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FORMULATION DEVELOPMENT AND EVALUATION OF PANTOPRAZOLE DELAYED RELEASE TABLETS

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ABSTRACT

Pantoprazole is a proton pump inhibitor, belongs to group of benzimidazole, used for the treatment of gastric and duodenum ulcers. The objective of the present investigation was to design and develop Pantoprazole Delayed Release Tablets. Delayed release tablets of Pantoprazole were prepared by wet granulation method using HPMC and polyvinyl pyrrolidone as polymer, Avicel PH 102 (MCC) as filler and starch as binder. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The higher concentration of HPMC showed better sustained release properties than the PVP as polymer.

KEY WORDS

Pantoprazole, Delayed release tablets, HPMC, Poly Vinyl Pyrrolidone and MCC.

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INTRODUCTION[1]

A tablet is a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. The excipients include binders, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrates to ensure that the tablet breaks up in the digestive tract; sweeteners or flavours to mask the taste of bad tasting active ingredients; and pigments to make uncoated tablets visually attractive. A polymer coating is usually applied to hide the taste of the tablet's components, to make the tablet smoother and easier to swallow, to make it more resistant to the environment and extending its shelf life.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into four categories8:

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

Delayed release drug delivery systems[1,2]

The goal in designing delayed or enteric coated delivery systems is to improve the acid sensitive drugs and reduce the gastric irritation. If one were to imagine the ideal drug delivery system, two prerequisites would be required. First, it would be a single dose for duration of treatment, whether it is for days of weeks, as with infection, or for lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the drug directly to the site of action, thereby minimizing or eliminating side effects. This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body.

Advantages of delayed and sustained release drug delivery [8,10,11]

Following are the potential advantages of delayed and sustained release products

1. Enteric coatings have been applied to solid oral dosage forms to improve the chemical stability of acid-sensitive drugs, to decrease gastric irritation and to target drug release to the intestine.
2. Decreased local and systemic side effects reduced gastrointestinal irritation.
3. Better drug utilization reduction in total amount of drug used.
4. Improved efficiency in treatment, optimized therapy and more uniform blood concentration.
5. Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly and less reduction in drug activity with chronic use.

Disadvantages of delayed and sustained release drug delivery[5]

The disadvantages of delayed and sustained release drug delivery system are

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
2. Poor *in vitro – in vivo* correlation.
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
4. Reduced potential for dose adjustment of drugs normally administered in varying strengths.

MATERIALS AND METHODS

Materials

Pantoprazole, HPMC and polyvinyl pyrrolidone as polymer, Avicel PH 102 (MCC) as filler and starch as binder.

Methods

Preparation of Pantoprazole sodium sesquihydrate tablets

An ideal mixture of granules were directly punched into tablets weighing about 200 mg containing 40 mg of Pantoprazole sodium sesquihydrate, using rotary tablet compression machine using 8 mm diameter concave punches. The different batches of Pantoprazole tablets were collected and stored in air tight containers.

The tablets prepared are undergo precompression and post compression parameters like Angle of Repose, Hausner's ratio, CI, Thickness, Hardness and Invitro Dissolution etc.

Enteric coating of Pantoprazole sodium sesquihydrate compressed tablets by dipping method

The compressed tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate or Drug coat L100) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for its weight variation, thickness,

uniformity of drug content and in vitro dissolution study.

Physicochemical evaluation of coating films

The same polymer solution was used to prepare the polymeric films and was subjected for

- Film thickness
- Film weight
- Film solubility

In vitro drug release studies[13]

USP dissolution apparatus type II was employed to study the in vitro drug release from various formulations prepared. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 10 h. The tablet was kept in to the basket. The temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV- visible spectrophotometer at 283.5 nm (pH 1.2) and at 288.5 nm (pH 6.8) against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time. The results are tabulated in the table no.

Release kinetics

Data obtained from the in vitro release studies of cellulose acetate phthalate coated Pantoprazole sodium sesquihydrate tablet formulations were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsmeyer- Pappas model.

Drugs Polymer Interaction Study by FTIR spectrophotometer

FT-IR spectroscopy study was carried out separately to find out, the compatibility between the drug Pantoprazole and the polymers hydroxypropyl methylcellulose, Cassava starch, polyvinyl pyrrolidone used for the preparation of tablets. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer.

