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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF PANTOPRAZOLE

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ABSTRACT

In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets, also called as Oral disintegrating tablets of Pantoprazole using four different Superdisintegrants like Croscarmellose sodium, Sodium starch glycolate (SSG), Micro crystalline cellulose and cross povidone by direct compression method. Tablets and capsules which need rapid disintegration, the inclusion of the right disintegrant is a prerequisite for optimal bioavailability. Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1- 10 % by weight relative to the total weight of the dosage unit. The present study comprises the various kinds of superdisintegrants which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance. Evaluation of the tablets showed that all the tablets were found to be within official limits and the disintegration time for the formulations ranged from 15 s to 25 seconds.

***Keywords*:** Pantoprazole, superdisintegrants, croscarmellose sodium, sodium starch glycolate, microcrystalline cellulose and cross povidone, direct compression method.

INTRODUCTION:

Oral drug delivery system is the most convenient and widely accepted route of administration for various therapeutic agents. Among many oral drug delivery systems, oral disintegrating drug delivery systems have gained importance over past 3 decades. Other than other conventional dosage forms like capsules oral disintegrating tablets are defined as one of the sophisticated novel drug delivery systems that have medicinal substances which dissolve or disintegrate rapidly in the mouth without water [2] or chewing. Oral disintegrating tablets are suitable for patients who have dysphasia [3], paediatric, geriatric [1] and psychiatrics. It is also suitable for patients with nausea, vomiting and motion sickness.

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Other synonyms for oral disintegrating tablets are orodispersible tablets, mouth dissolving tablets, quick dissolving tablets, fast melt tablets. Oral disintegrating tablets dissolve within 60 seconds when placed in mouth. Oral disintegrating tablets works on the mechanism that the mucous membrane absorbs the active ingredients present in the tablet to mouth and then enter into blood stream. Oral disintegrating tablets are effective when they show increased bioavailability and fast onset of action.

Criteria for development of oral disintegrating tablets:

1. Oral disintegrating tablets should dissolve or disintegrate in the mouth in matter of seconds without water.

2. Oral disintegrating tablets should leave minimal or no residue in mouth after administration.

3. Properties of drug and excepients should not affect the nature of the drug delivery system.

4. Exhibit low sensitivity to environmental conditions such as humidity and temperature.

5. Should be compatible with pleasant mouth feel.

Advantages of oral disintegrating tablets:

1. It may produce rapid onset of action [4-9] by rapid dissolution of drug and absorption.

2. Good mouth feel property of oral disintegrating tablets helps to change the psychology of medication as bitter pill particularly in paediatric patients.

3. Convenience of administration and actuate dose as compared to liquids.

4. Ease of administration to patients who refuse to swallow a tablet such as paediatric, geriatric, mentally ill, disabled and uncooperative patients.

ODT mechanism:

1. Tablet containing rapidly disintegrating agents when come in contact with saliva of oral cavity causes disintegrating agents to swell and create channels/pores for saliva to enter inside the tablet creating swelling and pressure.

2. Tablet disintegrates rapidly in mouth. Resins and other sweeteners mask the presence of bitter taste.

3. Physicochemical and biopharmaceutical properties of drug substance aids in solubilisation and its absorption across gastro intestinal tract.

Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1- 10 % by weight relative to the total weight of the dosage unit. The present study comprises the various kinds of superdisintegrants which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance. The disintegration with the help of superdisintgrants occurs by five steps of mechanism processes like swelling, wicking, deformation, particle repulsive forces and enzymatic reaction. Some of the superdisintegrants used in this study are cross carmellose sodium, sodium starch glycolate, micro crystalline cellulose and cros povidone.

MATERIALS AND METHODS:

Pantoprazole was obtained from matrix lab (Hyderabad, A.P.).All the other reagents and chemicals are of analytical grade.

Preformulation studies:

Compatibility studies

Fourier transform infrared (FT-IR) spectra were obtained. The spectra were recorded in a thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions.

