International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 3, Issue 2, 2011

Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF GRANISETRON HYDROCHLORIDE BY DIRECT COMPRESSION TECHNIQUE

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Received: 21 Dec 2010, Revised and Accepted: 20 Jan 2011

ABSTRACT

Granisetron hydrochloride is a selective 5-HT_3 receptor antagonist, which may have beneficial therapeutic effects in the treatment of vomiting and nausea resulting from cancer therapy. In the present work fast dissolving tablets of Granisetron hydrochloride have been prepared by direct compression method. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. The prepared tablets were evaluated for post compressional parameters such as hardness, friability, thickness, *in-vitro* dispersion time, wetting time, and water absorption ratio. The prepared tablets were characterized by FTIR studies. Effect of superdisintegrants [such as croscarmellose sodium, sodium starch glycolate and crospovidone,] on wetting time, *in-vitro* dispersion time and stability parameter has been studied. No chemical interaction between drug and excipients was confirmed by FTIR studies. From this study it is concluded that fast dissolving tablets could be prepared by direct compression method using different superdisintegrants enhanced dissolution will lead to improved bioavailability, improved effectiveness of Granisetron hydrochloride.

Keywords: Fast dissolving tablet, Granisetron hydrochloride, croscarmellose sodium, sodium starch glycolate, crospovidone,

INTRODUCTION

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[1-3]. 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[4,5]. 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[6].

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[7]. The proper choice of superdisintegrant and its consistency of performance are of critical importance to the formulation development of fast dissolving tablets[8].

The present work enhance the dissolution will lead to improves the bioavailability of Granisetron hydrochloride. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion) [9]. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

MATERIALS AND METHODS

Granisetron hydrochloride was a gift from Natco Pharma Ltd. (Hyderabad, India). Croscarmellose sodium used was procured from Loba Chemicals, Mumbai. crospovidone and Sodium starch glycolate used were procured from Merck Limited, Mumbai. All other reagents and chemicals used were of analytical grade.

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 1).

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:

Table 1: Formulation of granisetron hydrochloride fdt

Ingredients	Formulation Code														
	G_1	G_2	G_3	G_4	G_5	G_6	G_7	G_8	G_9	G_{10}	G_{11}	G_{12}			
Granisetron hydrochloride	2.4		2.4		2.4		2.4		2.4	2.4		2.4	2.4	2.4	2.4
Crospovidone	3		6		9		12		--	--		--	--	--	--
Crosscarmellose sodium	--		--		--		--		3	6		9	12	--	--
Sodium starch glcolate	--		--		--		--		--	--		--	3	6	9	12
Microcrystalline cellulose	30		30		30		30		30	30		30	30	30	30	30
Mannitol	57.6		54.6		51.6		48.6		57.6	54.6		51.6	48.6	57.6	54.6	51.6	48.6
Aspartame	5		5		5		5		5	5		5	5	5	5	5	5
Magnesium stearate	1		1		1		1		1	1		1	1	1	1	1	1
Talc	1		1		1		1		1	1		1	1	1	1	1	1
(Total) mg	100		100		100		100		100	100		100	100	100	100	100	100

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

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^{0}C. 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