Summary

Pantoprazole sodium sesquihydrate granules were prepared by wet granulation method using different concentration of HPMC and PVP as release retarding polymers, Avicel PH 102 (MCC) as filler and starch paste (5%) as binding agent. Magnesium Stearate and talc were used as a glidant and lubricant respectively.

The granules were evaluated for percentage yield, mean particle size, angle of repose, bulk density, tapped density and compressibility index. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility index and angle of repose signify good flowability of the granules for all the batches. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets. The results were tabulated in the Table No. 4.

The compressed tablets were evaluated for its hardness, weight variation, content uniformity and friability. These are showed in Table No.3.

The in vitro dissolution studies were carried out for compressed and coated tablets using USP dissolution apparatus type II. The cumulative percentage of drug release from the tablets varied and depends on the type of polymer used and its concentration. The Formulation-1(F1) was not shown any sustained release. This can be explained by the fact that Formulation-1(F1) was prepared by omitting the release retarding polymer. The results were tabulated in Table No. 5 and 6.

The IR studies show there is no interactions between the pure drug and the polymers used in the formulations.

Table No.1: Spectrophotometric data for standard graph of Pantoprazole sodium sesquihydrate in pH 1.2 acidic buffer

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.062
3	4	0.128
4	6	0.199
5	8	0.255
6	10	0.317

Table No.2: Spectrophotometric data for standard graph of Pantoprazole sodium sesquihydrate in pH 6.8 phosphate buffer

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.058
3	4	0.144
4	6	0.183
5	8	0.245
6	10	0.306
7	12	0.371

Table No.3: Physicochemical evaluations of Pantoprazole sodium sesquihydrate tablets

Batch code	Parameter			
	Hardness (kg/cm^2) *	Friability(%)**	Average weight(g) ***	Drug content (%) ****
F_1	8.40 ±0.02	0.011 ±0.021	0.201 ±0.02	98.85 ±0.21
F_2	5.80 ±0.12	0.012 ±0.015	0.199 ±0.12	97.71 ±0.15
F_3	6.20 ±0.35	0.016 ±0.025	0.204 ±0.009	96.85 ±0.34
F_4	4.9 ±0.21	0.05 ±0.034	0.203 ±0.024	94.57 ±0.18
F_5	4.93 ±0.15	0.023 ±0.015	0.208 ±0.031	96.85 ±0.16
F_6	4.73 ±0.42	0.024 ±0.017	0.205 ±0.015	97.14 ±0.09

F_7	5.66 ±0.17	0.017 ±0.035	0.199 ±0.019	96.01 ±0.15
F_8	6.2 ±0.16	0.24 ±0.026	0.209 ±0.008	95.42 ±0.38
F_9	5.60 ±0.24	0.11 ±0.016	0.198 ±0.007	92.28 ±0.42
F_{10}	5.73 ±0.25	0.11 ±0.016	0.203 ±0.004	98.55 ±0.48
F_{11}	5.12 ±0.34	0.090 ±0.026	0.202 ±0.016	95.24 ±0.36

Table No.4: Physicochemical evaluations of Pantoprazole sodium sesquihydrate granules

