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A Direct Compression Technique for Improved Granisetron Hydrochloride Dissolution and Bioavailability

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ABS TRAC T

In this study, an attempt was made to produce fast-dissolving tablets of the drug using the direct compression method using plantago ovata mucilage and sodium starch glycolate as super disintegrants (2.5 to 10% w/w). For formulations, precompressional properties such as Hausner's ratio, angle of repose, and Carr's compressibility index were evaluated. The tablets were evaluated for weight uniformity, thickness, hardness, friability, drug content, wetting time, in-vitro dispersion time, and in-vitro dissolution research. Plantago ovata formulations show faster drug release because their mucilage expands more than that of sodium starch glycolate formulations. 50% and 90% of the drug were released for formulation GPO4 in 0.42 and 2.51 minutes, respectively. The medication's compatibility with other substances was tested using FTIR studies; the results demonstrated that the drug and other excipients did not interact.

Keywords: *Plantago Ovata Mucilage, Sodium Starch Glycolate, Granisetron Hydrochloride, Fast-Dissolving Pills, and Superdisintegrants.*

INTRODUCTION

Granisetron hydrochloride (Fig. 1) is a selective 5-HT3 receptor antagonist that is chemically endo-1-methyl-N- (9-methyl-9-azabicyclo [3.3.1] non-3-yl)-H-indazole-3-carboxamide hydrochloride. It may be useful in treating nausea and vomiting brought on by cancer treatment. Compared to other 5-HT3 receptor antagonists, it has a longer duration of action, a better tolerability and side effect profile, and a decreased risk of medication interactions. Additionally, it is a well-tolerated and effective medication for treating post-operative nausea and vomiting in adults and children as well as nausea and vomiting brought on by radiation and chemotherapy4, 5. Its primary action is to lessen the activity of the vagus nerve, which stimulates the medulla oblongata's vomiting center. Granisetron hydrochloride has a 60% bioavailability and significant hepatic first pass metabolism. After oral administration, the terminal elimination half-life is three to fourteen hours. About 65% of granisetron hydrochloride is attached to plasma proteins.

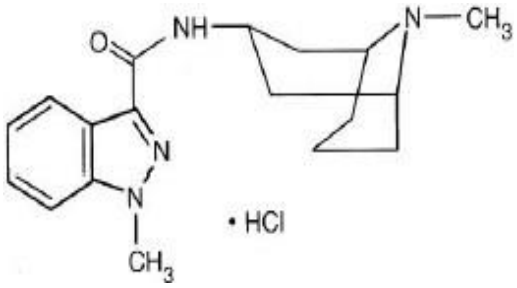

Fig 1: Structure of Granisetron hydrochloride

The tablet is the most popular dosage form due to its simplicity of production, compactness, and self-administration. The need for more patient-friendly and compliant dose forms has increased during the last ten years. The need to create new technologies has thus been growing every year. Pharmaceutical companies are currently concentrating on the development of new drug

dosage forms for existing drugs with improved safety and efficacy along with reduced dosing frequency and the production of more cost-effective dosage forms because the development cost of a new drug molecule is very high.7. Many patients disregard their prescriptions because they have trouble swallowing thick gelatin capsules and tablets. This leads to a high rate of disobedience and unsuccessful treatment. The goal of the current study is to develop fast dispersible tablets of granisetron hydrochloride, investigate the impact of superdisintegrant functionality differences on tablet properties, and enhance patient compliance without sacrificing therapeutic efficacy. The formulation development of fast dispersible tablets depends critically on the choice of superdisintegrant and its consistency of performance.

MATERIALS AND METHODS

Natco Pharma Ltd. (Hyderabad, India) gave granisetron hydrochloride as a gift. Plantago ovata seeds were bought from the Gulbarga, Karnataka, local market. The source of the sodium starch glycolate was Merck Limited in Mumbai. The remaining chemicals and reagents were all of analytical grade.

