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THE PHARMA RESEARCH, A JOURNAL

The Pharma Research (T. Ph. Res.), (2011), 5(2); 221-230.

Published on- 15 Sep 2011

Original Article

ISSN 0975-8216

FORMULATION AND EVALUATION OF FAST DISSOLVING GRANISETRON HYDROCHLORIDE TABLETS: EFFECT OF FUNCTIONALITY OF SUPERDISINTEGRANTS

Basawaraj S.Patil[1a*], N.G. Raghavendra Rao[2]

Affiliated to:

[1]Research scholar, Singhania University, Pacheri Bari, Dist. Jhunjhunu - Rajasthan, India [a]Department of Pharmaceutics, R.M.E.S College of Pharmacy, Gulbarga – Karnataka, India
[2]Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga – Karnataka, India.


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ABSTRACT

Fast dissolving tablets (FDT) of Granisetron hydrochloride were prepared by direct compression method after incorporating superdisintegrants croscarmellose sodium and crospovidone in different concentrations (2.5, 5, 7.5 and 10 mg). Eight formulations having superdisintegrants at different concentration level were prepared to assess their efficiency and critical concentration level. Different type of evaluation parameters for blends and tablets were used. The prepared tablets were characterized by FTIR studies. No chemical interaction between drug and exciepients was confirmed by FTIR studies. The formulation GCS_4 containing croscarmellose sodium showed superior *in vitro* dispersion time and drug release, as compared to other formulations. GCS_4 tablet showed good dissolution efficiency and rapid dissolution. The 50% and 90% of drug release of tablet GCS_4, was found within 0.45 and 2.59 min.

Keywords: **Granisetron hydrochloride, fast dissolving tablet, direct compression, superdisintegrant.**

INTRODUCTION

Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency[1]. As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements. On the other hand wet granulation not only increases the cycle time, but also has certain limits imposed by thermolability and moisture sensitivity of the active. So pharmaceutical industry is now focusing increasingly on this process[2,3]. The unnecessary exposure of any drug to moisture and heat can never be justified[4]. Tablets produced by direct compression method give lower microbial levels than those prepared by the wet granulation method. The compaction process exerts lethal effect on the survival of microorganisms[5]. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with the dissolution fluid and exhibit a comparatively faster dissolution[6]. The serious limitation of direct compression is the use of more than 30% of the drug in the formulation, mainly for drugs that present low flowability and segregation[7].

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[8-10]. 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[11, 12]. 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.

The objective of this study was to enhance safety and efficacy of drug molecule, achieve better compliance, solve the problem of difficulty in swallowing, enhance onset of action, and provide stable dosage form.

MATERIALS AND METHODS

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

Preparation of blends and tablets

The superdisintegtants (croscarmellose sodium and crospovidone) in varying concentration (2.5, 5, 7.5 and 10 mg) were used to develop the tablets. All the ingredients (shown in Table 1) were passed through mesh no. 60. All the ingredients were co-ground in a pestle mortar for 5 minutes. The mixed blend of excipients was compressed using a 6mm round flat punches on 10-station rotary tablet machine (Rimek) to produce tablets weighing 100 mg each, with diameter of 6 mm. A minimum of 50 tablets was prepared for every batch[13].

Table 1: Formulation of Granisetron hydrochloride fast dissolving tablets

Ingredients	Formulation Code							
	GCP_1	GCP_2	GCP_3	GCP_4	GCS_1	GCS_2	GCS_3	GCS_4
Granisetron hydrochloride	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Crospovidone	2.5	5.0	7.5	10	--	--	--	--
Croscarmellose sodium	--	--	--	--	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 weight (mg)	100	100	100	100	100	100	100	100

Evaluation of blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulation variables and process variables involved in the mixing step, and all these can affect the characteristics of blends produced. The blends were characterized by mass-volume relationship (bulk density, tapped density, Hausner's ratio and compressibility index) and flow properties (static angle of repose)[14].

Evaluation of tablets

Prepared tablets were evaluated for hardness (Monsanto hardness tester),

friability (Roche friabilator), thickness, weight variation, *in vitro* dispersion time, water absorption ratio and drug content[15, 16]. Using type II apparatus as specified in United State Pharmacopoeia at 100 rpm performed in vitro dissolution studies of fast dissolving tablets; and Sorenson's buffer (pH, 6.8), 900 ml, was used as dissolution medium. Temperature of dissolution medium was maintained at 37 ± 0.5^0 C. aliquot of dissolution medium was withdrawn at a specified time interval and it was filtered. Absorption of filtered solution was checked by UV spectroscopy (PG instrument T_{80} model UV/VIS spectrophotometer) at 302 nm, and drug content was determined from standard calibration curve. Dissolution rate was studied for all designed formulations[17].

