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Delayed Release Formulation of Pantoprazole Using Sureteric Aqueous Dispersion System

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ABSTRACT

The challenge up-front in formulating an efficient oral dosage form for a proton pump inhibitor like pantoprazole is delivering the acid liable drug unaffected to the intestinal milieu, for which enteric coating possibly will be a most plausible solution. Sureteric is a specially blended optimized aqueous coating combination of polyvinyl acetate phthalate, which exhibits a number of properties desirable for an enteric film formation. The present study aimed at formulation of enteric coated tablets of pantoprazole and to assess the influence of appropriate additives on the performance of the final product. The influence of different diluents, disintegrants and binders upon the precompression characters and physico-chemical properties of the tablets were studied and an optimized formulation with passable quality was selected for enteric coating. The optimized core formulation was then shroud around in a seal coat using 12% HPMC dispersion in order to increase the mechanical integrity and avoid any possible interaction between the drug and the enteric polymer. The seal coating was followed by enteric coating by the application of sureteric at different theoretical weight gains. The enteric coated tablets were evaluated for disintegration time, acid uptake and drug release. Formulation F19 coated up to 10% weight gain, disintegrated rapidly with in 8 min and showed <2.5% of acid uptake. The sureteric coating could resist the drug release in 0.1N HCl up to 2h but propelled the release of about 84% of drug within 30 min in the intestinal pH. Results of the stability tests were satisfactory with the dissolution rate and assays well within acceptable limits. The gastrointestinal behaviour of enteric tablets performed in rabbits using a fluoroscopic material revealed that the tablets remained intact in the stomach and then dissolved on reaching the small intestine. Thus the study ascertained the influence of additives on the effectiveness of the end formulations and also the suitability of the sureteric aqueous dispersion successful development of delayed release, dosage forms for proton pump inhibitors.

Key words: Enteric coating; Sureteric; Pantoprazole; Disintegration; acid uptake, drug release;

INTRODUCTION

Pantoprazole is a derivative of benzimidazole, which is metabolized in the parietal cells to activate sulfenamide metabolites that in sequence inactivate the sulfhydryl group of the proton pump, thereby reducing the hydrogen ion secretion [1]. Pantoprazole, like other proton pump inhibitors is susceptible to degradation in acidic and neutral media. Thus the drug degrades when it is exposed to the acid milieu, well before reaching the proximal small intestine where the drug is absorbed [2]. Therefore, there is a need for a delivery system which would protect the drug from degradation during its passage through the stomach and take it unaffected to its site of absorption. Delayed release formulations such as enteric coated tablets could accomplish the dual benefits of protecting the drug from the detrimental effects of gastric contents and to deliver the drug to a specific region of the intestine.

The pH of the stomach, even in the fed condition, will seldom reach a pH level of 5-6 but will surpass this level in the duodenum, where secretion of bicarbonate neutralizes the acidic chyme, leaving the stomach. Thus, a polymer with a dissolution threshold pH in the range 5 to 6 is considered suitable for use as an enteric coat [3]. The

proportion of ionizable monomers in the polymer chain is probably the most important determinant of threshold dissolution pH, but other factors play a role in delineating this pH [4]. The quality of the enteric film formed by the coating composition is controlled by a number of factors, such as, tensile strength of the film which is dependent up on the properties of the polymer, the elasticity of the film, which depends on the quantity of the plasticizer used and the film- tablet surface interaction which is affected by every ingredient used in the making of the coating composition [5]. Apart from the coating composition, the characteristics of the polymeric membranes, for instance, their mechanical resistance, water permeability and dissolution behaviour depend up on the type of coating composition as either organic solutions or aqueous dispersions. Therefore, it is obligatory to use the most optimized coating formulation to acquire the best film properties [6-8].

Phthalates such as cellulose acetate phthalate, hydroxylpropyl methyl cellulose phthalate are used as a common functional excipient in a number of oral formulations, especially for their ability to resist the degradation of capsule or tablet in the acidic environment and to render flexibility to solid dosage forms for quality purposes such as prevention of cracking. Polyvinyl acetate phthalate (PVAP) is one of the most preferred materials for designing enteric formulations in terms of performance and acceptability [9]. PVAP is the product obtained as a result of reaction between polyvinyl alcohol and phthalic anhydride [10]. Aqueous dispersions of enteric polymers have gained importance over the organic solutions in the recent times, with regard to manufacturing safety concerns, toxicological and ecological deliberations [11]. Sureteric is a specially blended optimized aqueous film coating combination of polyvinyl acetate phthalate, plasticizers and other processing ingredients, designed to meet the enteric coating needs of the solid oral dosage forms. However, the major limitation of many aqueous enteric coating formulations is the risk of premature drug release through the enteric coat in the stomach. This can be due to an increased permeability of aqueous film coatings [12-13]. Therefore, the present study aimed at formulation and evaluation of enteric coated pantoprazole tablets using an aqueous based sureteric enteric polymer system and thereby, to assess the potential of the polymeric system to protect the drug from the adverse effect of the gastric environment and its ability to favour its release in the intestine.

MATERIALS AND METHODS

Materials:

Pantoprazole sodium sesquihydrate was a gift from Kaushik therapeutics Pvt Ltd. The sub coating material was hydroxyl propyl methyl cellulose-methocel (Colorcon), and the enteric coating material was PVAP based Sureteric – 90G18506 White (Colorcon). Crospovidone, croscarmellose sodium, sodium starch glycolate were used as disintegrants. Lactose anhydrous, mannitol, and microcrystalline cellulose (Avicel PH 102) used as diluents, were purchased from SD Fine chemicals. Sodium carbonate, magnesium stearate isopropyl alcohol, dichloromethane, potassium dihydrogen orthophosphate, sodium hydroxide and all other chemicals used in the study were of analytical grade and comply with the pharmacopoeial standards (IP).