Isolation of Mucilage

Plantago ovate seeds were steeped in distilled water for 48 hours before being cooked for a short while to release all of the mucilage into the water (Washi, 1985). To filter and extract the marc, the material was compressed through muslin fabric. The mucilage was then precipitated by adding an equivalent amount of acetone to the filterate. Before being used, the separated mucilage was pulverised, sieved (#80), dried (in an oven at a temperature below 600 C), and kept in a desiccator.

Swelling index

The volume in millilitres that one gram of medication or any adherent mucilage occupies after swelling in an aqueous liquid for four hours is known as the swelling index (B.P. Vol. II, 1988). According to BP guidelines, the swelling index for Plantago ovata and sodium starch glycolate were studied. Three determinations' mean data were used to determine the swelling index (Table 1).

Table 1: Swelling index for superdisintegrants

Sl. No.	Name of the superdisintegrants	Swelling index (%v/v)
1	Sodium starch glycolate	57 ± 1.01
2	Plantago ovata mucilage	98 ±1.24

Fourier transform infrared (FTIR) spectroscopy

Using FTIR spectroscopy—5300 (JASCO Japan), the Fourier-transform infrared spectra of granisetron hydrochloride and its combination with various excipients were acquired. The KBr pressed pellet method was used to prepare the samples. The resolution was 4 cm-1, and the scanning range was 400–4600 cm-1. Fig. 2 displays the spectrum.

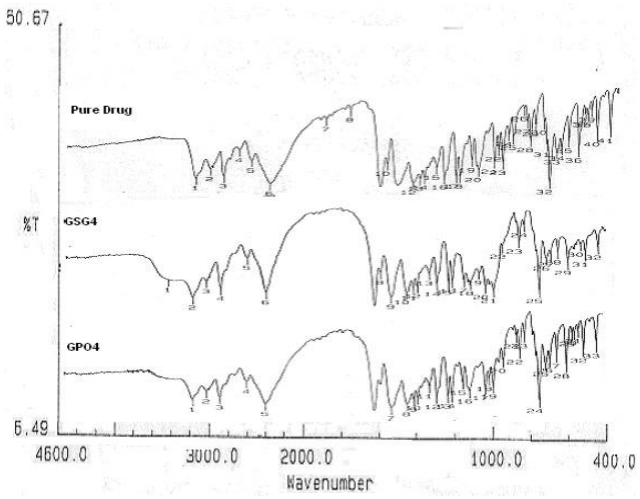

Fig 2: IR spectrum of Granisetron hydrochloride, GSG_4 and GPO_4

Preparation of fast dissolving tablets

Granisetron hydrochloride fast-dissolving tablets were made by direct compression. Each component was run through a 60-mesh screen independently. The components were then weighed, combined geometrically, and crushed into 100 mg tablets using 6 mm round flat punches on a 10-station rotating tablet machine (Rimek). For every designed formulation, a batch of fifty tablets was made. Table 2 lists several formulation compositions.

Table 2: Formulation of Granisetron hydrochloride FDTs

Ingredients	Formulation Code							
	GSG_1	GSG_2	GSG_3	GSG_4	GPO_1	GPO_2	GPO_3	GPO_4
Granisetron hydrochloride	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Sodium starch glycolate	2.5	5.0	7.5	10	--	--	--	--
Plantago ovata mucilage	--	--	--	--	2.5	5.0	7.5	10
Microcrystalline cellulose	30	30	30	30	30	30	30	30
Mannitol	60.1	57.6	55.1	52.6	60.1	57.6	55.1	52.6
Aspartame	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
(Total) mg	100	100	100	100	100	100	100	100

