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Formulation and Evalution of Fast Dissolving Tablet Containing Proton Pump Inhibitor

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ABSTRACT:
Pantoprazol is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of Peptic ulcers, Gastro-oesophageal reflux disease (GERD) Esophagitis, Zollinger- Ellison syndrome and other GI hyper secretory disorders.

It has poor bioavailability (~50%) and aqueous solubility, thus it is absorption and dissolution rate limited, delaying its onset of action. Pantoprazol is available as conventional tablet in the market and many patients find it difficult to swallow these, especially pediatric and geriatric subjects which results in high incidence of non-compliance and ineffective therapy. In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets of Pantoprazol using two different Suprdisintegrant viz. Carboxyl Methyl Cellulose (CMC) and Sodium starch glycolate (SSG) by direct compression method.

Keywords: Pantoprazole, Suprdisintegrant, Sodium starch glycolate, microcrystalline cellulose, Magnesium statedirectcompression.

I. INTRODUCTION:

A drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in man and animals. Drugs are rarely administered in their original pure state. They are administered in different dosage forms after converting them into a suitable formulation. Every dosage form is a combination of the drug and different kind of components called "additives". The additives are used to give a particular shape to the formulation, to increase its stability, palatability and to give more elegance to the preparation [1].

These difficulties have provided the impetus for exploring alternative routes for the delivery of drugs, which include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Transmucosal routes of drug delivery which is comprised of the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity offer excellent opportunities and potential advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and, depending on the particular drug, a better enzymatic flora for drug absorption [2].

Recently Fast Dissolving Drug Delivery Systems have started gaining popularity and acceptance as New Drug Delivery Systems [3].Pantoprazol is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of Peptic ulcers, Gastro-oesophageal reflux disease (GERD) Oesophagitis,Zollinger-Ellison syndrome and other GI hypersecretory disorders.

It has poor bioavailability (~50%) and aqueous solubility, thus it is absorption and Dissolution rate limited, delaying its onset of action. Pantoprazol is available as conventional tablet in the market and many patients find it difficult to swallow these, especially pediatric and geriatric subjects which results in high incidence of non-compliance and ineffective therapy. In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets of Pantoprazol using two different superdisintegrants viz. Carboxyl Methyl Cellulose (CMC) and Sodium starch glycolate (SSG) by direct compression method. (4)

II. MATERIALS AND METHODS:

Drug pantoprazol was obtained as a gift sample from Estrellas life sciences Ahmedabad. Sodium starch glycolate, microcrystalline cellulose,were obtained from Oxford Laboratory Mumbai.Magnesium state obtained from Loba chemicals.

III. EXPERIMENTAL WORK

Preformulation Parameters

Physical evaluation

A small quantity of drug was taken on butter paper and it was observed visually for colour and odour.

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Solubility:
Solubility may be defined as spontaneous interaction between two or more substances to form a homogeneous mixture .Qualitative determination of solubility of drug was calculated in different solvent water, methanol, ethanol, 0.1 N HCl, Phosphate buffer (pH 6.8).

Table no.1: Solubility profile according to BP

Descriptive term	Part of solvent required for part of solute
Very soluble	Less than 1ml
Freely soluble	From 1ml to 10ml
Soluble	From 10 to 30ml
Sparingly soluble	From 30 to 100ml
Slightly soluble	From 100 to 1000ml
Very slightly soluble	From 1000 to 10000ml
Practically insoluble	From 1000 or more

Melting Point

The melting point was determined by the capillary method using melting point apparatus. In this method one end of capillary tube was fused by heating it on Bunsen burner. Then capillary tube was filled by pressing the open end gently into pantoprazol (pure drug) sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot behind the eye-piece in the melting point apparatus. In other slot of melting point apparatus place a thermometer. Make sure the unit is plugged into the set to zero and then turn it on.

