equimolar or different molar quantities of Pantoprazole sodium and different co-formers such as sodium benzoate, sodium bicarbonate and gallic acid were dissolved in 5 ml methanol by keeping in water bath maintained at a temperature at 80°C to obtain clear solution. The solution was allowed to cool in ice bath for about 5 hour for thorough crystallization to occur. The crystals were dried in air for 24 hour, collected and finally stored in desiccators [13].

Table 1: Composition of different co-crystal formulations of Pantoprazole Sodium

S. No	Formulation Code	Molar Ratio (Drug: Coformer)	Drug (mg)	Sodium Benzoate	Sodium Bicarbonate	Gallic Acid
1	F1	1:1	100	100	-	-
2	F2	1:2	100	200	-	-
3	F3	1:3	100	300	-	-
4	F4	1:1	100	-	100	-
5	F5	1:2	100	-	200	-
6	F6	1:3	100	-	300	-
7	F7	1:1	100	-	-	100
8	F8	1:2	100	-	-	200
9	F9	1:3	100	-	-	300

Evaluation of Co-crystals of Pantoprazole Sodium:

Optical Microscopy:

In the process of co-crystallization, co-crystals of each batch were collected and stored at room temperature for further analysis. The co-crystal appearance and quality were observed by optical microscopy at a magnification of 40X [14].

Percentage yield:

The prepared co-crystals were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated using following formula [15]:

$$Production\ yield = \frac{Practical\ mass\ of\ Cocrystals}{Theoretical\ mass\ (Coformer + Drug)} X100$$

Solubility profile of Co-crystals:

Weighed about 50 mg of sample and put into a vial containing 20 ml of aqua DM, then dissolved with the aid of a magnetic stirrer at room temperature for 24 hours or until the solution saturated. The Suspension was filtered and its absorption is measured at the maximum wavelength using a UV-Vis spectrophotometer [15].

Particle Size:

SEM was used to study the morphology and structural features of the produced cocrystals. Self-adhesive carbon mounts were used to mount samples on aluminum pin stubs (Agar Scientific, Stansted, UK). SEM images of the mounted samples were collected using an FEI Quanta 400 scanning electron microscope [16].

Percentage Drug Content:

Drug content was determined by dissolving co-crystals quantity equivalent to 10 mg of pantoprazole sodium in 5 ml of methanol and the volume was adjusted to 10 ml with methanol. The solution was filtered through Whatman filter paper no 41 and 1 ml of the resulting solution was diluted with methanol. Absorbance of the resultant solution was measured at 290 nm using double beam UV spectrophotometer [17].

In-Vitro Drug Release Study:

Drug Release experiments were carried out using magnetic stirrer with controlled temperature. In this method distilled water and simulated gastric fluids (pH 1.2), were used as dissolution media. The rate of stirring was 100 ± 2 rpm. In all formulations the amount of pantoprazole sodium was 100 mg. The dosage forms were placed in 900 ml of simulated gastric fluids (HCl solution) and maintained at 36 ± 1 ˚C. For 60 minutes at appropriate intervals (1, 2.5, 5, 10 minutes and so on), 5 ml of sample were taken. The dissolution medium was replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were filtered through a 0.45 mm Millipore filter, diluted and analyzed at 290 nm by UV/visible spectrophotometer [18].

Drug release kinetics:

Model dependent methods are based on different mathematical functions, which describe the release profile. Once a suitable function has been selected, the release profiles are evaluated depending on the derived model parameters [19-21]. The data obtained from *ex vivo* permeation studies were plotted in different models of data treatment as follows; Zero Order model, First Order model, Higuchi‟s Model and Korsmeyer-Peppas model.

Result and discussion:

Determination of absorption maxima in methanol:

A double beam UV-visible spectrophotometer was used for quantitative analysis of the drug. A 30 µg/ml solution of Pantoprazole Sodium in methanol was scanned in the range of 200-400 nm. The result of UV spectrum of Pantoprazole Sodium is shown in Figure 1 and The maximum wavelength of Pantoprazole Sodium was observed at 290 nm.

