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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF GRANISETRON HYDROCHLORIDE

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ABSTRACT: Fast dissolving drug delivery systems offers a solution for those patients having difficulty in swallowing tablets/capsules etc. Granisetron hydrochloride was selected as the model drug. In the present study, an attempt had been made to prepare fast dissolving tablets of the drug using , *plantago ovata* mucilage and sodium starch glycolate as super disintegrants (2.5 to 10 % w/w) following by direct compression method. Formulations were evaluated for precompressional parameters such as angle of repose, carr's compressibility index and hausner's ratio. The tablets were evaluated for uniformity of weight, thickness, hardness, friability, drug content, wetting time, *in-vitro* dispersion time and *in-vitro* dissolution study. The prepared tablets were characterized by FTIR studies. No chemical interaction between drug and exciepients was confirmed by FTIR studies.

Keywords: Granisetron hydrochloride, Fast dissolving tablet, *Plantago ovata* mucilage, Sodium starch glycolate.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. For the past one decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[1].

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription. This results in high incidence of noncompliance and ineffective therapy[2]. The proper choice of superdisintegrant and its consistency of performance are of critical importance to the formulation development of fast dispersible tablets[3]. The objective of the present study is to develop fast dispersible tablets of Granisetron Hydrochloride and to study the effect of functionality differences of superdisintegrants on the tablet properties as well as to improve the patient compliance without compromising the therapeutic efficacy.

Granisetron hydrochloride is chemically endo-1-methyl-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-H-indazole-3-carboxamide hydrochloride, a selective 5-HT_3 receptor antagonist, which may have beneficial therapeutic effects in the treatment of vomiting and nausea resulting from cancer therapy[4-6]. It has an improved side effect and tolerabilility profile, a lower risk of drug interactions and a longer duration of action than other 5-HT_3 receptor antagonists. It is also an effective and well-tolerated agent in the management of chemotherapy-induced, radiotherapy-induced and post-operative nausea and vomiting in adults and childern[7,8]. Its main effect is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting center in the medulla oblongata. Granisetron hydrochloride undergoes extensive hepatic first pass metabolism with a Bioavailability of 60%. The terminal elimination half-life is 3 to14 hours after oral administration. Granisetron hydrochloride is about 65% bound to plasma proteins[9].

In the present study, an attempt was made to develop fast dissolving tablets of Granisetron hydrochloride and to improve its bioavailability.

MATERIALS AND METHODS

Granisetron hydrochloride was a gift from Natco Pharma Ltd. (Hyderabad, India). Seeds of *plantago ovata* were purchased from local market of Gulbarga, Karnataka. Sodium starch glycolate used was procured from Merck Limited, Mumbai. All other reagents and chemicals used were of analytical grade.

Isolation of Mucilage

The seeds of *Plantago ovate* were soaked in distilled water for 48 hours and then boiled for few minutes so that mucilage was completely released into water (Washi, 1985). The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filterate so as to precipitate the mucilage. The separated mucilage was dried (in oven at temperature less than 60^0 C), powdered, sieved (#80) and stored in a desicator until use.

Swlling index

Swelling index (B.P. Vol. II, 1988) is the volume in milliliters that is occupied by 1 gm of drug or any adhering mucilage after it has swollen in an aqueous liquid for 4 hours. The method of studying swelling index for *plantago ovata*, sodium starch glycolate were carried out as per BP specifications. Swelling index was calculated from mean readings of three determinations (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

Preparation of fast dissolving tablets of Granisetron hydrochloride by direct compression method:

Fast dissolving tablets of Granisetron hydrochloride were prepared by direct compression. All the ingredients were passed through 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100mg using 6mm round flat punches on 10-station rotary tablet machine (Rimek). A batch of 50 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions are given in (Table 2).