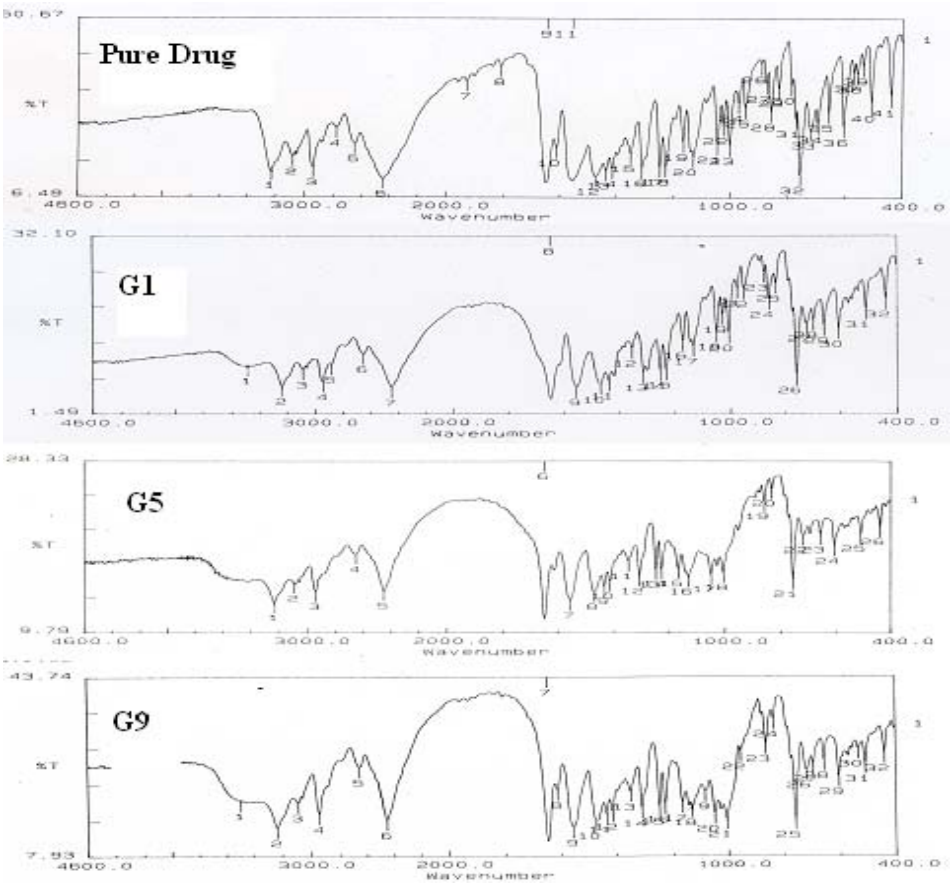

Fig. 1: IR spectrum of Granisetron hydrochloride, G_1,G_5 and G_9

RESULTS AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property, are given in Table 2. 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 98.31 to 100.16 %, which is within acceptable limits. Hardness of the tablets was found to be in the range of 3 to 4 kg/cm^2. *In-vitro* dispersion times were found to be in the range of 16 to 80 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 52 to 80 % and 17 to 92 sec respectively is given in Table 3 & 4. The dissolution profiles of formulations are shown in Fig 2 to 5. The dissolution profiles of formulations are shows the release of drug 99 % and the promising formulations i.e. G_3, G_4 and G_8 shows drug release within 5 min. Among the entire formulations G_4 shows maximum drug release around 99.65 % within 4 min.

In-vitro dissolution studies on the promising formulations. G_3, G_4 and G_8 were carried out in phosphate buffer in pH 6.8, and the various dissolution parameter values viz., percent drug dissolved in 1min, 2min, 3min, 4min and 5min (T1, T2, T3, T4 and T5), $t_{50\%}$ and $t_{90\%}$ are shown in Table 5. The formulation G_4 50% of drug release in 0.39min, and 90% 1.58min. FTIR studies revealed that there was no physico-chemical interaction between Granisetron hydrochloride and other excipients (Fig. 1).

Table 2: 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
G_1	25.28±1.23	0.5434±0.10	0.6341±0.02	14.3037±1.58	1.1669±0.01
G_2	27.20±1.41	0.5212±0.02	0.6294±0.01	17.1909±1.22	1.2075±0.09
G_3	25.14±0.57	0.5137±0.07	0.6098±0.01	15.7592±0.63	1.1870±0.05
G_4	24.19±0.69	0.5098±0.01	0.5998±0.02	15.0050±0.58	1.1765±0.01
G_5	26.41±1.20	0.5438±0.09	0.6401±0.02	15.044±0.60	1.1770±0.02
G_6	28.56±1.55	0.5345±0.15	0.6296±0.03	15.1048±0.75	1.1779±0.04
G_7	25.71±1.42	0.5121±0.02	0.6210±0.02	17.5362±1.23	1.2126±0.01
G_8	26.38±1.35	0.5342±0.13	0.6408±0.01	16.6354±0.67	1.1995±0.07
G_9	26.01±0.13	0.5088±0.01	0.5941±0.01	14.3578±1.51	1.1676±0.01
G_{10}	27.01±1.21	0.5147±0.02	0.6091±0.02	15.4982±1.59	1.1834±0.02
G_{11}	25.08±1.07	0.5218±0.03	0.6218±0.02	16.0823±1.19	1.1916±0.03
G_{12}	28.46±1.26	0.5401±0.04	0.6387±0.02	15.4376±1.08	1.1825±0.01