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

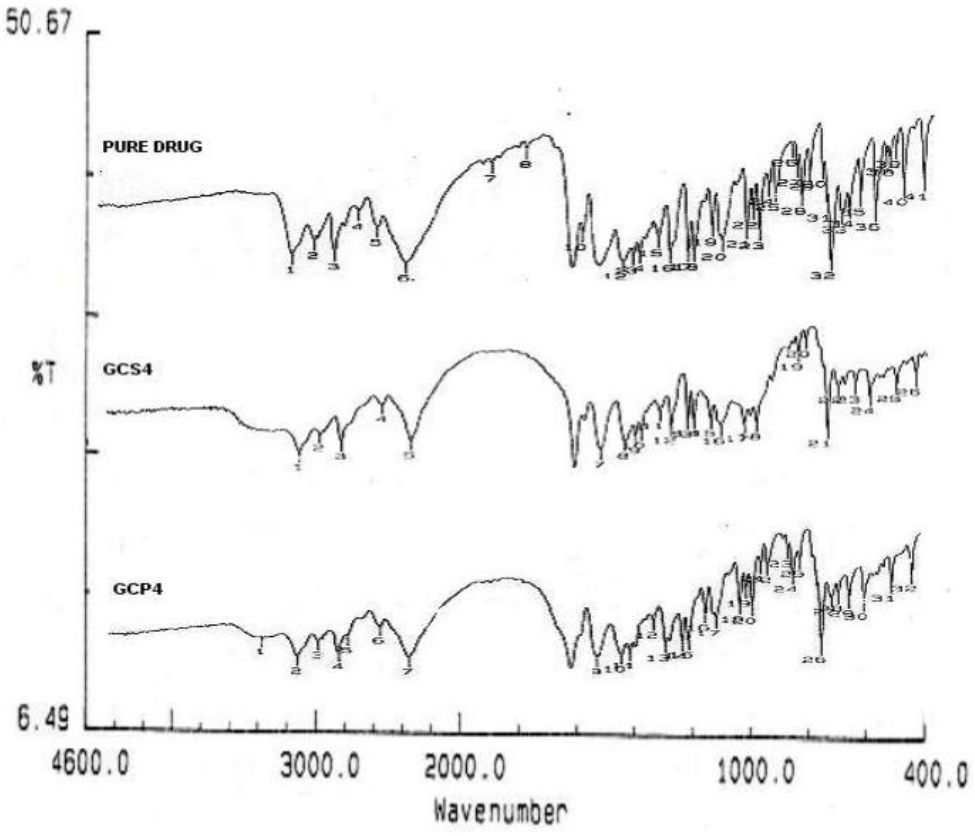

Fig. 1: IR spectrum of Granisetron hydrochloride, GCP_4 and GCS_4

RESULTS AND DISCUSSION

The use of superdintegrants for preparation of fast dissolving tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore to have an effect on dissolution characteristics as well.

Prepared fast dissolving tablet gets dispersed quickly and release the drug early. Two superdisintegrants were tried to achieve fast dispersion of tablets. Blends evaluated (Table 2) were found to have excellent flowability as determined by angle of repose and compressibility-flowability correlation data. However, tablets containing croscarmellose sodium showed fastest disintegration. Characteristics of tablets are tabulated in Table 3 and 4.

Table 2: Evaluation of blends of Granisetron hydrochloride

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
GCP_1	28.35 ± 1.31	0.36 ± 0.007	0.43 ± 0.001	14.78 ± 1.25	1.17 ± 0.01
GCP_2	30.14 ± 1.07	0.34 ± 0.002	0.41 ± 0.001	15.79 ± 1.21	1.18 ± 0.02
GCP_3	29.03 ± 1.16	0.36 ± 0.005	0.43 ± 0.002	14.15 ± 0.12	1.16 ± 0.02
GCP_4	28.26 ± 1.25	0.34 ± 0.007	0.41 ± 0.001	16.34 ± 1.18	1.19 ± 0.03
GCS_1	26.86 ± 1.56	0.36 ± 0.002	0.43 ± 0.002	14.86 ± 1.27	1.17 ± 0.04
GCS_2	28.04 ± 1.32	0.36 ± 0.004	0.43± 0.002	15.07 ± 1.35	1,17 ± 0.04
GCS_3	26.13 ± 1.48	0.36 ± 0.003	0.44 ± 0.001	15.99 ± 1.15	1.19 ± 0.02
GCS_4	27.14 ± 0.88	0.36 ± 0.007	0.43 ± 0.001	16.10 ± 1.13	1.19 ± 0.04