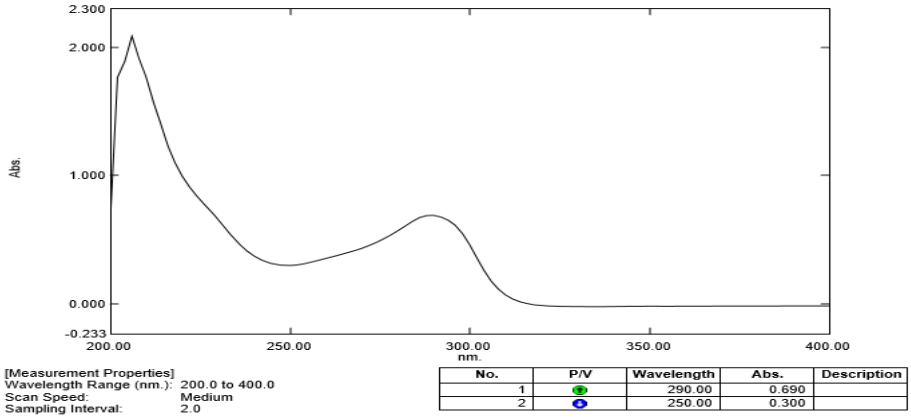


Figure 1: UV Spectrum of Pantoprazole Sodium in methanol

Table 2: Calibration curve of Pantoprazole Sodium in methanol (λ_{max} = 290 nm)

Sr. No.	Concentration (µg/ml)	Absorbance
01.	5	0.155±0.001
02.	10	0.268±0.002
03.	15	0.385±0.001
04.	20	0.492±0.001
05.	25	0.606±0.001
06.	30	0.729±0.001
07.	35	0.835±0.001
08.	40	0.956±0.002