Evaluation of Granisetron hydrochloride fast dissolving tablets

Hardness, thickness variation, weight variation, friability, disintegration time, wetting time, drug content, in-vitro dissolution experiments, and stability studies were all assessed for the produced tablets. The hardness of the tablets was measured using a Pfizer hardness tester. The force of the fracture was measured after the tablet was positioned between the plungers and the handle was squeezed. Using callipers (Mitotoyo; Japan), the thickness and diameter of three tablets were measured as they were being compressed. Twenty tablets were chosen at random from each formulation for weight variation, and each tablet was weighed separately using a Shimadzu digital scale. The average weight for the weight fluctuation was compared to the individual weights. A Roche friabilator of the USP type was used to assess the friability of a sample of twenty tablets. For four minutes, pre-weighed tablets were put in a plastic chambered friabilator that was connected to a motor spinning at 25 rpm. After dusting and reweighing the pills, the percentage of weight loss (friability) was determined. Drug Content Uniformity11: Ten pills were weighed and ground into a fine powder. Two milligrams of Granisetron hydrochloride were extracted from the powder into distilled water, and the liquid was filtered using a 0.22 m membrane filter disc (Millipore Corporation). After the proper dilution with distilled water, the absorbance at 302 nm was measured using a PG instrument T80 model UV/VIS spectrophotometer to determine the Granisetron hydrochloride concentration. A standard calibration curve was used to determine the drug content. Three measurements were averaged to get the mean percent drug content. One tablet was put in a beaker with 10 ml of pH 6.8 phosphate buffers at 37 ± 0.50 C in the Disintegration time12 research, and the amount of time needed for full dispersion was calculated. In the wetting time13 investigation, a petri dish with an internal diameter of 5 cm and 6 millilitres of water was filled with twice-folded tissue paper. The tissue paper in the petri dish was carefully covered with a tablet. The wetting time was defined as the amount of time needed for water to reach the tablet's top surface and fully wet it.

Ratio of water absorption (R) was then determined according to the following equation:

$R = 100 \times (wa - wb)/ wb$

Where the tablet weights before to and after water absorption were denoted by wb and wa, respectively.

The USP dissolution test equipment (Electrolab TDT-08 L Dissolution testers USP) type 2 (paddle) was used for the in vitro dissolution investigation. The temperature was maintained at 37 ± 0.50C while 900 cc of the dissolving media phosphate buffer pH 6.8 was placed in the tank. The paddle's speed was adjusted to 50 rpm. After removing five millilitres of the dissolving medium, the same volume of new medium was added. After passing the samples through a 0.22 μm membrane filter disc, the absorbance at 302 nm was measured to determine the drug concentration. The standard calibration curve was used to compute the drug concentration, which was then represented as the cumulative percent drug dissolved. Three replicates of the release experiments were conducted.

RESULTS AND DISCUSSION

Plantago ovata mucilage and sodium starch glycolate in varying amounts were used in the direct compression process to create each tablet. As a superdisintegrant and diluent, microcrystalline cellulose was used. Mannitol that is directly compressible is used as a diluent to improve mouthfeel. Plantago ovata mucilage had a higher swelling index than sodium starch glycolate, a synthetic superdisintegrant. Table 3 shows that the pre-compression parameter values that were assessed were within the recommended bounds and showed satisfactory free flowing characteristics. Tablets demonstrated strong mechanical resistance, according to data from post-compression characteristics in all formulations, where friability was less than 1%. The drug content was confirmed to be within permissible bounds, ranging from 99.07 to 100.67%. The tablets' hardness was determined to be between 3.1 and 3.5 kg/cm2. It was discovered that in vitro dispersion periods ranged from 21 to 53 seconds. Tables 4 and 5 show that the water absorption ratio and wetting duration, two crucial parameters for comprehending the ability of disintegrants to expand in the presence of a little quantity of water, were found to be in the range of 50 to 88% and 20 to 48 seconds, respectively. Figures 3 and 4 show the formulations' dissolving characteristics. All formulations' dissolving characteristics demonstrate that 99% of the medication is released in 12 minutes. The GPO4 and GSG4 formulations exhibit drug release in 5 and 8 minutes, respectively. Because plantago ovata mucilage swells more than sodium starch glycolate formulations, plantago ovata formulations exhibit quicker drug release. Granisetron hydrochloride's in vitro profile is shown in Table 6 and Fig. 5. For formulation GPO4, 50% and 90% of the medication was released in 0.42 and 2.51 minutes, respectively. Granisetron hydrochloride and other excipients did not interact physicochemically, according to FTIR analyses.