Methods:

Preparation of core tablets by granulation technique

Pantoprazole core tablets were also prepared by granulation technique. Required quantities of pantoprazole, diluents, disintegrant, binder were weighed according to Table 1. The contents were transferred in to a blender and mixed thoroughly. Isopropyl alcohol was then added to the above mixture and blending was continued until sluggy mass were formed. The mass was then passed through a sieve with aperture pore of 1.4 mm to obtain granules. The granules prepared were dried at 40^{o}C for 2 hours. The dried granules were screened through sieves of 0.71mm and 0.355mm and stored for further studies. Specified quantities of Aerosil and magnesium stearate were finally added and blended thoroughly. The granules were directly compressed into tablets each weighing about 200 mg in a 10 station rotary press using 6 mm round biconvex punches at a pressure of 4 to 6 kg/cm^2. The different batches of pantoprazole tablets were collected and stored in air tight containers [1].

Effect of formulation ingredients:

The functional attributes of the finished dosage forms are highly dependent on the amount and type of pharmaceutical excipients Thus, the pharmaceutical excipients establish the primary features and physicochemical properties of the tablet, such as the physical form, stability, dissolution, taste, and overall appearance [14]. In this study, attempt was made to study the influence of various excipients on the efficiency of the core tablets. The effect of diluents was studied by utilizing lactose and mannitol alone and in combination with microcrystalline cellulose. Three different disintegrants namely, croscarmellose, cross povidone and sodium starch glycolate were used at different concentrations to estimate their ability to impart faster disintegration to the tablets. Similarly, polyvinyl pyrrolidone at varying concentrations was utilized, with an aim to evaluate the effect of binder concentration on the core tablets of pantoprazole. The composition of the formulations is given in the Table 1.

Table 1: Composition of Pantoprazole core tablets

Ingredients (mg/tablet)	Batch Code															
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Pantoprazole sodium Sesquihydrate* sesquihydrate*	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10	45.10
Sodium Carbonate anhydrous	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Lactose	122.9	-	-	72.9	-	72.9	67.9	62.9	72.9	67.9	62.9	72.9	67.9	62.9	67.9	57.9
Microcrystalline cellulose	-	122.9	-	50	50	50	50	50	50	50	50	50	50	50	50	50
Mannitol	-	-	122.9	-	72.9	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	5.0	5.0	5.0	5.0	5.0	5.0	10.0	15.0			-	-	-	-	-	-
Cross povidone	-	-	-	-	-	-	-	-	5.0	10.0	15.0	-	-	-	15.0	15.0
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	5.0	10.0	15.0	-	-
PVP K 30	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5	15
Aerosil	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Magnesium stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Quantity per Tablet (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

**45.10 mg of pantoprazole sodium sesquihydrate is equivalent to 40.0 mg of pantoprazole*

Evaluation of pantoprazole tablet core:

After compression, all the tablets of different batches were subjected to various evaluations, derived from which the most suitable formulation was chosen for enteric coating.

Tablet Diameter and Thickness:

The tablets were evaluated for their diameter and thickness using a Vernier Calliper. Average of three readings were taken and tabulated.

Hardness:

The crushing strength was determined by compressing the tablets between the holding anvil and a piston of the Pfizer Hardness Tester. The hardness of the tablet was directly read from the force gauge dial.

Friability test:

The ability of the tablets to withstand mechanical shocks such as the abrasion and shock was tested using the Roche friabilator. Six tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of six inches with each revolution. After 100 revolutions, the tablets are dusted and reweighed. The percent weight loss was calculated.

Disintegration Test:

The disintegration time of core tablets was determined according to I.P. by placing one tablet in each of the six tubes of the basket rack assembly of the disintegration apparatus. The assembly was then suspended into a beaker containing water maintained at 37 ± 0.5°C. The time required for all the tablets to break up and for all particles to pass through a 10 mesh screen. Average of triplicate readings was computed.

Determination of drug content:

Six tablets of pantoprazole core tablets were randomly selected an crushed into powder in a mortar and weight equivalent to 40 mg of drug was taken into a volumetric flask. The drug was extracted completely from the tablets using pH 6.8 phosphate buffer under constant shaking for 24 h on an orbital shaker incubator (CIS 24, Remi). The solution was filtered and the filtrate (1 mL) was suitably diluted with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured with a UV-Visible spectrophotometer (Lamda 25, Perkin Elmer) at 289 nm.

Seal coating of core tablets

The optimized formulations were sub coated with a seal coating composition incorporated with HPMC. The seal coat was prepared by dispersing HPMC in solvent mixture of isopropyl alcohol and dichloromethane (2:1) with continuous stirring using a propeller mixer for 45 min. The dispersion was size reduced, if necessary through colloidal mill then filtered by passing through 250 µm sieve. The total solid content of the dispersion was made to 12% w/v.

Coating with Sureteric:
A variable speed mixer capable of producing and maintaining a vigorous vortex should be used to prepare the coating composition of sureteric. A high efficiency propeller stirrer with diameter equivalent to 25 to 30% of the total diameter of the mixing vessel is used for the preparation of enteric formulation. In order to accommodate the initial foam generated with the addition of sureteric powder, the mixing vessel is required to contain a liquid volume 20% greater than the total suspension being prepared. The amount of sureteric (0.33% of sureteric solids) and water required based on the quantity of tablets to be coated and the target coating weight was weighed. Coating dispersions were prepared by adding the dry aqueous enteric coating formulations directly into a mixing tank filled with deionised water (ambient ~20 ^{0}C). Mixer speed was controlled to produce and maintain a deep centre liquid vortex into which the powder was added. Immediately after the addition of the powder to the water, the mixer speeds were reduced to maintain gentle stirring. The suspension must be continuously mixed at low speed throughout the coating process. The dispersion was screened through a 250-mm sieve before coating. The suspension should be used the same day it is prepared.

Coating Methodology:
The core tablets of pantoprazole were coated in a conventional coating pan with a single spray gun. The coating pan was previously cleaned using alcohol 95%. The core tablets were loaded into the coating pan. Tablet cores were pre-heated to about 40°C utilizing a dryer and air compressor. Warm air was introduced into the coating pan (up to 50–55°C) during the entire coating process. The spray gun was filled with Sureteric white aqueous dispersion and operated at a proper flow rate. The pan was set into motion and seal coating dispersion was sprayed on to the falling cores under a suitable air pressure. As the tablets achieve the required weight gain, the heater was turned off and the tablets were blown dried for 20-25 minutes in the coating pan. The coating conditions and parameters were tabulated in Table 2.