Batch code	**Parameter**						
	Yield(%)	**Mean particle size(mm)**	**Bulk density (gm/ml)**	**Tapped density (gm/ml)**	**Carr's Index (%)**	**Hausner's Ratio**	**Angle of repose (θ)**
F_1	97.52	0.498 ±0.05	0.302 ±0.03	0.318 ±0.03	5.03 ±0.16	1.052 ±0.02	25.75 ±0.24
F_2	95.25	0.555 ±0.12	0.320 ±0.04	0.340 ±0.02	5.88 ±0.15	1.062 ±0.05	26.85 ±0.15
F_3	95.45	0.534 ±0.06	0.362 ±0.05	0.391 ±0.04	7.41 ±0.13	1.080 ±0.03	26.45 ±0.17
F_4	94.02	0.541 ±0.05	0.357 ±0.03	0.395 ±0.05	9.62 ±0.10	1.106 ±0.04	28.23 ±0.25
F_5	92.45	0.524 ±0.15	0.345 ±0.04	0.387 ±0.02	10.85 ±0.18	1.121 ±0.04	27.52 ±0.12
F_6	92.53	0.525 ±0.06	0.348 ±0.04	0.389 ±0.06	10.53 ±0.20	1.117 ±0.06	29.12 ±0.26
F_7	91.82	0.534 ±0.12	0.307 ±0.02	0.342 ±0.03	10.23 ±0.16	1.114 ±0.02	30.27 ±0.14
F_8	94.66	0.548 ±0.11	0.296 ±0.05	0.325 ±0.04	8.92 ±0.05	1.097 ±0.08	27.56 ±0.21
F_9	96.86	0.488 ±0.05	0.418 ±0.03	0.482 ±0.06	13.27 ±0.06	1.153 ±0.06	28.07 ±0.24
F_{10}	97.12	0.562 ±0.10	0.307 ±0.02	0.375 ±0.05	18.13 ±0.22	1.221 ±0.07	26.84 ±0.14
F_{11}	94.30	0.570 ±0.12	0.384 ±0.02	0.456 ±0.06	15.78 ±0.14	1.187 ±0.02	25.47 ±0.12

Table No.5: *In vitro* drug release profile of enteric coated Pantoprazole sodium sesquihydrate tablet formulations (F2 to F6)

pH	Time(h)	Cumulative Percentage of Drug Release				
		ECF2	ECF3	ECF4	ECF5	ECF6
1.2	0.5	0	0	0	0	0
	1.0	0.64	0.52	0.49	0.49	0.42
	1.5	1.01	1.21	1.17	1.19	1.15
	2.0	1.65	1.43	1.77	1.41	1.46
6.8	3	15.40	14.02	17.27	16.44	16.38
	4	25.93	26.12	30.28	29.52	28.46
	5	36.71	38.64	45.19	42.24	43.43
	6	52.07	54.92	55.55	53.14	52.84
	8	68.48	70.89	68.60	67.67	65.02
	10	82.90	83.76	85.72	84.40	83.71
	12	97.54	99.07	97.97	96.42	96.34
	14	97.56	99.37	97.99	96.51	96.40

Table No.6: *In vitro* drug release profile of enteric coated Pantoprazole sodium sesquihydrate tablet formulations (F7 to F11)

pH	Time(h)	Cumulative Percentage of Drug Release				
		ECF7	ECF8	ECF9	ECF10	ECF11
1.2	0.5	0	0	0	0	0
	1.0	0.69	0.58	0.63	0.74	0.07
	1.5	0.97	0.84	1.21	1.14	1.17
	2.0	1.56	1.43	1.67	1.8	1.6
6.8	3	18.21	18.45	17.54	16.21	16.61
	4	29.36	25.98	29.90	25.16	24.31
	5	43.11	40.41	42.61	41.14	42.14
	6	58.56	53.03	57.99	52.06	51.05
	8	75.94	70.12	75.51	73.47	72.75
	10	87.90	81.97	85.76	87.91	85.98
	12	97.67	90.02	97.75	97.07	96.52
	14	97.85	98.87	97.79	97.14	96.61