Table 2: Formulation of Granisetron hydrochloride FDT

Ingredients	Formulation Code							
	GSG_1	GSG_2	GSG_3	GSG_4	GPO_1	GPO_2	GPO_3	GPO_4
Granisetron hydrochloride	2	2	2	2	2	2	2	2
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	60.5	58.0	55.5	53	60.5	58.0	55.5	53
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:

The prepared tablets were evaluated for hardness, thickness variation, weight variation, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies, and stability studies. Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the plungers, and the handle was pressed, the force of the fracture was recorded. The thickness and diameter of 3 tablets were recorded during the process of compression using calipers (Mitotoyo; Japan). For weight variation[10] twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance. The individual weights were compared with the average weight for the weight variation. The friability of a sample of twenty tablets was measured using a USP type Roche friabilator. Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated. Drug Content Uniformity[11], ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 2 mg of Granisetron hydrochloride was extracted into distilled water and liquid was filtered (0.22 .m membrane filter disc (Millipore Corporation). The Granisetron hydrochloride content was determined by measuring the absorbance at 302 nm (a PG instrument T_{80} model UV/VIS spectrophotometer) after appropriate dilution with distilled water. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations. . In the Disintegration time[12] study one tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37 ± 0.5^0 C and the time required for complete dispersion was determined. In wetting time[13] study, twice-folded tissue paper was placed in a petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R= 100 \times (w_a - w_b)/ w_b$$

Where, w_b and w_a were tablet weights before and after water absorption, respectively.

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution testers USP) type 2 (paddle). 900 ml of the dissolution medium phosphate buffer pH 6.8 was taken in vessel and the temperature was maintained at 37 ± 0.5^0C. The speed of the paddle was set at 50 rpm. 5 ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The samples were filtered through 0.22 µm membrane filter disc and analyzed for drug content by measuring the absorbance at 302 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of three.

Characterization of Granisetron hydrochloride tablets:

FTIR Studies:

The Fourier-transform infrared spectra of Granisetron hydrochloride and mixture granisetron hydrochloride with other excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400-4600 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in Fig. 1