Table 2: Coating dispersion composition and coating process parameters

Parameters	Seal Coat layer	Enteric coat layer			
		F17	F18	F19	F20
Dispersion solid content (%)	12	15	15	15	15
Powder (g)	HPMC-48	Sureteric	Sureteric	Sureteric	Sureteric
Deionized water (g)	N/A	600	600	600	600
Isopropyl alcohol	117	N/A	N/A	N/A	N/A
Dichloromethane	235	N/A	N/A	N/A	N/A
Total dispersion (g)	400	700	700	700	700
Mixing time (min)	40	20-25	20-25	20-25	20-25
Theoretical weight gain (%)	2	5	8	10	15
Pan charge (kg)	3	1	1	1	1
Pan speed (rpm)	12	16-18	16-18	16-18	16-18
Inlet temperature (^{o}C)	45	55	55	55	55
Atomization air pressure (bar)	2.0	6	6	6	6
Pan size (inch)	12	12	12	12	12

Characterization of Coated tablets
Disintegration time:
The disintegration time of the coated tablets was determined using the The USP model disintegration appatatus (EI). Six tablets were placed in the basket rack assembly, and was run for 2 hours in 0.1 N HCl media with the discs. The tablets were removed from the solution, gently dried by bloating. The test was then continued by placing the tablets in phosphate buffer ph 6.8, for 1 h, maintaining the temperature at 37±2 ^{o}C [15,16].

Method for Acid-Uptake Measurement
Accurately weigh 6 to 50 tablets (Wo) and expose to the acid media (0.1N HCl or pH 4.5 acetate buffer) for two hours at 37°C in a disintegration apparatus. The tablets should remain intact if enteric coating is successful. Then remove the tablets, pat dry to remove surface moisture and reweigh (Wt). From the differences in weights before and after exposure to acid media, the percent acid uptake may be calculated as shown in the following,

$$\% \text{ acid uptake} = \frac{Wt-Wo}{Wo} x\ 100$$

Dissolution of Pantoprazole from coated tablets
The in vitro drug dissolution studies was conducted in an eight stage dissolution apparatus (TDT-08L, Electrolab) using an rotating paddle, at 50 rpm, in 900 ml of simulated gastric fluid, maintained at 37± 0.5 ^{o}C. Samples were withdrawn of the gastric media at 2 h and then, the vessel was drained off the acid and was replaced with 900 ml of

phosphate buffer pH 6.8. The samples were withdrawn at regular intervals, filtered and suitably diluted. The concentration in acid media and phosphate buffer was measured with a spectrophotometer (Lambda 25, Perkin Elmer) at 284 and 289 nm, respectively by comparison to a calibration curve [17].

Fourier Transform Infrared Spectroscopy (FTIR) Studies

The drug and polymer interactions were studied by infrared spectroscopy. The IR spectra were recorded in the wavelength region 400-4000 cm^{-1} for pure pantoprazole, sureteric and enteric coated pantoprazole tablets using Alpha E – FTIR (Bruker) instrument.

Stability Testing

To evaluate the stability of pantoprazole sodium tablets, the optimized formulations (F19) were packed in polyethylene bottles. Accelerated stability studies were conducted by reserving the tablets at 40± 2 ^{o}C and 75± 5 % RH, in a humidity chamber. The samples were withdrawn at the intervals of 0, 1, 2 and 3 months from the date of packing. The physical appearence, assay and the percentage drug release were evaluated to assess the constancy of the tablets.

Gastro intestinal transit behaviour:

The GI transit behaviour of the formulation was visualized using fluoroscopy under the supervision of a radiologist. The study protocol was approved by the Institutional Ethical Committee. Three healthy male rabbits, each weighing between 1.5 to 2 kg were selected for the study. The tablets containing radio-opaque marker (barium sulphate) were prepared by replacing the drug using 3mm biconvex punches using same proportion of ingredients in a similar manner to formulation F19. The tablets were administered to each animal with sufficient of water after the animals had fasted overnight. During the experiments the animals remained in a sitting or upright posture in neck stock cages. All X-ray films were taken in anterior positions at regular intervals up to 3 h from the time of administration to detect the intactness or disintegration of the test formulations.

RESULTS AND DISCUSSION

The advent of aqueous enteric formulations has led to the encroachment in the field of pharmaceutical coating technology. Though initially, adoption of such aqueous coating compositions had been complex and intricate over the established organic coatings, the introduction of coating pans, spraying systems and ancillary equipments specially designed for aqueous coating solutions has made the method more common and ease in practice. Sureteric is a specially blended aqueous enteric coating combination of poly (viny1acetate phthalate), plasticizers, and other ingredients, specifically intended as for solid oral dosage forms. The mechanism by which such enteric coating polymers function is by a variable pH solubility profile where the polymer remains intact at a low pH but at a higher pH will undergo dissolution to permit the release of the contents of the dosage form. However, in actual use, there are formulation considerations which tend to complicate this rather simplistic picture of pH dissolution. Therefore, the present study aimed at exploring the influence of various excipients upon the performance of the core tablets and then to investigate the suitability of sureteric as an enteric polymer to restrain the drug release in the acidic milieu and let the drug dissolve immediately in the intestinal region.

Influence of formulation ingredients:

The tablets were initially formulated using both direct compression and also granulation technique (data not included). Still, granulation technique was preferred over the direct compression due to the superior compressibility, mechanical strength, and integrity of the tablets. Various formulations of core tablets containing pantoprazole were prepared with the inclusion of different diluents, disintegrants and binder in varying concentration as shown in table 1. The precompression properties of the tablet blend such as angle of repose, Hausner's ratio and Carr's index were evaluated and are shown in the Table 3. The tablet blends were then compressed into tablets using round biconvex punches. The compressed tablets were evaluated for average weight, hardness, friability, drug content, and disintegration time. The physicochemical properties of the tablets were found to be well within the acceptable limits. The results were tabulated in the Table 4.