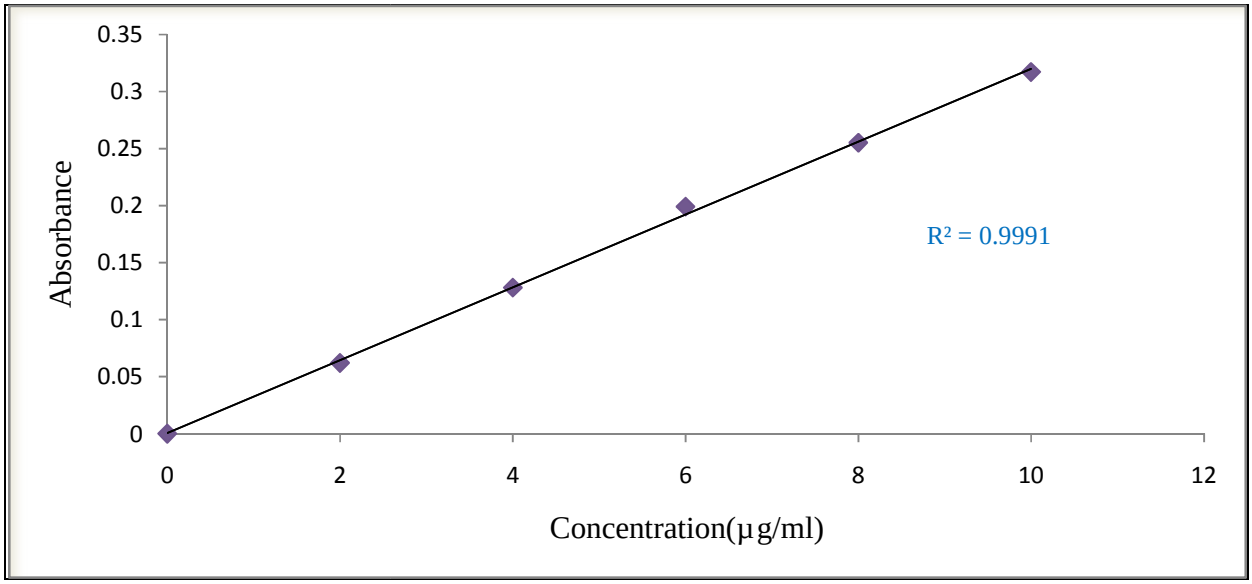

Figure No.1: Standard curve of Pantoprazole sodium sesquihydrate in pH 1.2 acidic buffer

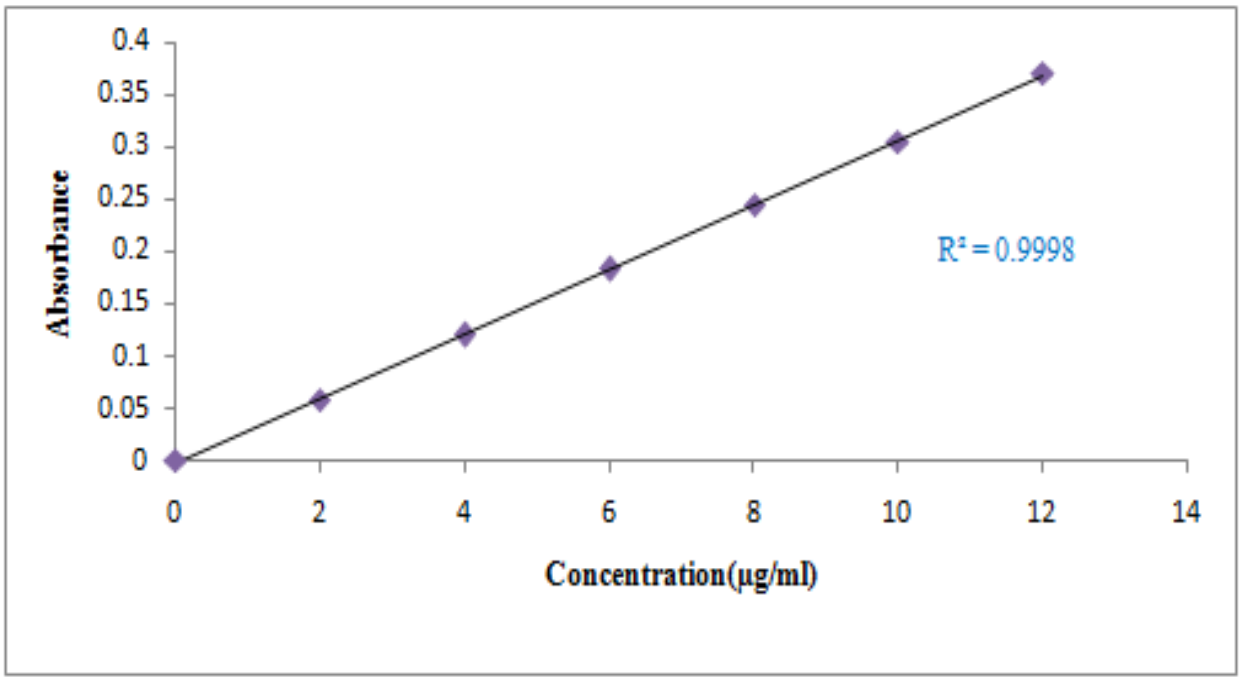

Figure No.2: Standard curve of Pantoprazole sodium sesquihydrate in pH 6.8 phosphate buffer