Calibration curve of pantoprazole:

10mg of pantoprazole is dissolved in 100ml mixture of phosphate buffer and further dilutions were made by using phosphate buffer to obtain concentrations ranging 2,4,6,8 and 10µg/ml. The absorbance of solution was measured at 292 nm using UV Visible Spectrophotometer. The readings obtained are tabulated in table and the graph was given in graph.

Angle of repose: Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the equation.

$$\mathbf{Tan\ \Theta = h/r}$$

Where h= height of cone and r = radius cone base respectively.

Angle of Repose less than 30 ° shows the free flowing of the material.

Bulk density: Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density can be calculated by using formula.

Bulk density = W.t of the powder / Vol. of the packing.

Tapped density: It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be Calculated by using formula

Tapped Density = (Wt of the powder / vol. of the tapped packing)

Compressibility index: The Compressibility Index of the blends is determined by compressibility index. Compressibility Index can be calculated by using formula:

Compressibility Index (%) = [(TD-BD) X 100] / TD]

Hausner's ratio: A similar index to indicate the flow properties can be defined by Hausner's ratio. Hausner's ratio can be calculated by using formula:

Hausner's ratio = (Tapped density x 100)/ (Poured density)

Hausner's ratio <1.25 – Good flow = 20%

Compressibility index

1.25 – Poor flow =33%

Void Volume: The volume of the spaces is known as the void volume "V" and is given by the formula

V= Vb – Vp

Where, Vb = Bulk volume (volume before tapping)

Vp = True volume (volume after tapping)

Preparation of oral disintegrating tablets:

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution. Superdisintegrants are newer substances which are more effective at lower

concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs. The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble superdisintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like Crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants [10, 11]

Four formulations are prepared by direct compression method. In first formulation drug is blended with required amount of sodium starch glycolate, microcrystalline cellulose, mannitol, spray dried lactose, saccharin sodium and name is as F_1.A required amount of drug and crospovidone, microcrystalline cellulose, mannitol, spray dried lactose and saccharin sodium are blended and name it as F_2. A required amount of drug, sodium starch glycolate, micro crystalline cellulose, mannitol, spray dried lactose, saccharin sodium are blended in mortar and pestle and name it as F_3. A required amount of drug, croscarmellose sodium, microcrystalline cellulose, mannitol, spray dried lactose, saccharin sodium are added in geometric method and blended and name it as F_4.

EVALUATION OF ORAL DISINTEGRATING TABLETS:

Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 10 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation [12].

Hardness: The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc [12].

Friability test: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. Dedust the all tablets and weigh again. The percentage of friability can be calculated using the formula [12].

$$\% \text{ Friability} = [(W_1-W_2)100]/W_1$$

Where, W_1= Weight of tablet before test,

W_2 = Weight of tablet after test

Wetting time: The wetting time of the tablets is measure by using a simple procedure. Place the five circular tissue papers of 10 cm diameter in a petridish containing 0.2% w/v solution (3ml). A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

Water absorption ratio: A small piece of tissue paper folded twice is placed in a small petridish containing 6 ml of water. Put a tablet on the paper and the time required for complete wetting is measured. The wetted tablet is then reweighed. Water absorption ratio, R is determined by using following formula [13].

$$R = 100 \times W_a - W_b / W_b$$

Where, Wa is the weight of tablet before water absorption

Wb is the weight of tablet after water absorption

Drug content: 10mg equivalent weight of drug formulation was dissolved in 100ml of 0.1 N Hcl which gives 100µg/ml. From this 1ml was taken and dissolved in 10ml to obtain 10µg/ml. The absorbance was measured at 292nm.

Disintegration test: The time for disintegration of ODTs is generally <1min and actual disintegration time that patience can experience ranges from 5 to 30s. The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration test for ODT should mimic disintegration in mouth with in salivary contents. The disintegration test was carried out using tablet disintegration apparatus [14].