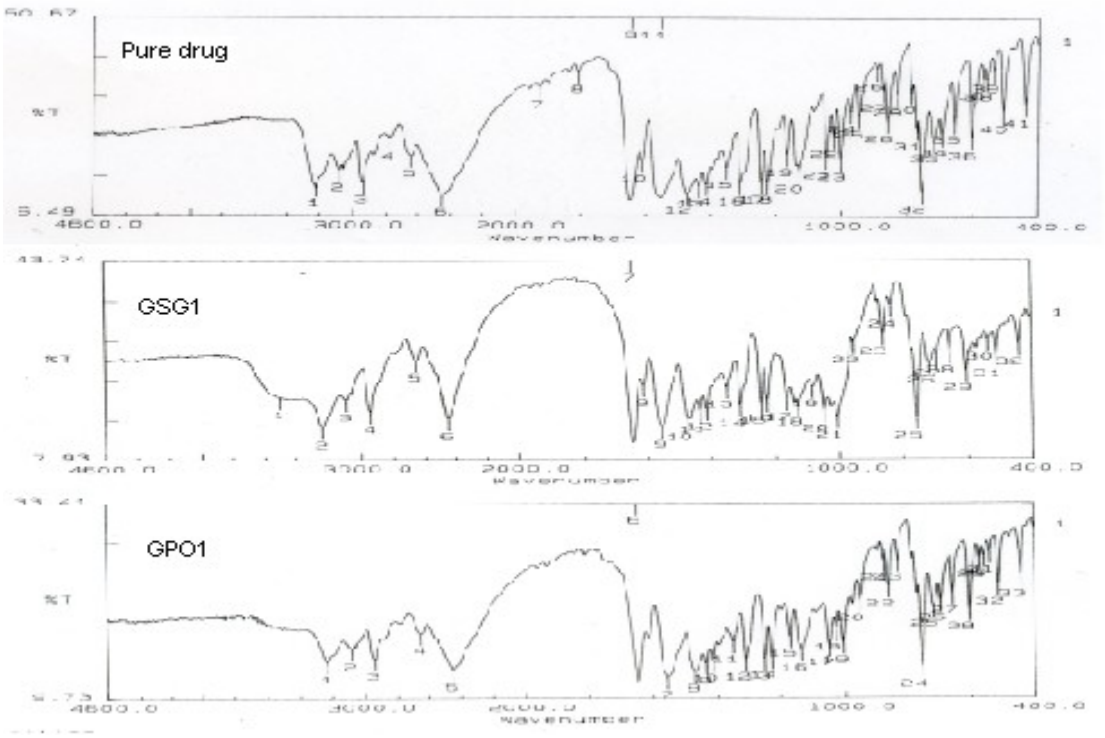

Fig. 1: IR spectrum of Granisetron hydrochloride, GSG_1 and GPO_1

RESULTS AND DISCUSSION

All the tablets were prepared by direct compression method using *plantago ovata* mucilage and sodium starch glycolate in different concentrations. Microcrystalline cellulose was used as diluent, it is also a superdisintegrant. Directly compressible mannitol used as a diluent to enhance mouth feel. Swelling index of *plantago ovata* mucilage was more than that of synthetic superdisintegrant sodium starch glycolate. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing properties are given in Table 3. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 99.07 to 100.67 %, which is within acceptable limits. Hardness of the tablets was found to be in the range of 3.1 to 3.5 kg/cm^2 (Fig.2). *In-vitro* dispersion times were found to be in the range of 21 to 53 sec. The water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, were found to be in the range of 50 to 88 % and 20 to 48 sec respectively are given in Table 4 & 5. The dissolution profiles of formulations are shown in Fig 3 & 4. The dissolution profiles of all formulations are shows the release of drug 99 % within 12 min. The formulations $GPO_4$and GSG_4 shows drug release within 5 & 8 min. Compare to sodium starch glycolate formulations, *plantago ovata* formulations shows faster release of drug, this is due to more swelling property of *plantago ovata* mucilage. In case of formulation GPO_4, the 50% and 90% of drug release was found within 0.43 and 2.51min. FTIR studies revealed that there was no physico-chemical interaction between granisetron hydrochloride and other excipients.

Table 3: Pre-compressional parameters of Granisetron hydrochloride FDT

Formulation Code	Angle of repose (θ) (± SD), n=3	Bulk density (gm/ml) (± SD), n=3	Tapped density (gm/ml) (± SD), n=3	Carr's index (%) (± SD), n=3	Hausner's ratio (± SD), n=3
GSG_1	21.10±0.81	0.37±0.007	0.41±0.002	10.15±1.13	1.11±0.02
GSG_2	20.14±0.63	0.32±0.007	0.35±0.002	09.10±1.01	1.10±0.04
GSG_3	24.19±1.07	0.34±0.004	0.37±0.002	07.94±0.35	1.08±0.02
GSG_4	23.18±1.23	0.36±0.004	0.39±0.002	06.63±1.27	1.07±0.02
GPO_1	24.01±1.27	0.33±0.003	0.36±0.002	09.53±1.05	1.10±0.04
GPO_2	22.36±1.63	0.35±0.004	0.39±0.001	09.53±1.11	1,10±0.03
GPO_3	25.31±1.07	0.36±0.007	0.39±0.001	07.08±1.36	1.07±0.03
GPO_4	21.25±0.70	0.37±0.007	0.43±0.001	14.75±1.55	1.17±0.02

Table 4: Post-compressional parameters of Granisetron hydrochloride FDT

Formulation Code	Weight variation (%) (± SD), n=3	Thickness (mm) (± SD), n=3	Hardness (kg/cm^2) (± SD), n=3	Friability (%)
GSG_1	97 ± 0.61	3.27± 0.15	3.4 ± 0.142	0.69
GSG_2	101 ± 1.41	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 ± 1.32	3.30 ± 0.10	3.1± 0.35	0.21
GPO_4	99 ± 1.47	3.31± 0.15	3.4 ± 0.20	0.17