From the results of precompression evaluation, it was observed that formulations prepared with microcrystalline cellulose (F2) as the diluent possessed most suitable Carr's index and Hausner's ratio confirming the excellent compaction behaviour of MCC, although the flow property was slightly sluggish. Formulation F1 prepared with inclusion of lactose, on the other hand, exhibited good compressibility with superior flow characters. However, the formulations were brittle which is imparted due to the high brittle fracture index of lactose. Mannitol containing granules, though less brittle as compared to lactose, revealed less compressibility and flow ability [18]. Considering the above, the formulation F4 containing the combination of MCC and lactose as diluents was selected for further

optimization due to hybrid character and adequate properties. The tablets belonging to F4 batch showed acceptable mechanical strength and rigidity.

The disintegrants had a profound impact on the flow ability and compressibility of the tablet blends. The results showed that as the concentration of the disintegrants were increased from 2.5%w/w to 7.5%w/w, flow properties were enhanced due to their small particle size and lubricity while the compressibility decreased and the tablet strength got reduced. On increasing the concentration of the binder, the strength of the tablets increased with lesser thickness. PVP was reported to exhibit low values of Young's modulus showing that it is the most deformable binder [10]. This high deformability of PVP aids in consolidation during compaction.

Table 3: Evaluation of precompression properties of pantoprazole core tablet blend

Batch	Angle of repose	Bulk Density	Tapped Density	Hausner's	Carr's
F1	27.38	0.57	0.66	1.15	13.63
F2	31.21	0.48	0.55	1.14	12.72
F3	29.13	0,560	0.698	1.24	19.70
F4	29.68	0.561	0.65	1.16	13.84
F5	30.32	0.58	0.687	1.18	15.4
F6	30.21	0.547	0.642	1.17	14.79
F7	29.21	0.576	0.681	1.18	15.41
F8	29.59	0.536	0.652	1.22	17.79
F9	27.61	0.541	0.632	1.16	14.39
F10	25.68	0.559	0.667	1.19	16.19
F11	26.68	0.549	0.661	1.2	16.94
F12	31.0	0.557	0.674	1.21	17.36
F13	29.42	0.528	0.649	1.23	18.64
F14	28.82	0.563	0.698	1.24	19.34
F15	31.61	0.480	0.561	1.17	14.43
F16	30.38	0.516	0.584	1.13	11.64

Table 4: Evaluation of Physico chemical properties of compressed tablets

Batch	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)	Disintegration Time (sec)
F1	200.56±0.22	4.6	0.53	4.143±0.067	99.65	108
F2	203.76±0.31	4.8	0.28	3.89±0.065	97.27	93
F3	201.16±0.10	3.6	0.46	4.45±0.084	100.33	126
F4	201.87±0.09	4.4	0.43	4.24±0.012	99.14	101
F5	199.89±0.18	4.0	0.42	4.28±0.073	98.79	117
F6	201.87±0.09	4.4	0.43	4.24±0.012	101.14	101
F7	202.76±0.08	4.2	0.46	4.42±0.024	98.56	94
F8	201.26±0.19	4.2	0.54	4.40±0.018	98.71	81
F9	199.34±0.24	4.5	0.44	3.92±0.027	101.56	94
F10	200.45±0.08	4.4	0.48	4.16±0.032	99.43	84
F11	200.67±0.17	4.2	0.50	4.24±0.017	98.61	74
F12	201.76±0.21	4.2	0.52	4.42±0.016	100.22	102
F13	203.51±0.18	4.0	0.52	4.50±0.026	97.97	94
F14	202.86±0.09	3.8	0.56	4.65±0.110	99.45	89
F15	200.67±0.17	4.2	0.50	4.24±0.017	98.61	81
F16	203.56±0.41	4.8	0.38	3.97±0.101	99.01	114

With intent to achieve rapid disintegration, once the tablets arrive at the alkaline zone in the GIT, super disintegrants were included in the formulations at variable concentrations. The influence of the disintegrants on the disintegration time of the tablets was shown in the Fig.1. For a similar concentration of disintegrant, crosspovidone induced faster disintegration than croscarmellose and sodium starch glycollate. This behaviour could be ascribed to the inherent properties of these materials such as, their chemical structure, particle size, and porosity.