Drug excipients compatibility by FT-IR

FTIR spectra of the selected formulations were taken and compared with the spectrum of pure drug. The characteristic peaks of drug were obtained by scanning in the range of 400-4000 cm-1 by using the Fourier transform spectrophotometer. FT-IR is a technique used to determine the chemical interaction between drug and polymers**.**

Estimation of Absorption Maxima of Pantoprazole in phosphate buffer (pH 6.8)

Potassium Dihydrogen phosphate 11.45gm was taken and transfer in a 1000 ml volumetric flask. This was dissolved by adding a little volume of distilled water. To it added 28.80gm of disodium hydroxide phosphate and dissolve. The final volume was made up to 1000 ml with distilled water to get a phosphate buffer solution pH 6.8 according to IP 1996.

The drug (pantoprazol) was accurately weighed 20mg using the digital weighing balance and the drug was transferred to the 100ml volumetric flask. This was dissolved by adding a 20ml of phosphate buffer pH 6.8 to get a stock solution- From above sto0.ck solution pipette out 1ml of the solution and dilute it up to 20 ml by adding phosphate buffer pH6.8 to obtain sub stock solution. From this sub stock solution pipette out 0.2ml, 0.3ml, 0.4ml, 0.5ml and 1ml and dilute it up to 10ml by adding phosphate buffer pH6.8 to obtain required concentrations of 1µg/ml, 2µg/ml, 3µg/ml, 4µg/ml, 10µg/ml, respectively.

Formulation procedure of fast dissolving tablet

Fast dissolving tablets consisting of pantoprazole were prepared by direct compression method. In these preparation different ratios of sodium starch glycolate (SSG), Carboxy Methyl Cellulose (CMC) was taken. Microcrystalline cellulose was used as superdintegrant.Carboxy Methyl Cellulose was used as a sustain release polymer and aspartame was used as a sweetening agent (taste masking agent), vanilla essence was used as flavouring agent, Mannitol as diluent. Magnesium Stearate and Talc as lubricant and glidant. The formulations composition is shown in table no 2. The drug and polymer mixture was prepared by mixing the drug and all other accurately weighed ingredients which are triturated in a mortar and pestle for about 15-20 min. The mixture (250mg) was then, compressed using 8mm diameter die in a tablet compression machine (Shakti ten station punching tablet machine, India)**(5).**

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Table no 2: Composition of fast dissolving pantoprazol tablet

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Pantoprazol	20mg	20mg	20mg	20mg	20mg	20mg
2	Sodium starch glycolate	10mg	35mg	34.5mg	0	0	0
3	Carboxy Methyl Cellulose	0	0	0	10mg	35mg	34.5mg
4	Microcrystalline cellulose	185.5mg	183mg	170.5mg	195.5mg	183mg	170.5mg
5	Magnesium stearate	1.5mg	2mg	2mg	2mg	2mg	2mg
6	Mannitol	20mg	20mg	20mg	20mg	20mg	20mg
7	Talc	6mg	6mg	6mg	6mg	6mg	6mg
8	Aspartame	1mg	1mg	1mg	1mg	1mg	1mg
9	Vanilla flavour	Qs	Qs	Qs	Qs	Qs	Qs
	Total Weight (mg)	250mg	250mg	250mg	250mg	250mg	250mg

Evaluation parameter:

Hardness:

Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of FDTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

Friability:

Friability Attempts for decreasing the disintegration time increase the friability of FDTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 50 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as: [6]

% Friability = 1- (loss in weight / Initial weight) X 100

Weight variation:

Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 2007). 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 10 of tablets differ by more than the percentage listed in table no tablets differ in weight by more than double that percentage**.**

Thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using Vernier caliper.

Wetting Time

A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the centre of the upper surface of the tablet was noted as wetting time.

Disintegration Time

Six tablets were placed in each tube of disintegration apparatus. Buffer solution of pH 6.8 was placed in the basket and temperature was maintained at 37°C ± 2°C.pH of the solution was checked by pH meter. The time taken by tablets for complete disintegration was recorded.

In – Vitro Dissolution Time

In vitro dissolution study of fast mouth dissolving tablets pantoprazol was performed using phosphate buffer (pH 6.8) maintained at a temperature of 37 ± 0.5oC in USP II dissolution

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test(Electro lab TDT, Mumbai, India. paddle type) apparatus and at rotation speed of 50 rpm. At a predetermined time interval, samples were withdrawn and filtered through Whitman filter paper. Absorbance of suitably diluted samples was determined by UV spectrophotometer at 392 nm and the percentage of drug release was calculated. The dissolution experiments were conducted in triplicate.