Dissolution test: The development of dissolution methods for ODT is comparable to approach taken for conventional tablets and is practically identical when ODT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. Other media such as 0.1 N Hcl, pH 4.5 and pH 6.8 buffers should be used for evaluation of ODT in the same way as their ordinary tablet counterparts. Experience has indicated that USP 2 paddle apparatus is most suitable and common choice for dissolution test of ODT tablets, where a paddle speed of 50 rpm is commonly used. Typically the dissolution of ODTs is very fast when using USP monograph conditions. Hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets approaching or exceeding one gram and containing relatively dense particles may produce a mound in the dissolution vessel, which can be prevented by using higher paddle speeds. These two situations expand the suitable range of stirring to 25-75 rpm. The USP 1 (basket) apparatus may have certain applications for ODT but is used less frequently due to specific physical properties of tablets. Specifically tablet

fragments or disintegration tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible results in dissolution profile [14].

RESULTS AND DISCUSSION:

Evaluation for powder blends:

Angle of repose:

The powder blend of first formulation F_1 made to pass through funnel by using fixed funnel method. Angle of repose of first formulation F_1 was found to be 26.56°.Angle of repose of second formulation F_2 was found to be 24.70°.Angle of repose of third formulation F_3 was found to be 25.45°. Angle of repose of fourth formulation F_4 was found to be 29.68°.Angle of repose of formulations was found to be free flow.

Bulk density:

The powder blend of first formulation F_1 is weighed and weight is noted down. Then it is taken in a measuring cylinder and note down the volume occupied by the powder blend. Bulk density of first formulation F_1 was found to be 0.306 g/ml. Bulk density of second formulation F_2 was found to be 0.314 g/ml. Bulk density of third formulation F_3 was found to be 0.260 g/ml. Bulk density of fourth formulation F_4 was found to be 0.257 g/ml.

Tapped density:

The powder blend was taken in a measuring cylinder and initial volume was noted down. After tappings were done final volume of measuring cylinder was noted down. Tapped density of first formulation F_1 was found to be 0.325 g/ml. Tapped density of second formulation F_2 was found to be 0.33 g/ml. Tapped density of third formulation F_3 was found to be 0.2675 g/ml. Tapped density of fourth formulation F_4 was found to be 0.2769 g/ml.

Compressibility:

The compressibility index of first formulation F_1 was found to be 5.8%.Compressibility index of second formulation F_2 was found to be 4.8%.Compressibility index of third formulation F_3 was found to be 2.8%.Compressibility index of fourth formulation F_4 was found to be 7.1 %.

Hausner's ratio:

The ratio of tapped density and bulk density is hausner's ratio. Hausner's ratio of first formulation F_1 was found to be 1.062. Hausner's ratio of second formulation F_2 was found to be 1.050. Hausner's ratio of third formulation F_3 was found to be 1.028. Hausner's ratio of fourth formulation F_4 as found to be 1.077.

Void volume:

Void volume for first formulation F_1 was found to be 0.2.Void volume for second formulation was found to be F_2 was found to be 0.1.Void volume for third formulation F_3 was found to be 0.1.Void volume for fourth formulation F_4 was found to be 0.3.

10.2. Evaluation of tablets:

Hardness Test:

Hardness of first formulation F_1 was found to be 2.2.Hardness of second formulation F_2 was found to be 4.Hardness of third formulation F_3 was found to be 2.8. Hardness of fourth formulation F_4 was found to be 3.6.

Weight variation Test:

Weight variation was calculated for four formulations. First formulation F_1 was found to be 114 mg. Second formulation was found to be F_2 151 mg. Third formulation F_3 was found to be 139 mg. Fourth formulation F_4 was found to be 135mg.

Friability Test:

The friability of the tablet was determined using Roche friabilator. It is expressed in percentage (%). For first formulation F_1 was found to be 0.536. Second formulation F_2 was found to be 0.475. Third formulation F_3 was found to be 0.399. Fourth formulation F_4 was found to be 0.598.

Wetting time:

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. For first formulation F_1 was found to be 7.75 seconds. Second formulation F_2 was found to be 7.5 seconds. Third formulation F_3 was found to be 8.05 seconds. Fourth formulation F_4 was found to be 7.75 seconds.

Water Absorption ratio:

Water absorption ratio of tablets was determined. For first formulation F_1 was found to be 36.22. Second formulation F_2 was found to be 31.89. Third formulation F_3 was found to be 33.69. Fourth formulation F_4 was found to be 35.21.