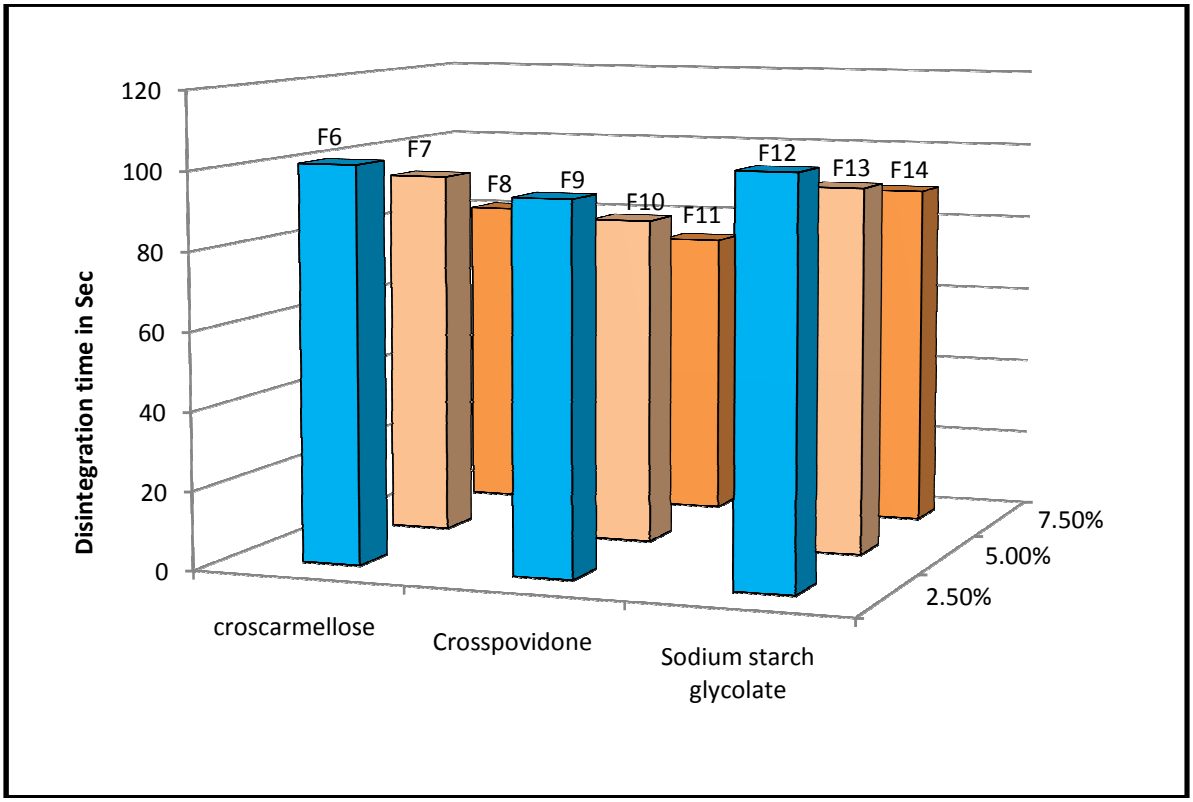

Fig. 1. Influence of disintegrants on the disintegration time of compressed tablets

Their porous particle morphology enables crosspovidone to rapidly absorb liquids into the tablet by capillary action and to generate rapid volume expansion and hydrostatic pressures that result in tablet disintegration. While cross povidone rapidly disintegrate into more or less fine particles due to wicking and quick hydration [19], tablets containing croscarmellose and sodium starch glycolate disintegrate much slowly after tremendous swelling and their outer edge appeared gel like, while the centre remained dry and hard [20, 21]. Thus, inclusion of cross povidone at 7.5% w/w was found to improve the disintegration of the tablets. In view of the above mentioned results, formulation F11 was considered most favourable batch, owing to its high mechanical strength, faster disintegration and acceptable precompression properties. Hence, F11 was selected as the core tablets for enteric coating.

In most situations, it is recommended that a precoat be applied to the substrate prior to application the sureteric coating. While this approach may not be necessary in all cases, it is certainly beneficial to minimize interaction between the drug and enteric coating that may otherwise have a negative impact on enteric performance. It was necessary to separate the core from the functional coating layer. A polymeric sub coat sheath the acid liable drug from the aqueous enteric coating composition, thus prevents the migration of water soluble drugs in to polymeric film, and thereby avoid the drug-polymer interactions [22]. In the present study, the subcoating was provided using HPMC dispersion (12% w/v) was made up to 2% weight up on the core tablets. The subcoating was followed by enteric coating at a theoretical weight gain of 5%, 8%, 10% and 15% to prepare formulations F17, F18, F19 and F20 respectively using sureteric aqueous dispersion with 15% solid content. The spray applications were continuous from start to finish, and spray rates were held constant throughout the coating trials. The tablets were white in appearance smooth surfaced without any incidence of defects. The tablets were not dried further after the application of the coatings other than during a cool down period in the pan before unloading.

The thickness of the coating applied has a major impact on the performance of the final product. For any barrier coating (including enteric coatings) to be effective, a minimum thickness of coating must be present across the surface of a product that is coated. However, the quantity of polymer that may be necessary shall differ based on the nature of core drug and the desired release pattern. Tablets were subjected to disintegration and acid uptake evaluations. All the batches of tablets remained stable and acid resistant for 2h in 0.1 M HCl while in phosphate buffer pH 6.8. All the formulations demonstrated reproducible tablet break up, well within 10 min. The time for disintegration slightly increased as the actual coating weight gain increased (Table 5). All four enteric formulations were tested for acid uptake in 0.1 M HCl. Formulation F17, coated with weight gain up to 5% was the only batch which resulted in more than 14% acid uptake while the other formulations with greater weight gain exhibited less than 5% of acid uptake.

Table 5: Results for disintegration, acid uptake and dissolution tests of enteric coated tablets of pantoprazole

Test	Media	Results			
		F17	F18	F19	F20
Disintegration (min)	0.1M Hydrochloric acid	No signs of softening or cracking up to 120 min			
	pH 6.8 Phosphate buffer	4.5	6.5	7.25	8.90
Acid uptake (%)	0.1M Hydrochloric acid	12.5	4.2	2.3	1.6
Dissolution (%)	0.1M Hydrochloric acid at 120 min	12.32	4.96	1.9	0.22
	pH 6.8 Phosphate buffer at 30 min	97.21	93.28	84.12	70.89

The solubility characteristics of polyviny1acetate phthalate produce a rapid breakdown of the enteric coating when the drug has passed from the stomach into the intestine allowing for release of the active ingredient. Six tablets each from four different formulations coated with different weight gains, i.e. 5%, 8%, 10% and 15% were subjected to in vitro dissolution testing in 0.1 N HCl for 2h followed by testing in pH 6.8 phosphate buffer for 1 hour in a USP dissolution bath. Tablets showed complete acid resistance for 2h, except F17 tablets coated with least amount of polymer, which let about 12.13% of drug released in acid media at the end of 2 h. However, the release of pantoprazole in buffer pH 6.8 met the criteria outlined in this study i.e. not less than 80% dissolved after 60 minutes. All the tablet formulations released the drug rapidly on exposure to the alkaline media, although the percentage of drug released at a given time point was ascertained by the amount of polymer used for coating the tablets. Hence, F17 with least weight gain released at a faster rate while F20 fabricated with 15% polymer weight gain, released at a slower pace (Fig 2). Such an observation was made by Naser and Aiman for enteric coated diclofenac sodium tablets using Sureteic, which released more than 80% of drug with 30 min in alkaline media [23]. Thus manipulation of performance by variation of the quantity of the applied enteric-coating agent has a powerful part to play.