Value is expressed as mean ± SD; n = 3

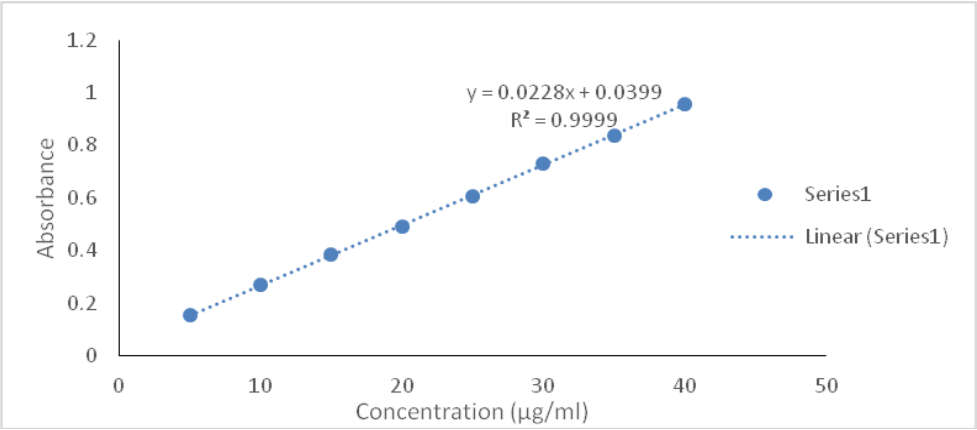


Figure 2: Standard calibration curve of Pantoprazole Sodium in methanol

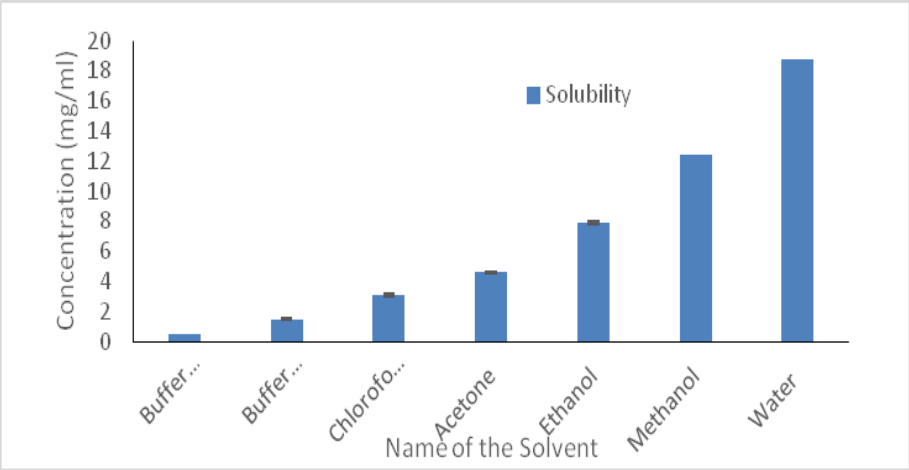
Solubility studies:

Solubility of drug in various solvents, were carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 290 nm.

Table 3: Solubility studies of Pantoprazole Sodium for different solvents

Sr.no	Solvent	Solubility in (mg/ml)
1	Phosphate Buffer pH 6.8	0.490±0.006
2	SGF Buffer	1.483±0.066
3	Chloroform	3.095±0.454
4	Acetone	4.604±0.667
5	Ethanol	7.864±0.436
6	Methanol	12.377±0.909
7	Water	18.781±0.436

Value is expressed as mean ± SD; n = 3



From the above data, it is clearly seen that Pantoprazole Sodium is highly soluble in ethanol, methanol and water.

Partition coefficient determination:

Partition coefficient of the Pantoprazole Sodium was determined using n-octanol and water. Log P greater than one indicates that the drug is lipophilic in nature, whereas those with partition coefficients less than one are indicative of a hydrophilic drug. This indicated the lipophilicity and purity of drug.

Table 4: Partition coefficient determination of Pantoprazole Sodium

Partition coefficient of drug	Solvent system	Log P Values	Reference
Pantoprazole Sodium	n-octanol: water	3.650 ± 0.011	3.55

Value is expressed as mean ± SD; n = 3

The partition coefficient of Pantoprazole Sodium in n-octanol: water was found to be 3.650 ± 0.011, this indicates that the drug is lipophilic in nature (table 4) which is similar to the literature.

FTIR Studies:

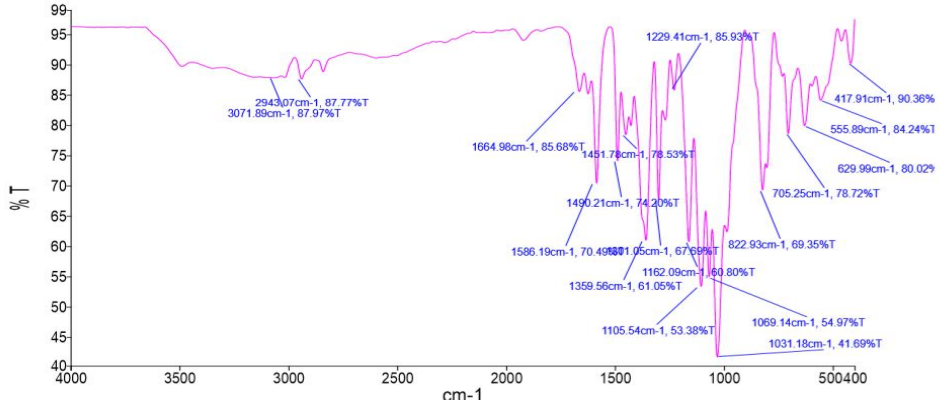


Figure 3: FTIR spectrum of Pantoprazole Sodium

Table 5: FTIR interpretation of Pantoprazole Sodium [19]

Reported (cm^{-1})	Observed (cm^{-1})	Characteristics Peaks
2941.3	2943.07	Aliphatic C–H Vibrations
1590.02	1586.19	C–N Stretching
1304.61	1301.05	C–F Stretching
1041.37	1162.09	S-O Absorption Peak

The principal IR absorption peaks of Pantoprazole Sodium at 3071.89 cm^{-1} (N–H Stretching), 1586.19 cm^{-1} (C–O Stretching), 1031.18 cm^{-1} (C–F Stretching), 1162.09 cm^{-1} (C=S Stretching), 822.93 cm^{-1} (sp^2 C–O aromatic ether stretch) were all observed in the spectra of Pantoprazole Sodium. These observed principal peaks confirmed the purity and authenticity of the Pantoprazole Sodium.