IV. RESULTS AND DISCUSSION:

Colour:

Pantoprazol is yellowish powder.

Odour:

The drug powder was found to be odourless.

Melting point:

The melting point of drug pantoprazole was found to be155^{0}C.

Solubility

The solubility of drug Pantoprazol is as follows: It is practically insoluble in water, It is slightly soluble in Ethanol and Methanol, It is very Sparingly solublein 0.1 N NaOH, It is Freely soluble in Phosphate buffer.

Drug excipients compatibility by FTIR –

Drug-excipients compatibility study was performed by FTIR technique. The IR spectra of the solution were taken, which indicate no interaction between pantoprazol and polymers FT-IR spectrum of drug and polymer mixture shows characteristic peaks at3180cm_1 indicates the presence of carboxylic group, 1488 cm_1 exhibits alkenes, 1453cm_1 indicates the presence of aromatic ring, 1359cm_1 exhibits carboxylic acids, 1298cm_1 indicates alkyl halides, 1226cm_1 indicate ester, 1162cm_1 indicates alkyl halide, and 1110cm_1 indicates amine oxide. From the spectral study it was observed that there was no significant change in the peaks of drug polymer mixture. Hence, no specific interaction was observed between the drug and the polymers used in the formulations

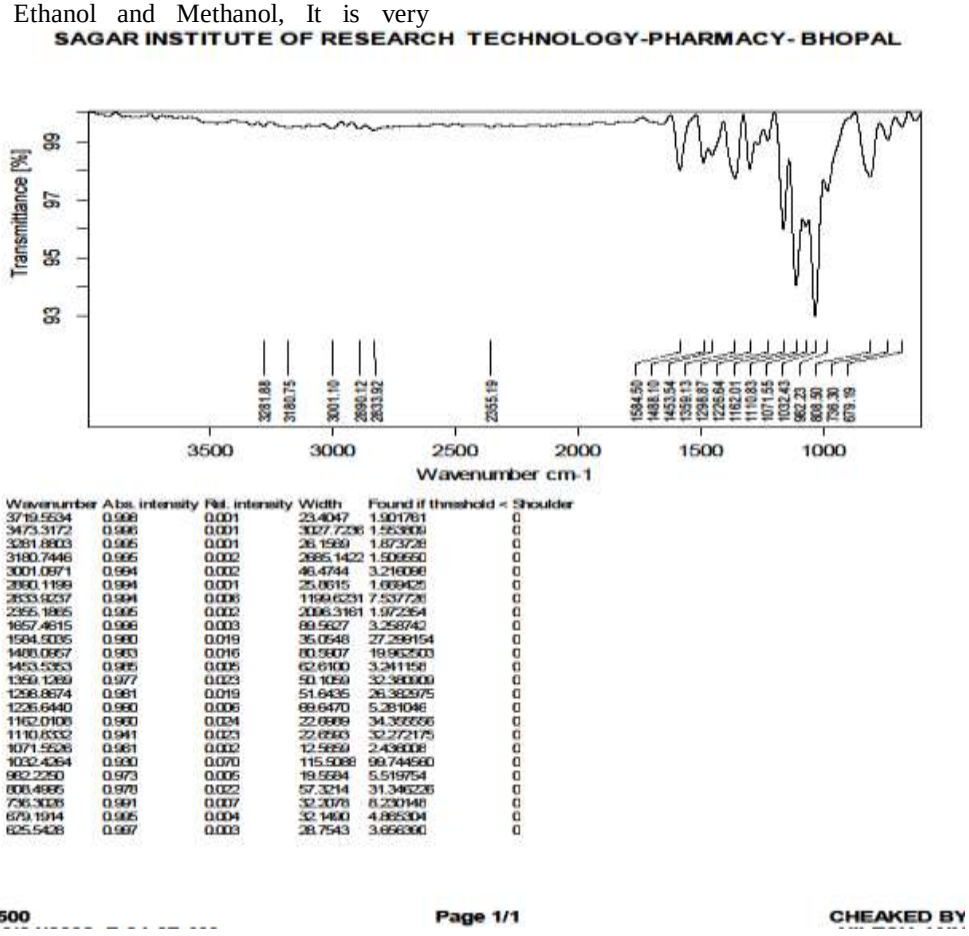

Fig 1: FTIR of pantoprazol

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UV estimation of drug pantoprazol:

Table no 3: calibration curve of Pantoprazol in phosphate buffer6.8pH

S.no	Conc (µg/ml)	Abs(at 392nm)
1	0	0
2	0.5	0.024±0.023
3	1	0.19±0.54
4	1.5	0.102±0.041
5	2	0.138±0.38
6	2.5	0.161±0.16

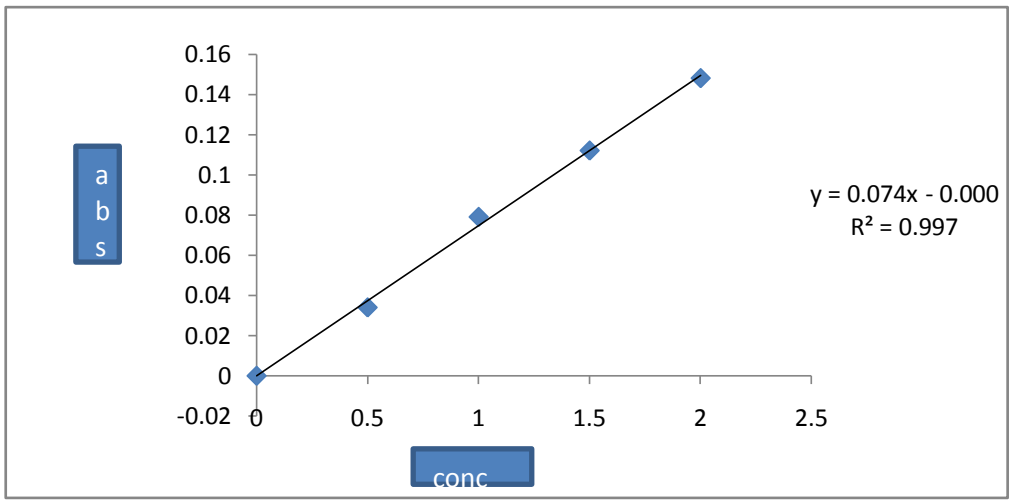

Fig no 2: Calibration curve of pantoprazol in phosphate buffer pH6.8

Flow properties of drug

Table no 4: Flow Properties of pantoprazole

Drug	Bulk density (g/cm3)	Angle of repose	Tapped density g/cm3	Hauser's ratio%
Pantoprazole	0.15±0.03	32.23±035	0.22±0.04	0.83±0.02

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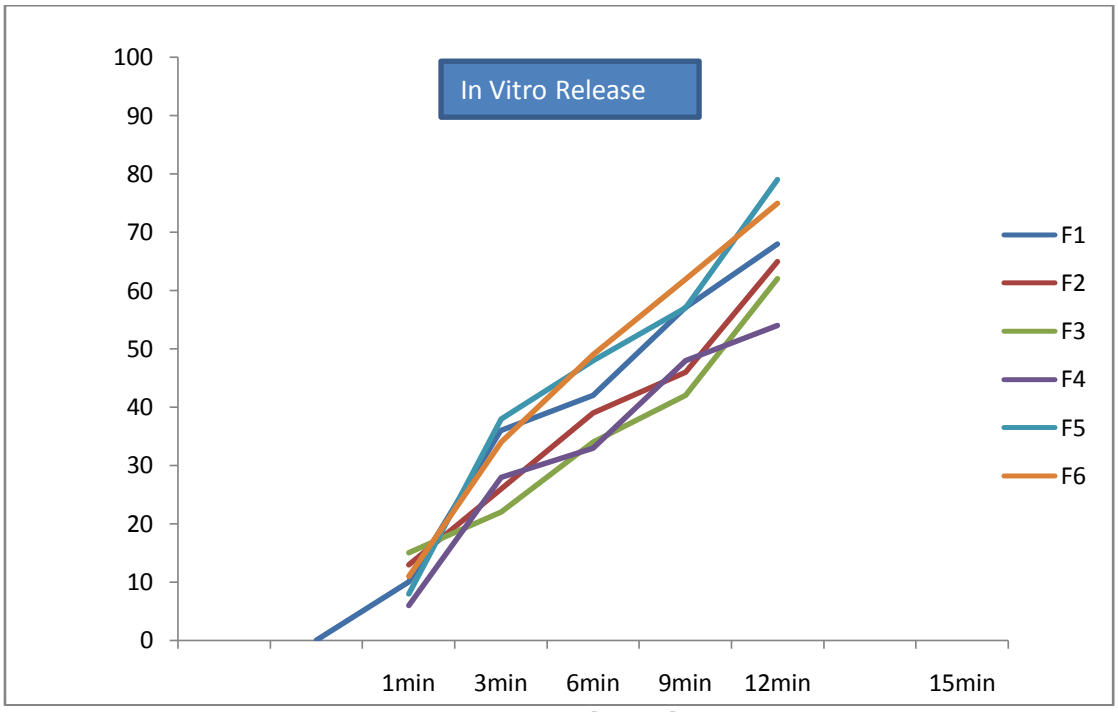
Table 8: Evaluation of various Parameters