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

Formulation Code	In-vitro dispersion time* time (sec) (± SD), n=3	Wetting time (sec) (± SD), n=3	Water absorption ratio (± SD), n=3	Drug content (± SD), n=3
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±2.4`	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±1.153	99.07±0.18

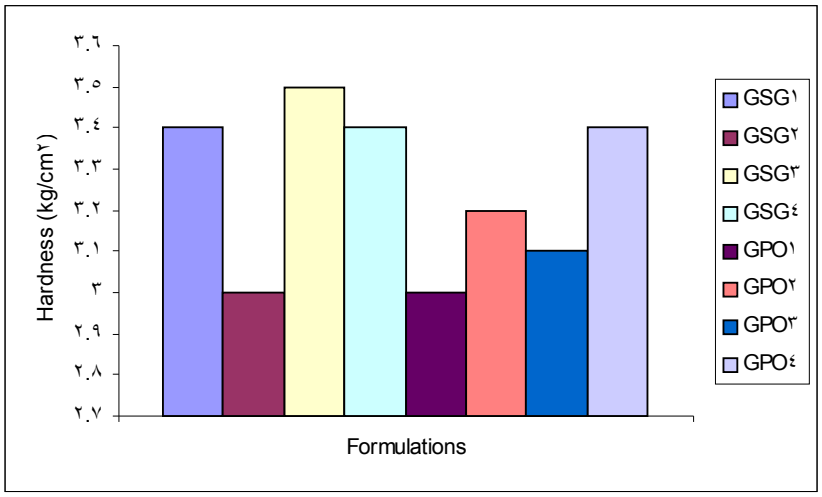

Fig. 2: Hardness of various Granisetron hydrochloride FDT formulations

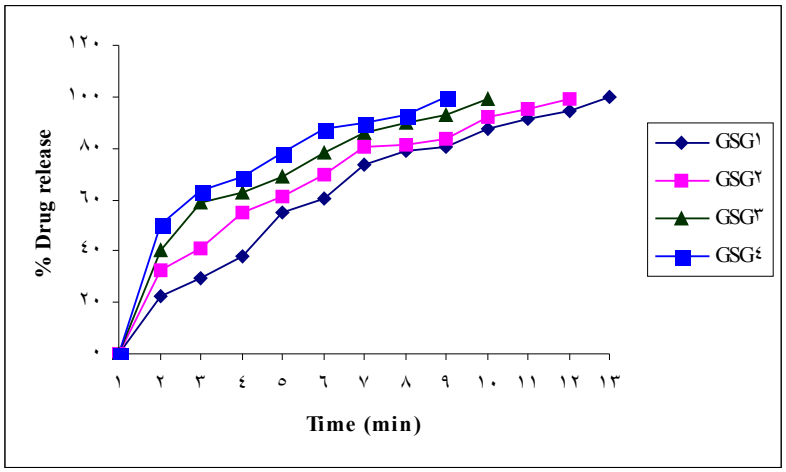

Fig.3. Dissolution profiles of formulations GSG_1- GSG_4

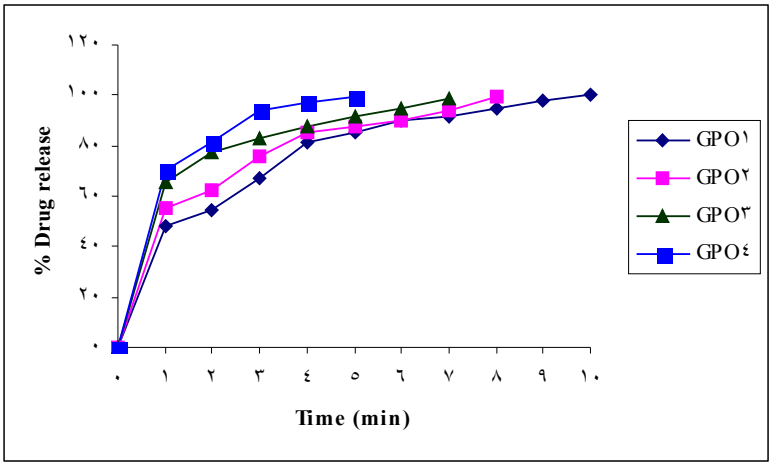

Fig.4. Dissolution profiles of formulations GPO_1- GPO_4

CONCLUSION

The present work revealed that the natural superdisintegrant *plantago ovata* mucilage showed better disintegrating and dissolution property than the most widely used synthetic superdisintegrants in the formulation of fast dissolving tablets.

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REFERENCES

1. Fu Y, Yang S, Jeong SH, Kimura S, Park K: Orally Fast Disintegrating Tablets Developments, Technologies, Taste- masking and Clinical Studies. Crit. Rev. Ther. Drug Carrier Sys. 2004; 21:433- 476.
2. Sharma S, Gupta GD. Formulation and characterization of fast dissolving tablet of promethazine theoclate. Asian J Pharmaceutics. 2008; 70-72.
3. Uddhav S, Bagul NS, Bagul MS, Gujar KN, Bidkar AA. Current status of tablet disintegrants review. http://www.pharmainfo.net.
4. Sanger GJ and Nelson PR. Selective and functional 5-Hydroxytryptamine 3 receptor antagonism, Eur. J. Pharmacol. 1989; 159: 113-124.
5. Upward JW, Amold BDC, Link C, Pieree DM, Allen A, and Tasker TCG. The Clinical Pharmacology of Granisetron, a novel specific 5-HT3 antagonist. Eur. J. Cancer. 1990; 26: S12-S15.