Preparation of Co-crystals of Pantoprazole Sodium:

In the present investigation, co-crystallization of Pantoprazole Sodium with the capability of providing immediate release was prepared using different co-formers such as sodium benzoate, sodium bicarbonate and gallic acid. The method of preparation of co-crystals was found to be simple and reproducible.

Evaluation of Co-crystals of Pantoprazole Sodium:

Optical Microscopy:

Figure 4: Optical Microscopy of co-crystals containing Pantoprazole Sodium in Formulation F9

From the figure 4, it was found that solvent evaporation method has successfully formed co-crystals of pantoprazole sodium. Co-crystals were formed with crystalline structure with varying size of co-crystals depending upon the molar ratios of drug to the co-former. So, might be this property play an important role in co-crystal formation.

Percentage Yield:

Table 6: Percentage yield of Cocrystals of Pantoprazole Sodium

S. No.	Formulation Code	Percentage Yield
1	F1	57.61±0.406
2	F2	65.16±0.465
3	F3	63.77±0.457
4	F4	48.54±0.219
5	F5	58.45±0.213
6	F6	53.77±0.825
7	F7	78.54±0.228
8	F8	85.12±0.219
9	F9	88.77±0.110

Value is expressed as mean ± SD; n = 3

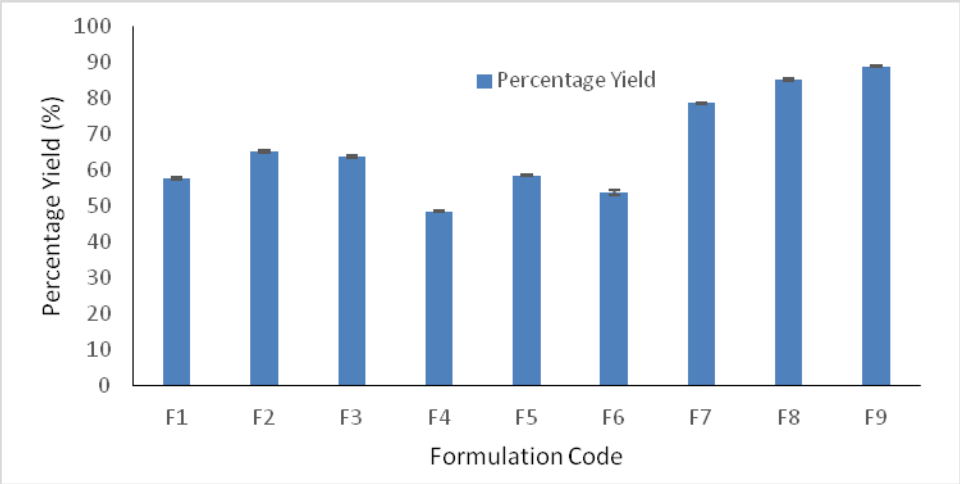


Figure 5: Percentage yield of Pantoprazole Sodium loaded Co-crystals

Percentage yield was calculated of the formulation which was found successful in co-crystal formation of pantoprazole sodium. The yield thus calculated was found in a range of 48.54±0.219 to 88.77±0.110 with the maximum yield possessed by F9 formulation, which was 88.77±0.110.