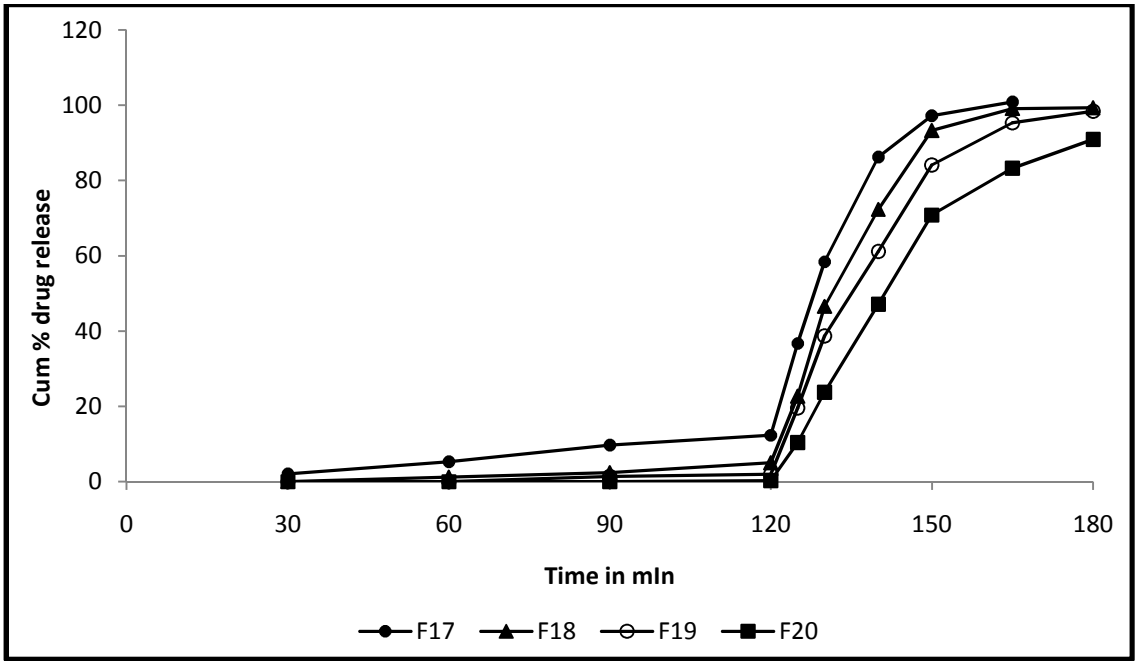

Fig. 2. Drug release profile of enteric coated tablets with different weight gains, F17(-■-) with 5% WG, F18 (-○-) with 8 % WG, F19 (-▲) with 10 % WG and F20 (-●-) with 15 % WG

The IR spectra of the pure drug, enteric polymer and the coated tablets were shown in the Fig. 3, 4 and 5 respectively. The IR spectra of pantoprazole revealed its characteristic peaks at 1587 cm^{-1} due to C=N and C=C stretches, 1452 cm^{-1} showing CH_2 bending, 1271 cm^{-1} corresponds to S=O stretches and peak at 1165 cm^{-1} reveals Sp^2 C-O aromatic ether stretches. The above-mentioned characteristic peaks were present at the exact wave numbers in the coated tablets. This confirms that there was no interaction between the drug and the polymer in the coated formulation.