***In- Vitro* Dispersion Time:**

In-vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 (simulated saliva fluid). The time for the tablet to completely disintegrate into fine particles was noted. For first formulation F_1 was found to be 14.2 seconds. For second formulation F_2 was found to be 12.54 seconds. For third formulation F_3 was found to be 14.14. For fourth formulation F_4 was found to be 9.68.

***In – Vitro* Disintegration Time:**

The disintegration time of the tablets was determined as per Indian Pharmacopoeia monograph. The test was carried out using Tablet disintegration apparatus. For first formulation F_1 was found to be 16 seconds. For second formulation F_2 was found to be 24 seconds. For third formulation F_3 was found to be 23.5 seconds. For fourth formulation was found to be 12.5 seconds.

***In – Vitro* Dissolution Studies:**

An *in-vitro* drug release study for Oral disintegrating tablets of Pantoprazole was studied using Dissolution apparatus II USP XX1 model [Paddle type] for the fabricated batches. 900ml of 0.1 N Hcl was used as the dissolution medium. The tablet was placed in the dissolution medium and rotated at a speed of 50 rpm maintained at a temperature of 37 - 0.5°C. 5ml of sample was withdrawn at periodic intervals 0, 5th, 10th, and 15th minute. 5ml of fresh dissolution medium maintained at the same temperature) was replaced after each time of withdrawal of samples. The samples were analyzed spectrophotometrically at 292 nm for the drug content against the respective buffer blank. The mean percentage of Pantoprazole released at various time intervals was calculated from standard graph and plotted against time.

Fig 1: Standard curve of pantoprazole

Concentration(µg/ml)	Absorbance
0	0.000
2	0.002
4	0.004
6	0.0065
8	0.008
10	0.010