Solubility Profile of Co-crystals:

Table 7: Solubility Profile of Formulations in Simulated Gastric Fluid (SGF; pH=1.2)

S. No.	Formulation Code	Solubility in simulated gastric fluid (mg/ml)
1	F1	2.110±0.004
2	F2	6.851±0.045
3	F3	7.948±0.045
4	F4	2.896±0.021
5	F5	5.089±0.022
6	F6	11.668±0.021
7	F7	7.430±0.228
8	F8	14.155±0.219
9	F9	17.993±0.109

Value is expressed as mean ± SD; n = 3

The results showed in table 7 indicate that cocrystals improved the solubility of pantoprazole sodium. It was found that there was a maximum 15 fold increase in solubility when gallic acid was used as a coformer in the molar ratio of 1:3 (drug:coformer).

Particle Size:

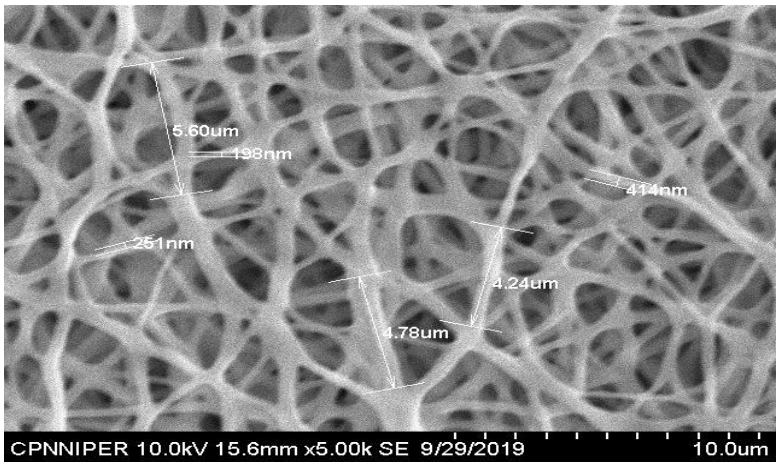


Figure 6: SEM Image of Formulation F9

Percentage Drug Content:

Table 8: Percentage Drug Content of Pantoprazole Sodium loaded Cocrystals

S. No.	Formulation Code	Percentage drug entrapment
1	F1	24.312±0.669
2	F2	27.967±0.668
3	F3	54.429±0.438
4	F4	26.359±0.438
5	F5	54.137±0.913
6	F6	71.827±1.103
7	F7	58.230±0.669
8	F8	81.038±0.253
9	F9	91.856±0.669

Value is expressed as mean ± SD; n = 3

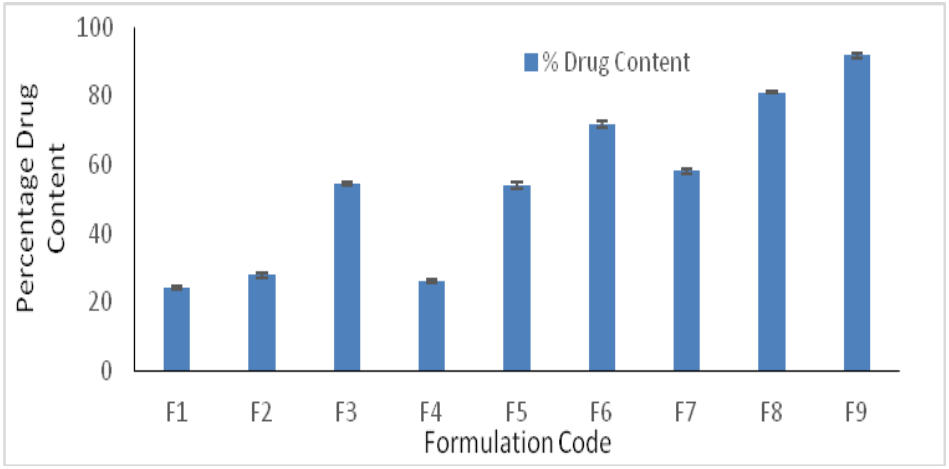


Figure 7: Percentage drug content of Co-crystals Pantoprazole Sodium

From the table 8, it was found that Percentage drug content of all formulation was found to be in a range 24.312±0.669 to 91.856±0.669. These results explain that there is a significant effect on percent drug content of co-crystals with respect to the co-former used as gallic acid was found to be the best fit for co-crystallization of pantoprazole sodium.