Table 3: 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 (%)
G_1	99±0.61	3.26±0.09	3.5±0.11	0.45
G_2	98±0.13	3.38±0.10	3.0±0.10	0.56
G_3	101±0.47	3.37±0.20	3.6±0.15	0.71
G_4	102±1.25	3.43±0.21	4.0±0.21	0.52
G_5	101±1.37	3.28±0.28	3.0±0.10	0.61
G_6	100±0.61	3.29±0.12	4.0±0.21	0.52
G_7	98±0.42	3.27±0.17	3.5±0.05	0.42
G_8	99±1.45	3.40±0.10	3.0±0.18	0.47
G_9	97±1.05	3.27±0.15	3.1±0.12	0.59
G_{10}	100±1.60	3.27±0.13	3.0±0.14	0.67
G_{11}	101±0.50	3.30±0.25	3.0±10	0.49
G_{12}	102±0.43	3.25±0.20	3.5±0.10	0.73

Table 4: Disintegration, wetting time, water absorption ratio and drug content of granisetron hydrochloride fdt

Formulation Code	In-vitro dispersion time (sec) (± SD), n=3	Wetting time (sec) (± SD), n=3	Water absorption ratio (± SD), n=3	Drug content (± SD), n=3
G_1	30±1.50	41±1.0	69±1.20	99.01±0.85
G_2	16±1.00	17±1.42	80±1.05	98.31±0.68
G_3	20±1.70	22±1.89	67±1.19	98.52±1.40
G_4	28±1.00	41±2.10	71±1.35	99.13±1.31
G_5	80±1.45	92±1.12	57±1.31	100.01±1.11
G_6	60±1.28	73±1.35	48±1.73	99.63±0.95
G_7	52±2.15	64±1.79	52±1.23	99.41±1.33
G_8	43±1.55	54±1.41	63±1.37	99.91±1.81
G_9	42±1.21	55±1.25	61±1.41	99.46±0.93
G_{10}	40±1.10	52±1.21	58±6.55	98.65±0.57
G_{11}	39±1.00	51±1.15	59±1.14	99.30±1.16
G_{12}	35±1.11	46±1.48	52±1.53	100.16±1.42

Table 5: *In-Vitro* dissolution parameters of different granisetron hydrochloride fdt formulations

Formulation Code	Parameters								
	T1	T2	T3	T4	T5	$T_{50\%}$	$T_{90\%}$		
G_3	65.37		83.28	91.39		94.55	99.02	0.45min	2.57min
G_4	75.52		91.25	94.39		99.65	--	0.39min	1.58min
G_8	51.39		75.52	84.25		93.35	99.17	0.58min	3.51min