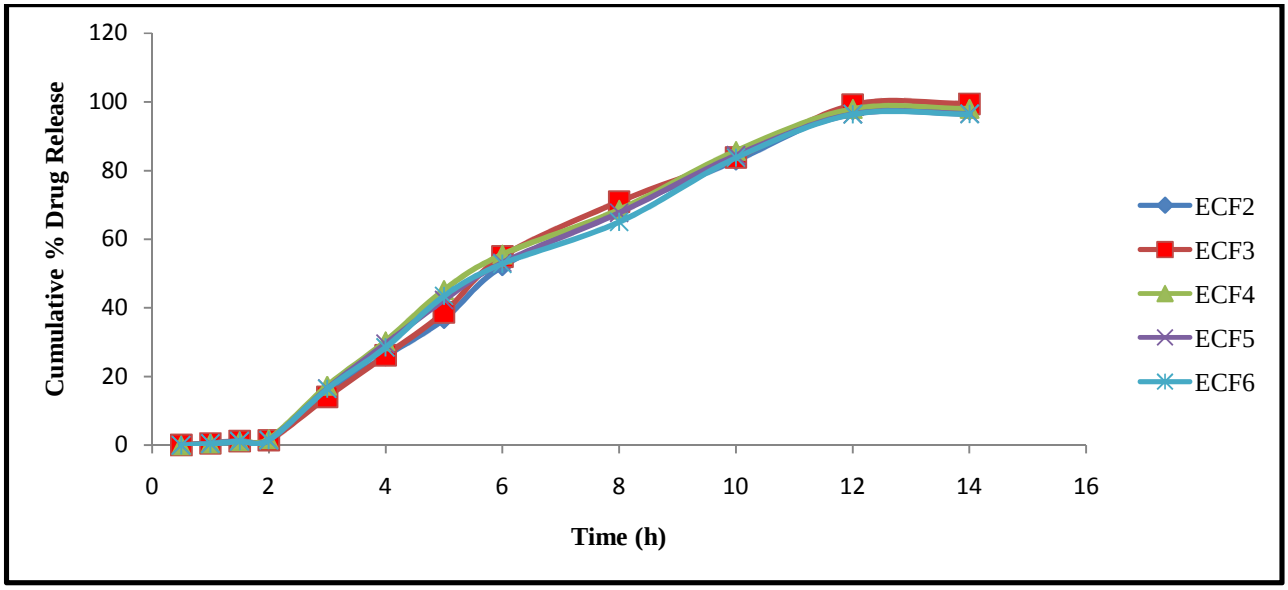

Figure No.3: *In vitro* drug release profile of enteric coated Pantoprazole sodium sesquihydrate tablet formulations (ECF2 to ECF6)