6. Carmichael J, Cantwell BMJ, Edwards CM, Zussman BD, Thomson S, Rapeport WG and Harris AL. A pharmacokinetic study of Granisetron, a selective 5-HT3 receptor antagonist: correlation with anti-emetic response. Cancer Chemother. Pharmacol. 1989; 24:45-49.
7. Yunyun Jiang, Mei Lin, Guorong Fan, Yi Chen, Zhen Li, Weiquan Zhao, Yutian Wu, Jinhong Hu. Rapid determination of Granisetron in human plasma by liquid chromatography coupled to tandem mass spectrometry and its application to bioequivalence study. J. Pharm. & Biomed. Anal. 2006. (Epub ahead of print).
8. Aapro M. Granisetron an update on its clinical use in the management of nausea and vomiting. Oncologist. 2004;9:673-686.
9. http;//en.wikipedia.org/wiki/granisetron.2011; 28th jan.
10. Gohel MC, Parikh RK, Brahmbhatt BK, Shah AR. Preparation and assessment of novel co processed super disintegrants consisting of crospovidone and sodium starch glycolate: A technical note. AAPS Pharm Sci Tech 2007; 8(1): Article 9: P. E1-E7.
11. Jacob S, Shirwarkar AA, Joseph A, Srinivasan KK. Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. Indian J Pharm Sci 2007; 69(5): 633-9.
12. Gohel MC, Parikh RK, Brahmbhatt BK, Shah AR. Improving the tablet characteristics and dissolution profile of ibuprofen by using a novel co processed superdisintegrant: A technical note. AAPS Pharm Sci Tech. 2007; 8(1): Article 13, P. E1-E6.
13. Musa El-Barghouthi, Ala's Eftaiha, Iyad Rashid, Mayyas Al-Remawi, Adnan Badwan. A novel superdisintegrating agent made from physically modified chitosan with silicon dioxide. Drug Dev and Ind Pharm 2008; 34: 373-83.