Formulation	Friability (%)	Weight Variation (mg) ±S.D	Wetting Time (sec) ±S.D(n=3)	Hardness	Thickness	Drug content
F1	Pass	247±1.79	9.50±0.24	3.0±0.27	3.42±0.023	83.62±0.03
F2	Pass	245±1.13	9.01±0.23	3.1±0.23	3.43±0.021	84.68±0.23
F3	Pass	248±0.89	8.01±0.25	3.2±0.53	3.64±0.034	86.09±0.36
F4	Pass	246±0.14	8.00±0.02	3.4±0.31	3.76±0.024	88.25±0.12
F5	Pass	241±0.98	7.50±0.27	3.8±0.8	3.82±0.013	93.06±0.23
F6	Pass	252±0.21	7.55±0.06	3.5±0.25	3.23±0.025	90.24±0.36

In vitro drug release:-

Table no 3: in vitro drug release

S.NO	TIME	F1	F2	F3	F4	F5	F6
		%Drug Release					
1	5min	10	12	15	17	25	20
2	10min	15	18	22	25	28	26
3	15min	20	25	30	45	48	47
4	20min	22	32	38	55	65	62
5	25min	27	42	45	62	75	85
6	30min	30	50	55	70	95	90



Figno2: in vitro drug release

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V. SUMMARY:-

Pantoprazol is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of Peptic ulcers. It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min.

Most of the MDTs include certain super disintegrant and taste masking agents.The mouth (oral cavity, buccal cavity) is where food enters the digestive tract. All prepared mouth dissolving tablets showed an acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeia specification.

No specific interaction was observed between the drug and the polymers used in the formulations.

Pantoprazol is yellowish powder. The melting point of drug was found to be 155^0C.Fast dissolving tablets of pantoprazol were prepared by direct compression method using. Carboxyl Methyl Cellulose (CMC) and Sodium starch glycolate (SSG) as superdisintegrants. The data obtained of post – compression parameters such as hardness, thickness, friability, weight variation, amount of drug content, disintegration tie such and water absorption ratio are shown in table.

The in-vitro cumulative drug release profile of formulation F1, F2, F3, F4,F5 and F6 owed in the range of 83.62% to 93.06%, respectively in 12 hrs. Among these, the formulation F5 was found to release the highest percentage of drug (93.06±0.23%). The dissolution profile of all factorial batches were fitted to various models such as kinetic of drug.

Difficulty in the swallowing of conventional tablets by geriatric and pediatric patients may lead to poor patient compliance and ineffective therapy. To overcome such problems, a new dosage form has been introduced, known as fast- mouth dissolving tablets.

This new dosage form provided the benefits of enhanced patient compliance, rapid onset of action, and increased bioavailability. The novelty in this study is demonstrated in formulating pantoprazole into fast-dissolving tablets. It is likely that a super disintegrating medium, break, and dissolve quickly, resulting in fast release and rapid dissolution of the drug, and hence improved absorption and bioavailability.

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