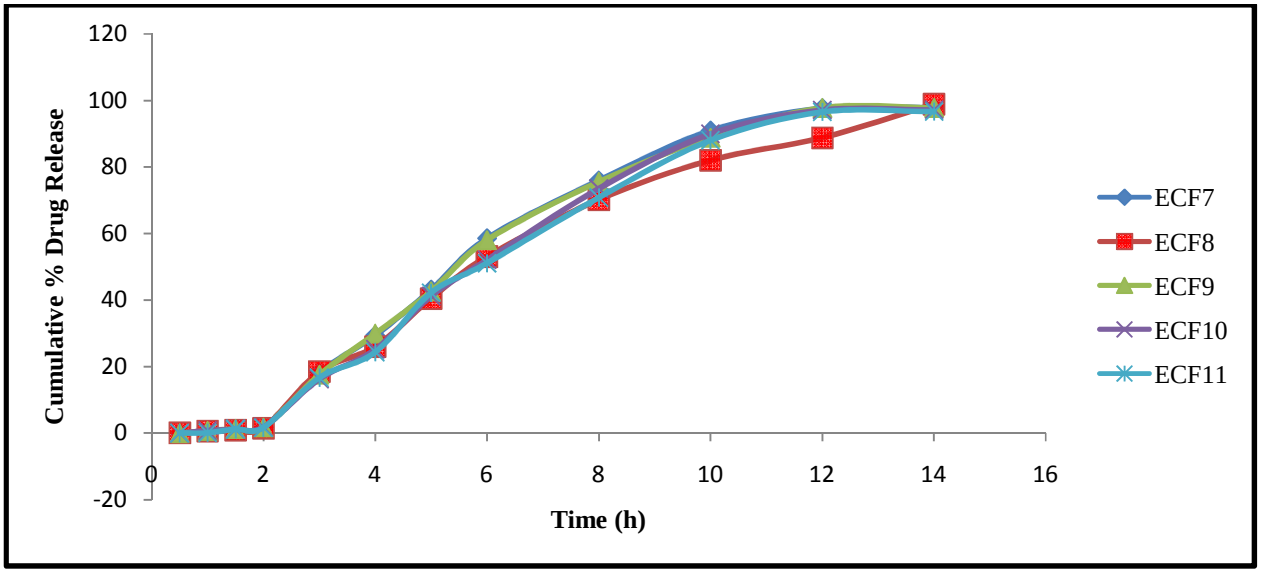

Figure No.4: *In vitro* drug release profile of enteric coated Pantoprazole sodium sesquihydrate tablet formulations (ECF7 to ECF11)

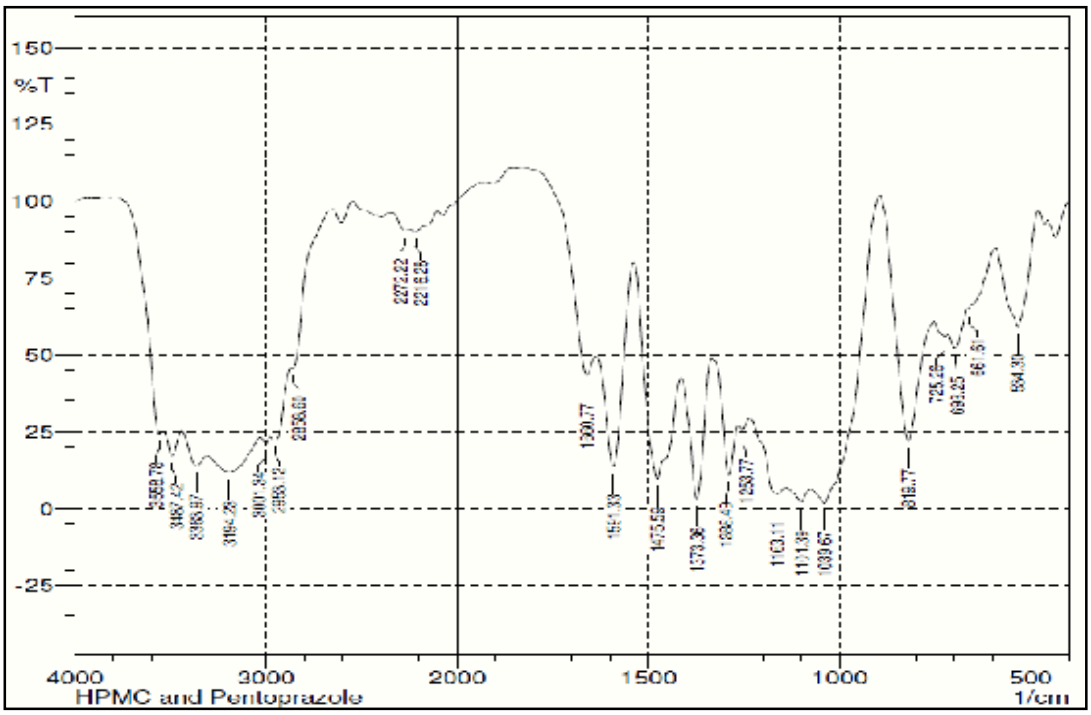

Figure No.5: IR spectrum of physical mixture of Pantoprazole sodium sesquihydrate and HPMC

CONCLUSION

Pantoprazole in combination with HPMC and PVP formulated Delayed release formulations. FT-IR spectral studies indicated there was no interaction between Pantoprazole and polymers used. Pantoprazole delayed release tablets were prepared with combination of these polymers and evaluated. From the results, it was observed that all parameters were suitable for maximum stability of the prepared formulations. The ECF3 shows the maximum drug release.

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