Table no 1: Standard curve of pantoprazole

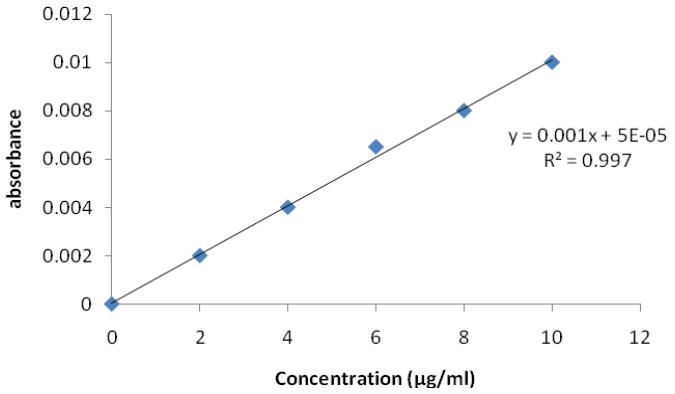


Fig 1: Standard curve of pantoprazole

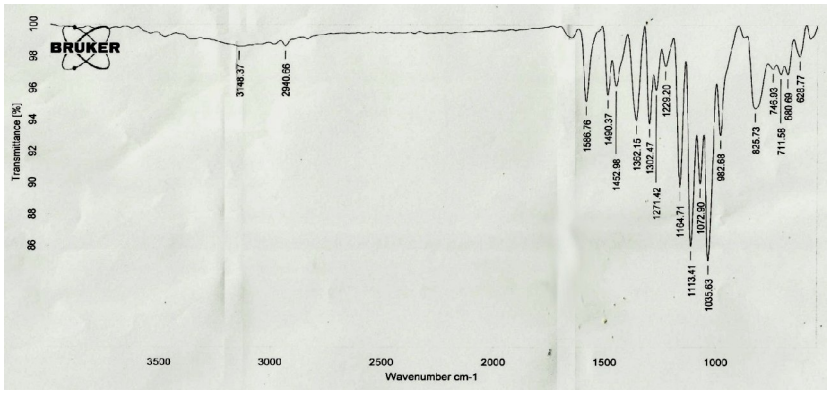


Fig.no1: FTIR spectrum of pantoprazole

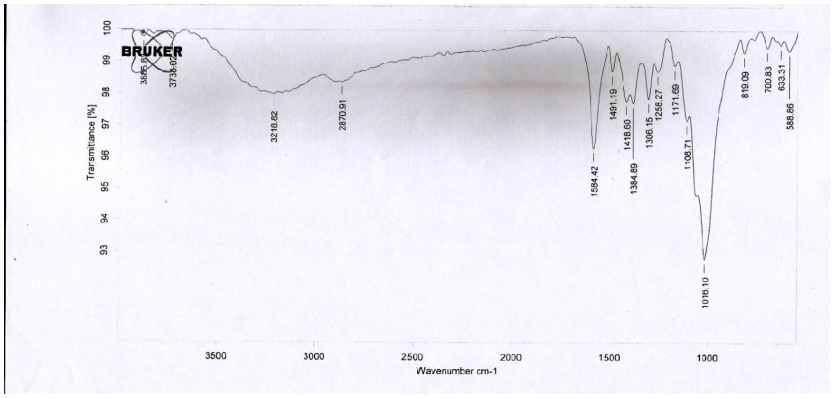


Fig No: 2 FTIR spectra of Pantoprazole and sodium starch glycolate

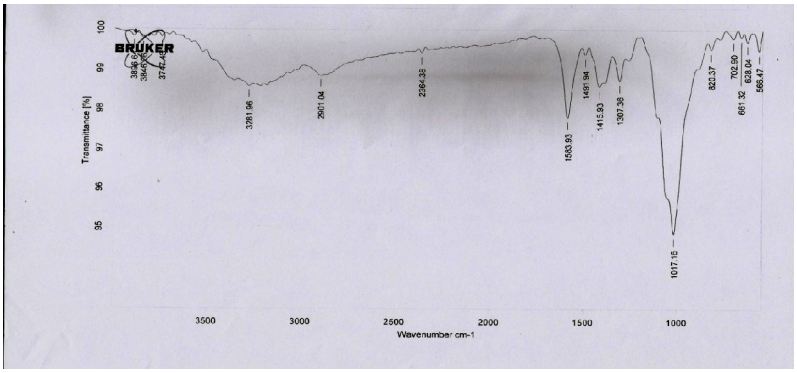


Fig No: 3 FTIR spectra of formulation pantoprazole and crosspovidone

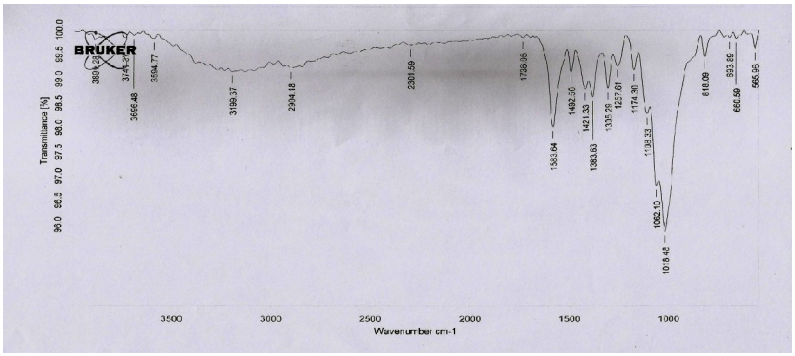


Fig No: 4 FTIR spectra of formulation pantoprazole and sodium starch glycolate

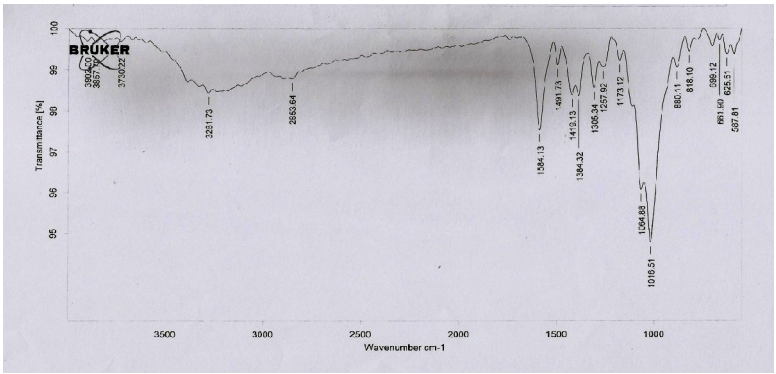


Fig No: 5 FTIR spectra of formulation pantoprazole and croscarmellose sodium

Table: 2 Composition of Oral disintegrating tablets of pantoprazole

Formulation	Drug (mg)	SSG (mg)	Crospovidone(mg)	CCS (mg)	MCC (mg)	Mannitol (mg)	SDL (mg)	Sod. saccharin	Mg stearate
F_1	40	50	-	-	366	30	4	4	4
F_2	40	-	75	-	341	30	4	4	4
F_3	40	50	-	-	391	30	4	4	4
F_4	40	-	-	75	341	30	4	4	4

SSG=Sodium starch glycolate; CCS= cross carmellose; MCC= microcrystalline cellulose;
SDL= spray dried lactose.

Table: 3 Flow properties of powder blend

S.No	Parameters	F_1	F_2	F_3	F_4
1	Angle of repose	26.56°	24.70°	25.45°	29.68°
2	Bulk density (g/ml)	0.306	0.314	0.260	0.257
3	Tapped density(g/ml)	0.325	0.33	0.2675	0.2769
4	Carrs index (%)	5.8	4.8	2.8	7.1
5	Hausners ratio	1.062	1.050	1.028	1.077
6	Void volume	0.2	0.1	0.1	0.3