Table 3: Evaluation of Granisetron hydrochloride fast dissolving tablets

Formulation Code	Weight variation (%) (± SD), n=3	Thickness (mm) (± SD), n=3	Hardness (kg/cm^2) (± SD), n=3	Friability (%)
GCP_1	98 ± 1.23	3.27 ± 0.12	3.4 ± 0.10	0.47
GCP_2	99 ± 1.10	3.37 ± 0.10	3.3 ± 0.15	0.39
GCP_3	100 ± 0.56	3.43 ± 0.17	3.3 ± 0.20	0.52
GCP_4	100 ± 0.55	3.24 ± 0.19	3.5 ± 0.21	0.69
GCS_1	102 ± 1.41	3.28 ± 0.28	3.6 ± 0.25	0.58
GCS_2	101 ± 1.27	3.29 ± 0.14	3.4 ± 0.47	0.60
GCS_3	98 ± 1.60	3.25 ± 0.20	3.2 ± 0.15	0.68
GCS_4	101 ± 1.18	3.40 ± 0.08	3.3 ± 0.10	0.57

Table 4: Dispersion time, wetting time, water absorption ratio and drug content of Granisetron hydrochloride fast dissolving tablets

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
GCP_1	47 ± 1.57	56 ± 0.77	57 ± 2.40	99.18 ± 0.76
GCP_2	42 ± 1.21	52 ± 1.28	60 ± 2.51	100.46 ± 0.27
GCP_3	36 ± 1.18	49 ± 1.47	51 ± 1.80	100.46 ± 1.06
GCP_4	31 ± 1.01	44 ± 1.29	49 ± 1.07	99.10 ± 0.48
GCS_1	41 ± 2.15	51 ± 1.21	67 ± 1.73	98.19 ± 1.23
GCS_2	37 ± 1.11	48 ± 1.07	70 ± 1.25	99.47 ± 1.67
GCS_3	29 ± 1.70	45 ± 1.80	72 ± 1.18	99.28± 1.71
GCS_4	23 ± 1.43	41 ± 1.62	61 ± 1.05	98.63 ± 0.59

The dissolution profiles of all the tablets are shown in Fig 2 and 3. GCS_4 tablet showed good dissolution efficiency and rapid dissolution. The 50% and 90% of drug release of tablet GCS_4, was found within 0.45 and 2.59 min (Table 5 and Fig. 4).