In-vitro Drug release study:

Table 9: Percentage drug release of Formulation F9 and Pure drug (184)

Time (mins)	% Drug release of pure drug suspension	% Drug release of F9 formulation
0	0	0
1	2.31±0.830	50.29±0.271
2.5	3.17±0.543	58.63±0.271
5	7.40±1.057	63.37±0.270
10	15.81±0.543	71.46±0.269
15	23.30±0.543	74.82±0.156
20	32.58±0.271	80.34±0.156
25	42.25±0.543	84.09±0.271
30	54.69±0.271	87.45±0.156
40	68.50±0.843	93.17±0.271
50	80.54±0.271	96.13±0.271
60	85.48±0.156	98.50±0.271

Value is expressed as mean ± SD; n = 3

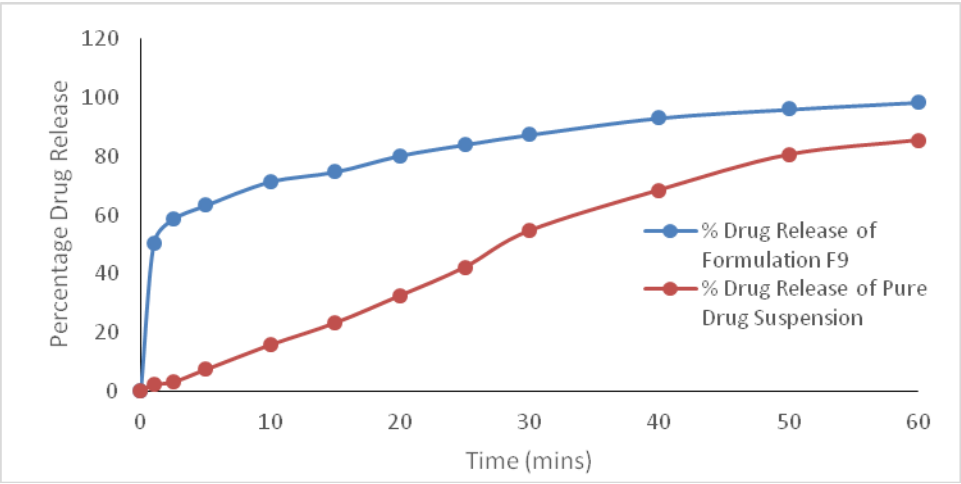


Figure 8: In-Vitro Drug release of Co-crystals of Pantoprazole Sodium and pure drug

The *in-vitro* release of drug from the co-crystals of pantoprazole sodium was found to be higher as compared to pure drug suspension that showed the effect of conformer in drug release property.

In-vitro drug release kinetic:

To understand the mechanism by which the drug was released from the Pantoprazole Sodium floating beads F9 formulation, various release kinetics model including zero order, first order, Higuchi and Korsmeyer-Peppas model were applied as shown in Figure 9-13.