Table 3: Pre-compressional parameters of Granisetron hydrochloride FDTs

Formulation Code	Angle of repose* (degree) ±SD	Bulk density* (g/cc) ± SD	Tapped density* (g/cc) ± SD	Carr's index* (%) ± SD	Hausner's Ratio* ± SD
GSG_1	21.10 ± 0.81	0.37 ± 0.07	0.41 ± 0.02	10.15 ± 1.13	1.11 ± 0.02

GSG_2	20.14 ± 0.63	0.32 ± 0.07	0.35 ± 0.02	09.10 ± 1.01	1.10 ± 0.04
GSG_3	24.19 ± 1.07	0.34 ± 0.04	0.37 ± 0.02	07.94 ± 0.35	1.08 ± 0.02
GSG_4	23.18 ± 1.23	0.36 ± 0.04	0.39 ± 0.02	06.63 ± 1.27	1.07 ± 0.02
GPO_1	24.01 ± 1.27	0.33 ± 0.03	0.36 ± 0.02	09.53 ± 1.05	1.10 ± 0.04
GPO_2	22.36 ± 1.63	0.35 ± 0.04	0.39 ± 0.01	09.53 ± 1.11	1,10 ± 0.03
GPO_3	25.31 ± 1.07	0.36 ± 0.07	0.39 ± 0.01	07.08 ± 1.36	1.07 ± 0.03
GPO_4	21.25 ± 0.70	0.37 ± 0.07	0.43 ± 0.01	14.75 ± 1.55	1.17 ± 0.02

* Average of three determinations

Table 4: Post-compressional parameters of Granisetron hydrochloride FDTs

Formulation Code	Weight variation* (mg) ± SD	Thickness* (mm) ± SD	Hardness* (Kg/cm²) ± SD	Friability (%)
GSG_1	97 ± 0.61	3.27 ± 0.15	3.4 ± 0.14	0.69
GSG_2	101 ± 0.41	3.17 ± 0.25	3.0 ± 0.15	0.60
GSG_3	102 ± 0.97	3.28 ± 0.09	3.5 ± 0.20	0.77
GSG_4	98 ± 0.63	3.16 ± 0.14	3.4 ± 0.10	0.73
GPO_1	101 ± 0.45	3.19 ± 0.11	3.0 ± 0.05	0.11
GPO_2	100 ± 0.36	3.25 ± 0.18	3.2 ± 0.10	0.14
GPO_3	102 ± 0.32	3.30 ± 0.10	3.1 ± 0.35	0.21
GPO_4	99 ± 0.47	3.31 ± 0.15	3.4 ± 0.20	0.17

* Average of three determinations

Table 5: Disintegration, wetting time, water absorption ratio and drug content of Granisetron hydrochloride FDTs

Formulation Code	*In vitro* disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Water absorption ratio* ± SD	Drug Content* (%) ± SD
GSG_1	53 ± 1.02	48 ± 1.60	50 ± 1.17	99.81 ± 0.90
GSG_2	50 ± 1.17	46 ± 1.43	55 ± 1.58	100.30 ± 0.38
GSG_3	48 ± 1.50	42 ± 1.36	53 ± 1.20	100.04 ± 0.29
GSG_4	40 ± 2.53	38 ± 0.80	58 ± 1.30	100.67 ± 0.42
GPO_1	40 ± 0.57	35 ± 2.40`	78 ± 1.21	99.40 ± 1.10
GPO_2	32 ± 0.52	28 ± 1.71	80 ± 1.54	99.90 ± 1.31
GPO_3	25 ± 0.43	21 ± 1.35	85 ± 1.86	99.47 ± 1.62
GPO_4	21 ± 0.45	20 ± 1.21	88 ± 1.15	99.07 ± 0.18