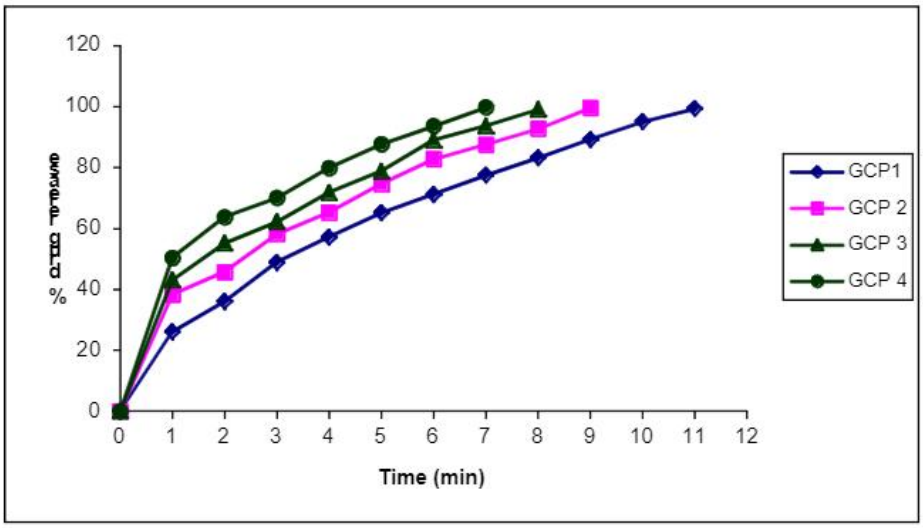

Fig.2. Dissolution profiles of formulations GCP_1- GCP_4

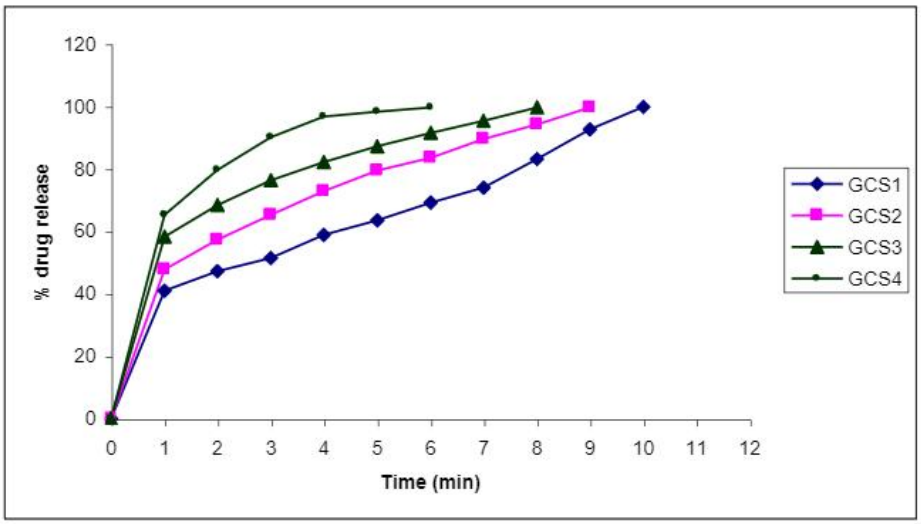

Fig.3. Dissolution profiles of formulations GCS_1- GCS_4

Table 5: Release profile of Granisetron hydrochloride fast dissolving tablets

Formulation Code	$t_{50\%}$ (min)	$t_{90\%}$ (min)
GCP_1	3.03	8.03
GCP_2	2.34	7.45
GCP_3	1.48	6.03
GCP_4	0.59	5.45
GCS_1	2.55	8.44
GCS_2	1.02	7.02
GCS_3	0.51	5.35
GCS_4	0.45	2.59

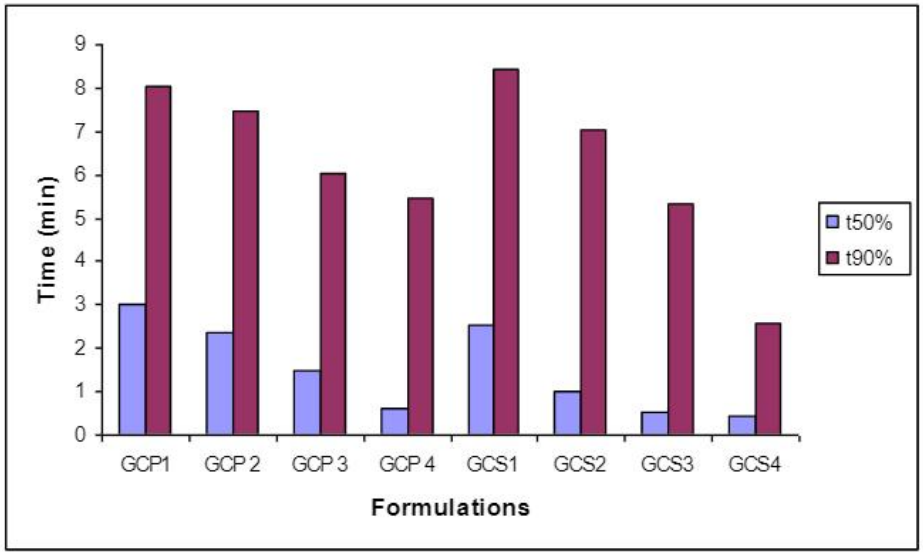

Fig. 4: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different tablet formulations

An IR spectrum of pure drug Granisetron hydrochloride shows characteristic absorption peaks due to C-H vibrations at 3082 cm^{-1} indicating that this molecule contain aromatic residue. In addition to this it also exhibited a peak at 2939 cm^{-1} due to C-H of the aliphatic bond of the molecule, the C=C absorption peaks are noticed at1647cm^{-1} and 1612 $cm^{-1.}$ This is the characteristic area were in C=C absorption of appearing the IR spectrum of this compound suggest that molecule and investigation contains aromatic moiety along with aliphatic residue also it contains more than one double bond in the molecule hence one can concluded that the drug is aromatic in nature contains more than one chromophore of C=C. These peaks are present in IR scan of all formulations, so it confirms that, presence of undisturbed drug in the formulations. Hence there are no drug-excipient interactions.

CONCLUSION

The study shows that the dissolution rate of Granisetron hydrochloride can be enhanced to a great extent by direct compression technique with the addition of superdisintegrants, which gives quick relief from emesis.

ACKNOWLEDEMENT

The authors are thankful to Natco Pharma Ltd. (Hyderabad, India) for providing Granisetron hydrochloride drug sample.

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