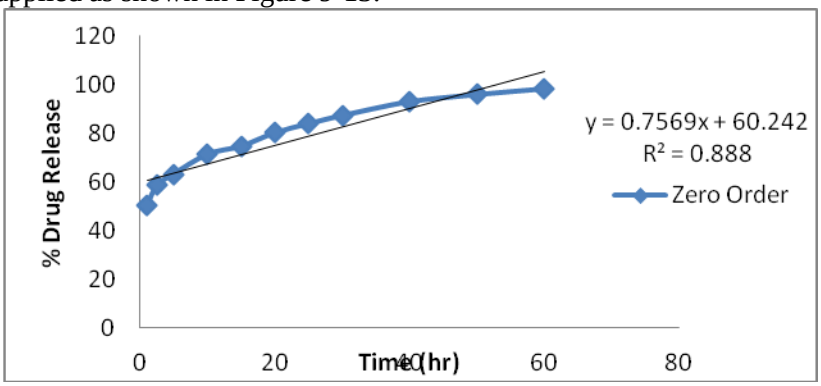


Figure 9: Zero order release kinetics of optimized F9 formulation

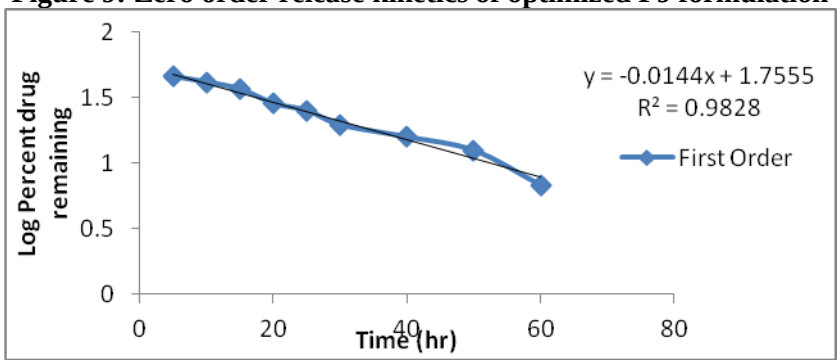


Figure 10: First order release kinetics of optimized F9 formulation

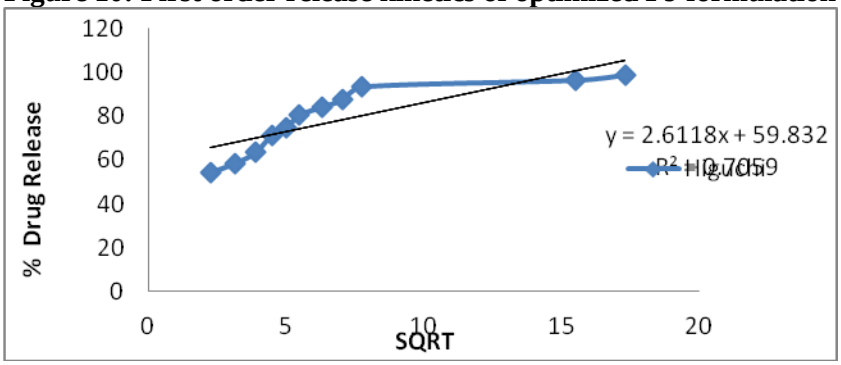


Figure 11: Higuchi order release kinetics of optimized F9 formulation

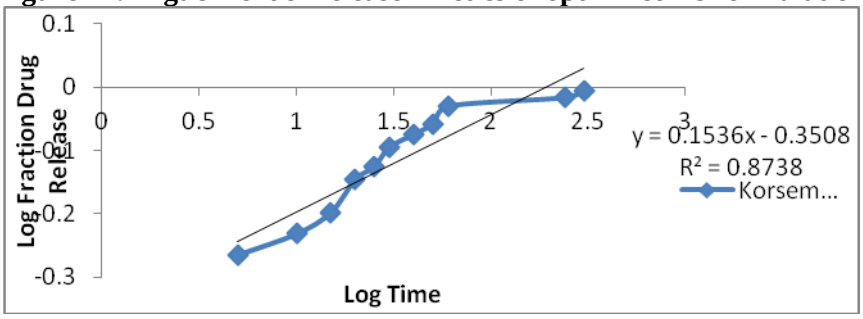


Figure 12: Korsmeyer peppas release kinetics of optimized F9 formulation

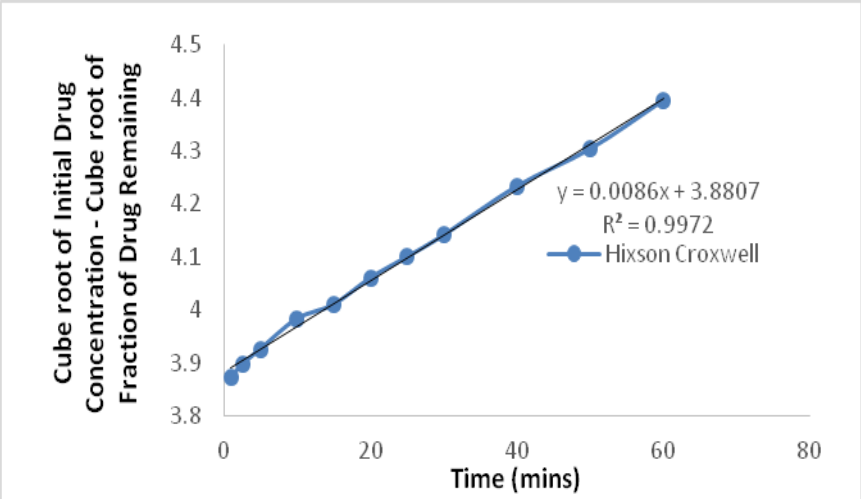


Figure 13: Hixson Crowell release kinetics of optimized F9 formulation

Table 10: Kinetic equation parameter of formulation F9

Formulation name	Zero order		First order		Higuchi		Peppas		Hixson	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F9	0.888	0.756	0.982	-0.014	0.705	2.611	0.838	0.153	0.997	00086

In each case, R^2 value was calculated from the graph and reported in table 10 and figure 9 to figure 13. Considering the determination coefficients, Hixson crowell model was found (R^2=0.997) to fit the release data best. This demonstrates that Pantoprazole Sodium molecules loaded in the cocrystals and the drug was released from cocrystals by an immediate mechanism.

Discussion:

Designing of pharmaceutical co-crystals is feasible among e.g. carboxylic acid, alcohol-amine and alcohol-pyridine moieties of the parent API and co-crystal formers. Co-crystals are sensitive to dissociation in aqueous microenvironment that is why a co-operation is needed among chemists, analysts and formulations experts to protect and monitor the physical integrity of these special APIs. Critical physio-chemical and pharmaceutical parameters of a co-crystal containing formulation development were explored. Pharmaceutical co-crystals can provide a solution in case of bioavailability issue justified on SAR1 co-crystal. The faster solubility and dissolution kinetic of co-crystals is responsible for higher absorption however keeping the integrity of the co-crystal as a pharmaceutical active ingredient is essential to reach the targeted effect and ensure the robustness of the