* Average of three determinations

Table 6: Release profile of Granisetron hydrochloride FDTs

Formulation Code	$t_{50\%}$ (min)*	$t_{90\%}$(min)*
GSG_1	3.59	9.50
GSG_2	2.43	8.49
GSG_3	1.55	7.02
GSG_4	0.59	6.08
GPO_1	1.49	6.53
GPO_2	0.58	5.58
GPO_3	0.45	4.01
GPO_4	0.42	2.51

* Average of three determinations

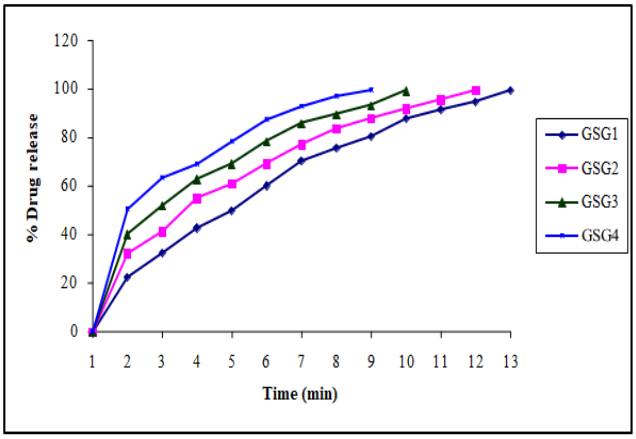

Fig 3: Dissolution profiles of formulations GSG_1-GSG_4

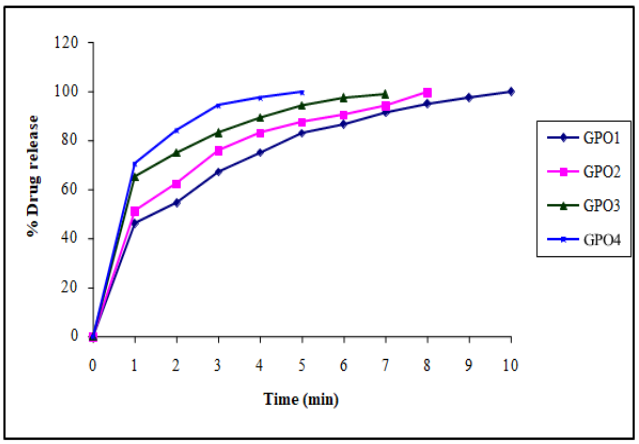

Fig 4: Dissolution profiles of formulations GPO_1-GPO_4

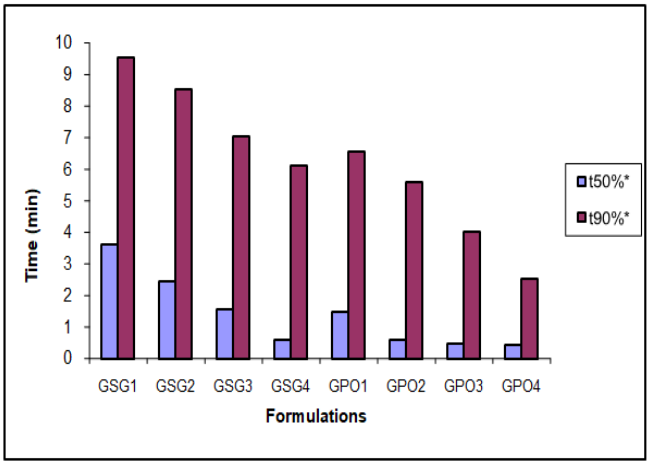

Fig 5: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different formulations

CONCLUSION

In the formulation of fast-dissolving tablets, the natural superdisintegrant plantago ovata mucilage demonstrated superior disintegration and dissolving properties compared to the most popular synthetic superdisintegrants, according to the current study.

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