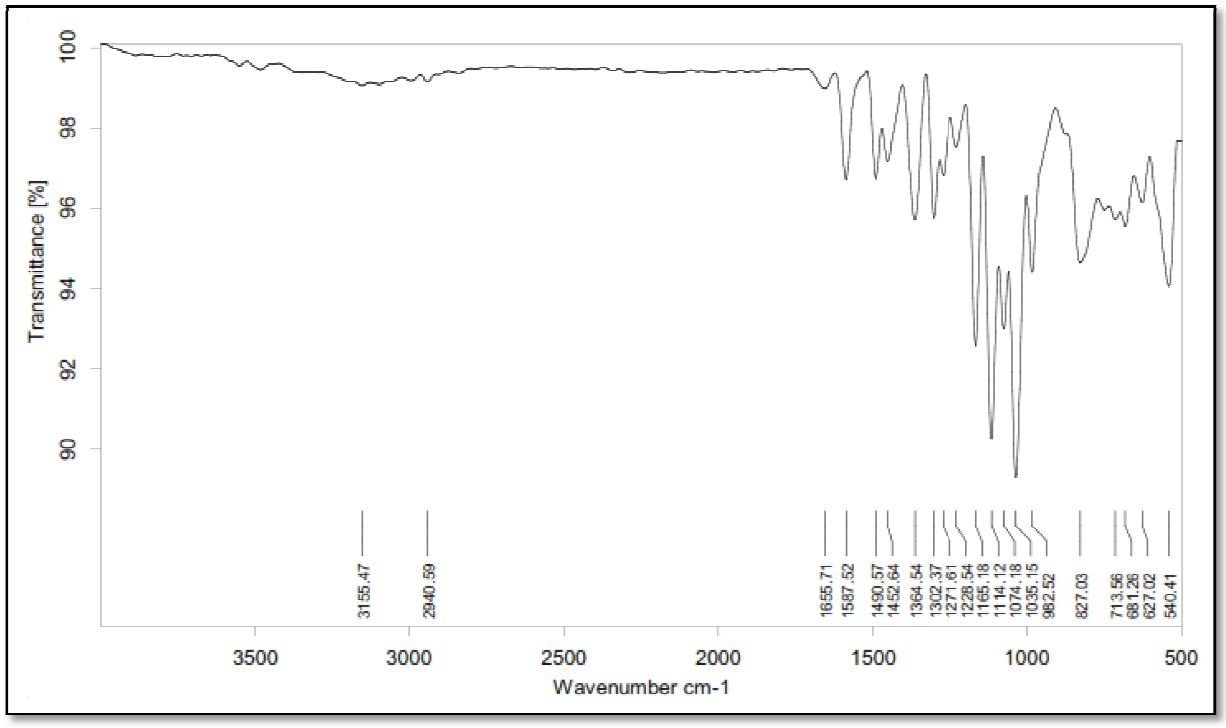

Fig. 3. IR Spectra of Pantoprazole pure drug

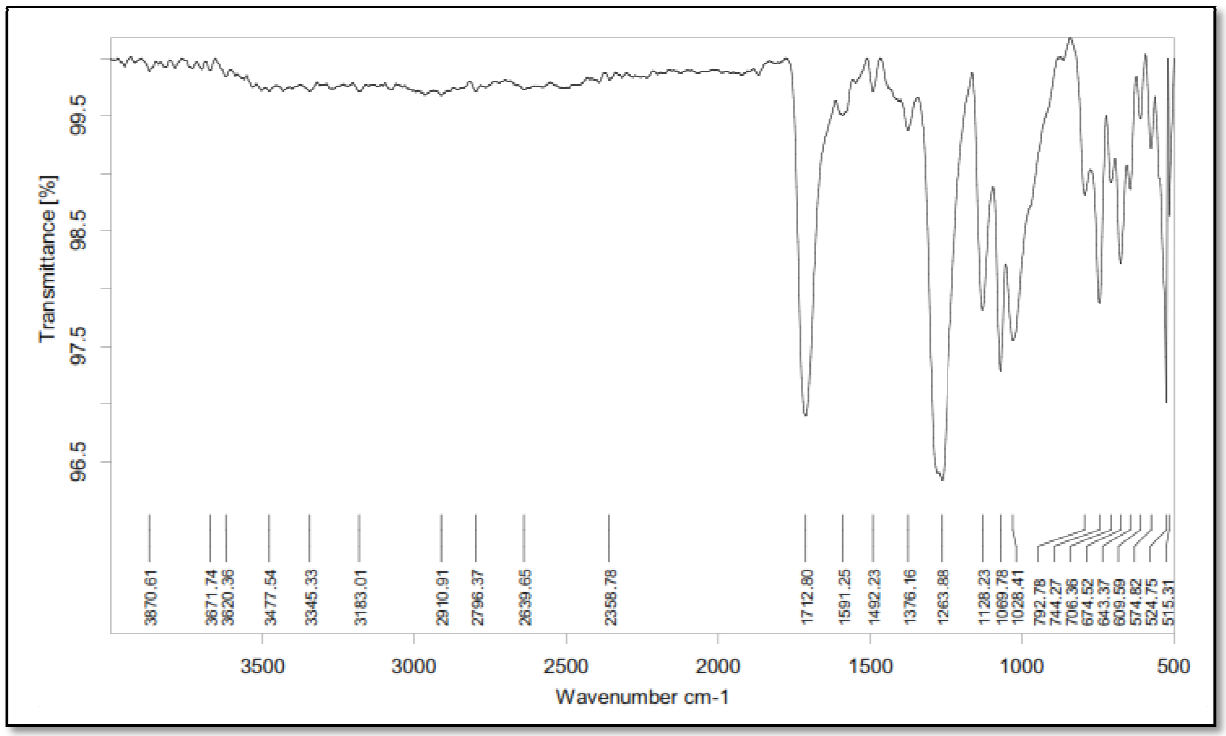

Fig. 4. IR Spectra of Sureteric coating polymer

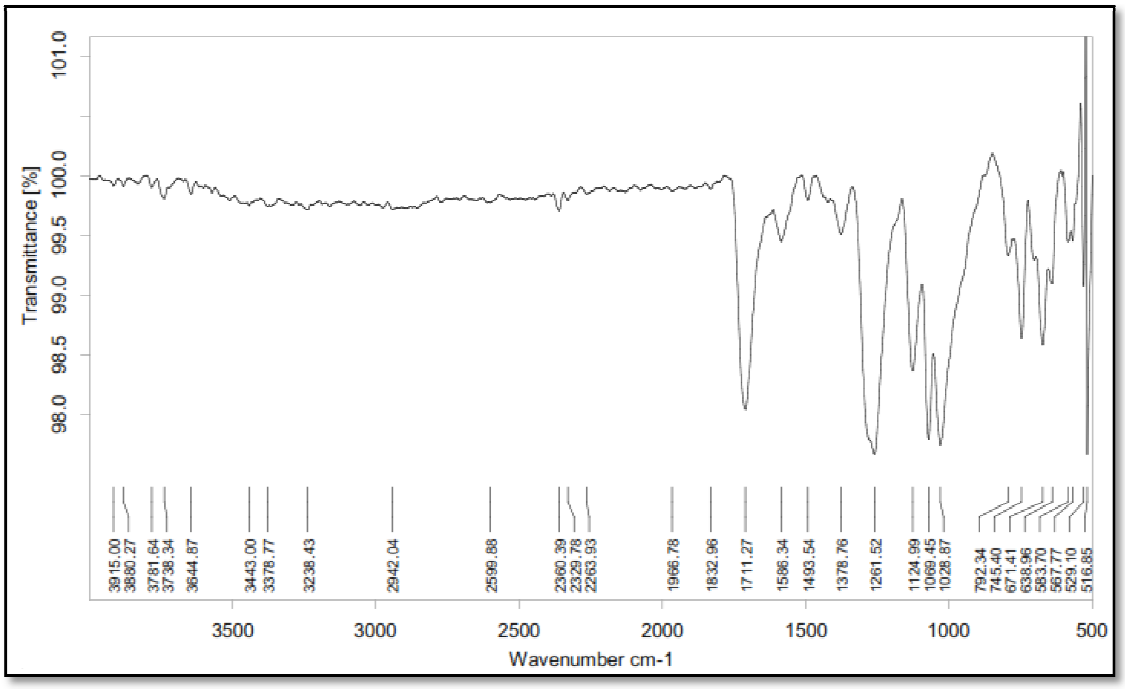

Fig. 5. IR Spectra of enteric coated tablets of pantoprazole coated using sureteric

The results obtained for the disintegration, acid uptake and the in vitro dissolution studies revealed that formulation F19, coated up to 10% weight gain held most desirable properties. Hence F19 was subjected to accelerated stability studies to assess its long term keeping properties by storing up to 3 months in a humidity chamber at at 40 ± 2 ^{o}C and 75 ± 5 % RH. The samples were tested at regular intervals to examine any possible changes in the physico chemical properties, disintegration, drug content and release pattern. Poly (viny1 acetate phthalate) is not hydrophilic due to its vinyl backbone, making it less subject to water vapour effects. The study disclosed the absence of any significant transformation in the physical properties such as colour, appearence, hardness and disintegration time of the enteric coated tablets. The drug content and the dissolution benaviour remained the same without any significant changes. The percantage of dissolution and assay were well with in the acceptable limits as shown in the Fig. 6.