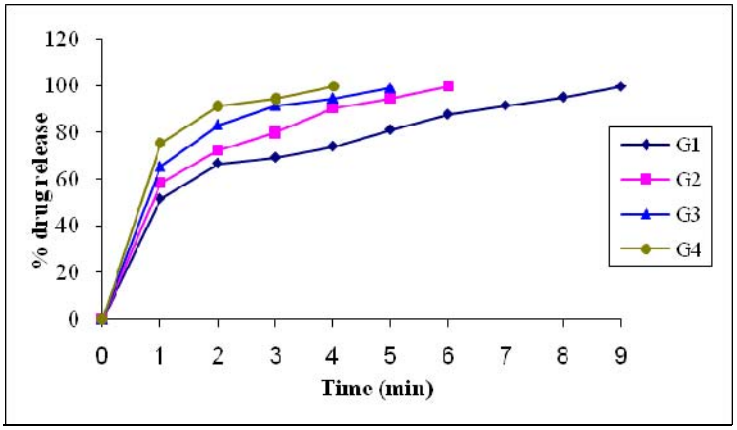

Fig. 2: Dissolution profiles of formulations G_1-G_4

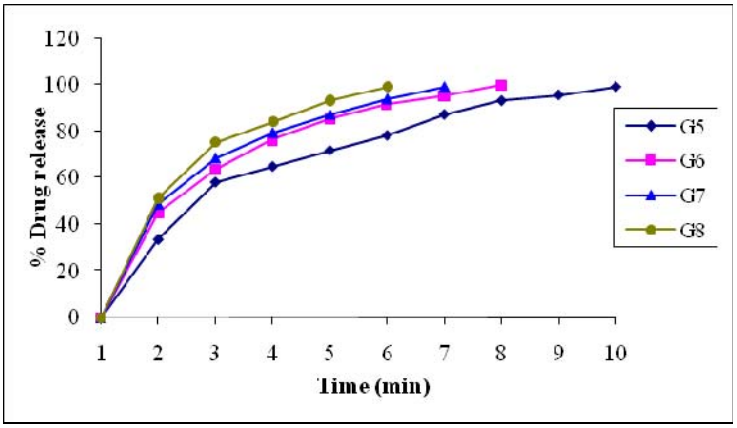

Fig. 3: Dissolution profiles of formulations G_5-G_8

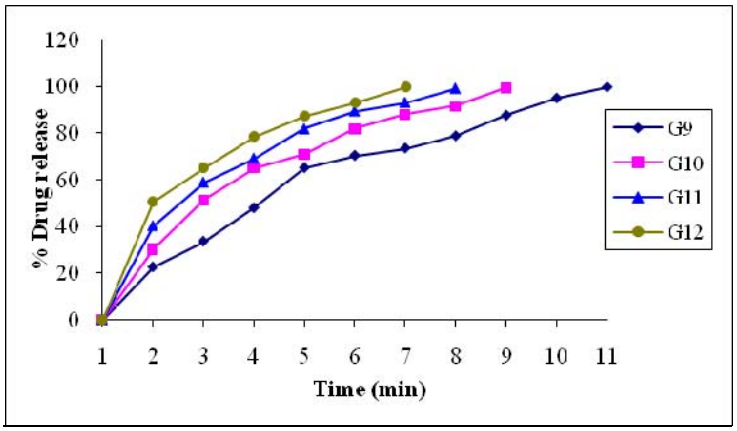

Fig. 4: Dissolution profiles of formulations G_9-G_{12}

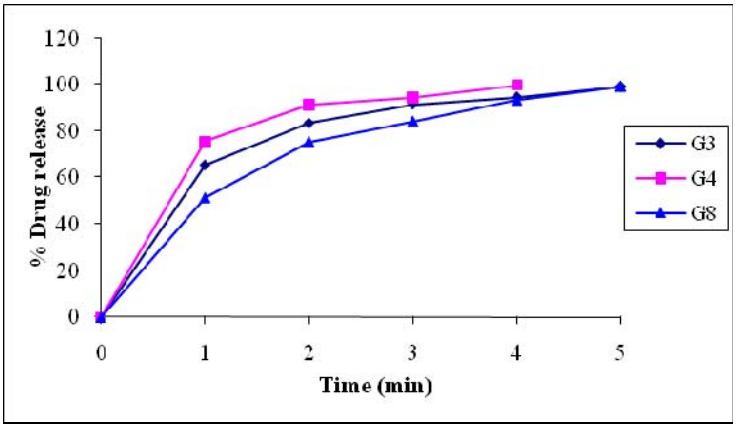

Fig. 5: Dissolution profiles of best formulations G_3, G_4, G_8

CONCLUSION

In present study, four types of superdisintegrants in different concentrations differed in their ability to disintegrate the model Granisetron hydrochloride tablets. Such difference can potentially affect drug dissolution and is proposed as model formulation for disintegrants performance testing and quality control purposes. Hence, enhanced dissolution of fast dissolving tablets of Granisetron hydrochloride will lead to improved bioavailability, improved effectiveness and hence better patient compliance.

ACKNOWLEDEMENT

The authors are thankful to Natco Pharma Ltd. (Hyderabad, India) for providing gift sample and also very much thankful to Prof. Kishoresingh K.Chatrapathi President, R.M.E.S's College of Pharmacy Gulbarga, for his valuable support and providing necessary facilities to carry out the research work. . The authors also thankful to Dr. M. G. Purohit, Emeritus Professor, Luqman College of Pharmacy, Gulbarga for their valuable suggestions in carrying out this research work.

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