Table: 4 Evaluation of tablets

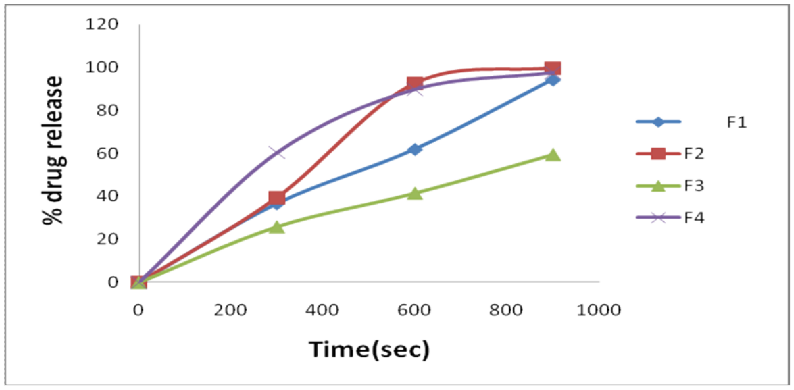
Formulation Code	Hardness	Friability (%)	Weight variation(mg)	Wetting time(sec)	Water absorption ratio
F_1	2.2	0.536	114	7.75	36.22
F_2	4	0.475	151	7.5	31.89
F_3	2.8	0.399	139	8.05	33.69
F_4	3.6	0.598	135	7.75	35.21

Table: 5: *In-vitro* drug disintegration time studies

Formulation code	*In-vitro* dispersion time(sec)	*In-vitro* disintegration time	Drug content
F_1	14.2	16	83.7
F_2	12.54	24	89.9
F_3	14.14	23.5	84.8
F_4	9.68	12.5	82.45

Table: 6: *In-vitro* drug release studies

Time(sec)	Percentage drug release			
	F_1	F_2	F_3	F_4
0	0	0	0	0
300	36.67	39.49	25.85	60.38
600	61.95	92.55	41.43	89.88
900	90.28	95.78	59.33	93.71



CONCLUSION:

The present study indicates a good oral disintegrating tablets containing pantoprazole showing faster onset of action and used for dysphasia patients. The oral disintegrating tablets were prepared by direct compression method. Formulation F_2 containing crospovidone with appropriate amount of other excipients was considered to be optimized formulation with desired drug release of 95.78%.The Oral disintegrating tablets Formulation of pantoprazole provides instant relief from hyper-gastric disorders. The prepared formulation show improved patient compliance both in geriatrics and paediatrics, ease of administration and improved bioavailability.

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