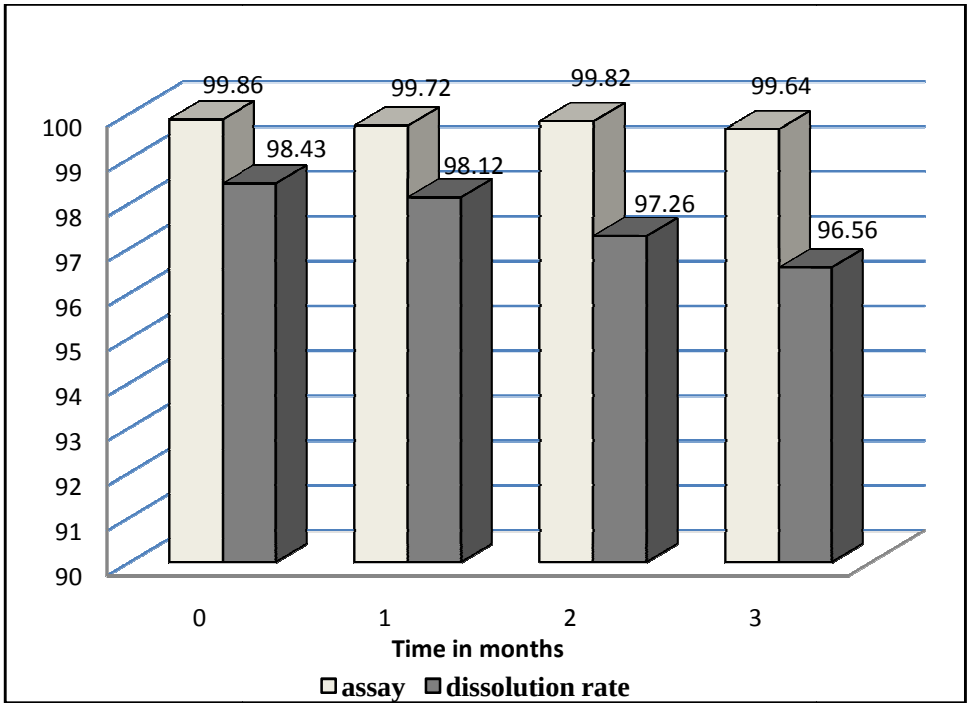

Fig. 6. Stability studies showing assay and percentage dissolution rate of enteric coated tablets of F19 batch at different time intervals

The fluoroscopic study revealed that the enteric coated tablets remained in the stomach for 30–120 minutes during which the tablet remained intact as shown in the Fig. 7, and then passed into the upper intestinal tract where on exposure to the alkaline environment in the small intestine could have dissolved the tablet completely and therefore, the intact tablet was not seen in the image taken at 150 min. Thus, it could be supposed that the sureteric coated tablets must inhibit the drug's release in gastric fluid but allow it to release rapidly once it reaches the intestinal tract.

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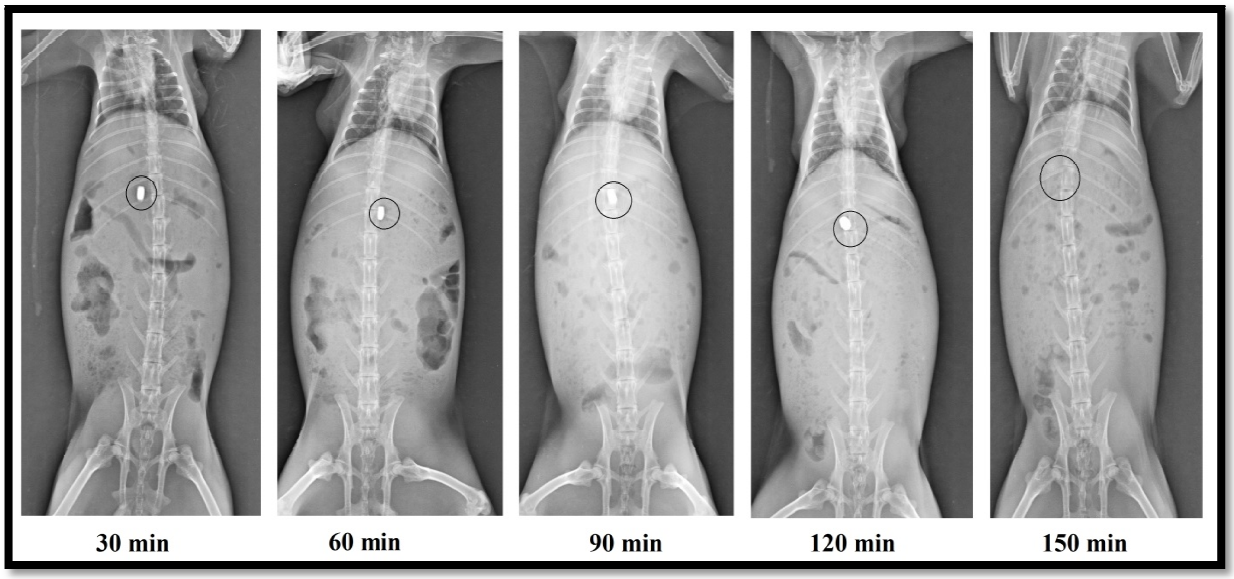

Fig. 7. X-ray photographs recorded at different intervals after oral administration of blank formulation of F19 in animal model

CONCLUSION

The present investigation anticipated to develop a delayed release formulation of pantoprazole sodium, an acid sensitive proton pump inhibitor using aqueous enteric coating composition based on polyvinyl acetate phthalate. Imperative aspects of formulation development such as, influence of additives and coating compositions on the efficiency of end product were assessed. The results of the study revealed the definitive role of the formulation additives up on the functioning of the dosage form. The solubility characteristics of sureteric at pH 5 led to a rapid breakdown of the enteric coating when the drug has passed from the stomach into the intestine allowing for release of the active ingredient. The thickness of the coating applied had a major impact on the release of the drug from the final product. The optimized formulation had all the desirable properties in terms of efficiency, stability and safety. Thus, employing sureteric for enteric coating of acid prone drugs could be more beneficial than conventional organic coatings from the stand point of ease of use, stability, economic and environmental prospects.

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