formulation. On physicochemical evaluation, melting point of Pantoprazole Sodium was found to be 142.2°C. On UV spectrophotometer analysis absorption maxima was found to be 290 nm in methanol. Drug was freely soluble in methanol, ethanol and water and less soluble in chloroform. The partition coefficient of Pantoprazole Sodium in n-octanol: water was found to be 3.650 ± 0.011, this indicated that the drug is lipophilic in nature. On FTIR spectroscopy analysis there was no incompatibility between drug and lipid. An attempt is made to prepare co-crystals of Pantoprazole Sodium using different co-former (sodium benzoate, sodium bicarbonate and gallic acid). The method of preparation of co-crystals was found to be simple and reproducible. Percentage yield was found in a range of 48.54±0.219 to 88.77±0.110. Percentage drug content of drug was obtained in all formulations in a range of 24.312±0.669 to 91.856±0.669. The solubility of co-crystals in gastric fluid medium was between 2.110±0.004 to 17.993±0.109 mg/ml. The in vitro data indicated that co-crystals prepared in formulation F9 showed 100% drug release within an hour. According to model fitting methods the highest regression coefficient (R^2) value was 0.997 through Hixson Crowell order model. Hence from all aspects; we concluded that the release of drug Pantoprazole Sodium from co-crystals was in an immediate mechanism. This could be achieved by proper designing of the formulation and selection of a suitable method of preparation.

Conclusion:

It is concluded that the method of preparation of co-crystals was found to be simple, reproducible, provides good yield, solubility and drug content. The *in vitro* data obtained for co-crystals of

Pantoprazole Sodium showed increases solubility in acidic pH. Prepared formulation showed immediate release behaviour when compared with its pure Pantoprazole Sodium. Thus, gallic acid can be considered as an effective carrier for the crystallization of the drug in order to inhibit its degradation in acidic medium.

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