Research in Pharmacy 1(2): 20-27, 2011 ISSN : 2231-539X
www.researchinpharmacy.com

Regular Article

Formulation and evaluation of fast disintegrating tablets of Granisetron HCl using natural polymers

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The present research work is to formulate and evaluate fast disintegrating tablets of Ganisetron HCl using natural polymers. Tablets were prepared by direct compression method using different drug polymer concentration. Fourier Transform Infrared Spectroscopy (FT-IR) study revealed no chemical interaction between drug and polymers used. Precompression and postcompression parameters were within the limits for the tablets. Disintegration and dissolution data of tablets were directly proportional to the superdisintegrants concentration. Selected fast dissolving tablet F8 containing plantago ovate 5%w/w has released 99.66 % within 3min.

Keywords: Ganisetron hydrochloride, Plantago ovate, Agar.

Difficulty in swallowing (Dysphagia) is a common problem of all age groups especially elderly and pediatrics, because of physiological changes associated with this group of patients. The concept of fast dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Granisetron HCl is a novel serotonin 5-HT3 receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy (http://en.wikipedia.org/wiki/File:Granisetron.svg 2010). The bioavailability of Granisetron HCl is only 65% indicating extensive first pass metabolism in liver which is an ideal feature for rapid release drug delivery system (www.thomsonhc.com/home/dispatch, 2011). The present study aimed at developing & evaluating fast disintegrating tablets of Granisetron HCl using natural super disintegrants like Plantago ovate and Agar.

MATERIALS AND METHODS

Granisetron HCl was a gift sample from Natco Pharma Ltd., Hyderabad. Plantago ovate was a gift sample Crystal colloid. Mumbai, Agar was a gift sample from Hiedialabtrs pvt Ltd. Mumbai, Directly compressible mannitol (DC Mannitol) was a gift sample from Torrent Pharma Ltd. Ahmedabad, Microcrystalline cellulose (MCC), Magnesium Stearate, Aerosil were gift samples from S.D. Fine. Pvt. Ltd., Mumbai and all the other chemicals used in the formulations were of analyltical grade.

Preparation of Fast Disintegrating Tablets (FDT) by direct compression technique

Tablets containing 2 mg of Granisetron HCl were prepared by direct compression

method. The drug, diluents, super disintegrants and sweetening agents were passed through sieve no.40 and mixed together (in a plastic container). Magnesium stearate and aerosil passed through mesh no.80 were mixed and blended with above mixture in a plastic container followed by compression of the blend. The tablets were prepared by direct compression method using 4 mm flat punches on a 10 station rotary compression machine (**Table 1**).

Table 1: Composition of Granisetron HCl fast dissolving tablets containing natural superdisintegrants

Ingredients (mg)	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Granisetron HCl	2	2	2	2	2	2	2	2
Agar	4	6	8	10	-	-	-	-
Plantago ovate	-	-	-	-	4	6	8	10
MCC	136	134	132	130	136	134	132	130
SD Mannitol	50	50	50	50	50	50	50	50
Talc	2	2	2	2	2	2	2	2
Mg Stearate	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2
Na. saccharin	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200

Scanning of drug in PH 6.8

Accurately weighed 5 mg of Granisetron HCl and dissolved in 100 ml of phosphate buffer of pH 6.8. From the above stock solution 5 ml was withdrawn and made up to 10 ml with phosphate buffer of pH 6.8 to obtain a concentration of 25 µg/ml. The absorption maxima of the solution were scanned in between 200-400nm using UV-Spectrophotometer against blank (**Fig 1**).

Fourier transform infrared spectroscopy studies (FTIR)

The pure drugs, physical mixture of excipients were subjected for FTIR analysis. The samples were prepared on KBr-press (Startech Lab, India). The samples were scanned over a range of 4000-500 cm-1 using Fourier transformer infrared spectrophotometer (8600, Shimadzu Corporation, Japan). Spectra were analyzed for drug polymer interactions (**Fig 2, Fig 3**).

Micromeritic properties

Angle of Repose

A funnel was fixed at a particular height on a burette stand. A graph paper was placed below the funnel on the Table. The blended powder was passed through the funnel until it forms a pile. The radius of the pile was noted down. Angle of repose of the powder material was calculated using the formula (Aulton 2002).

$$\textbf{Angle of repose } (\theta) = \tan^{-1} (h/r)$$

Where, **h** is height of the pile and **r** is radius of the pile.

Apparent Bulk Density

The bulk density, as a measure used to describe packing materials or granules, was determined by transferring the accurately

weighed amount of blend to the graduated cylinder (10 ml) with the aid of a funnel. The volume was noted. The ratio of weight of the sample to the volume occupied was calculated (Aulton 2002).

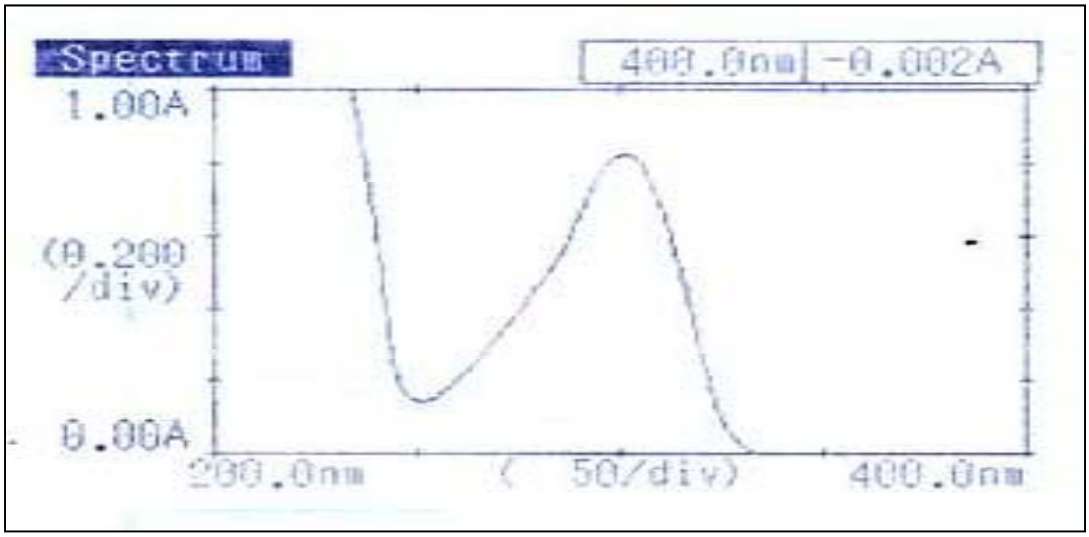

Fig 1: UV absorbance spectra of Granisetron HCl in phosphate buffer of pH 6.8

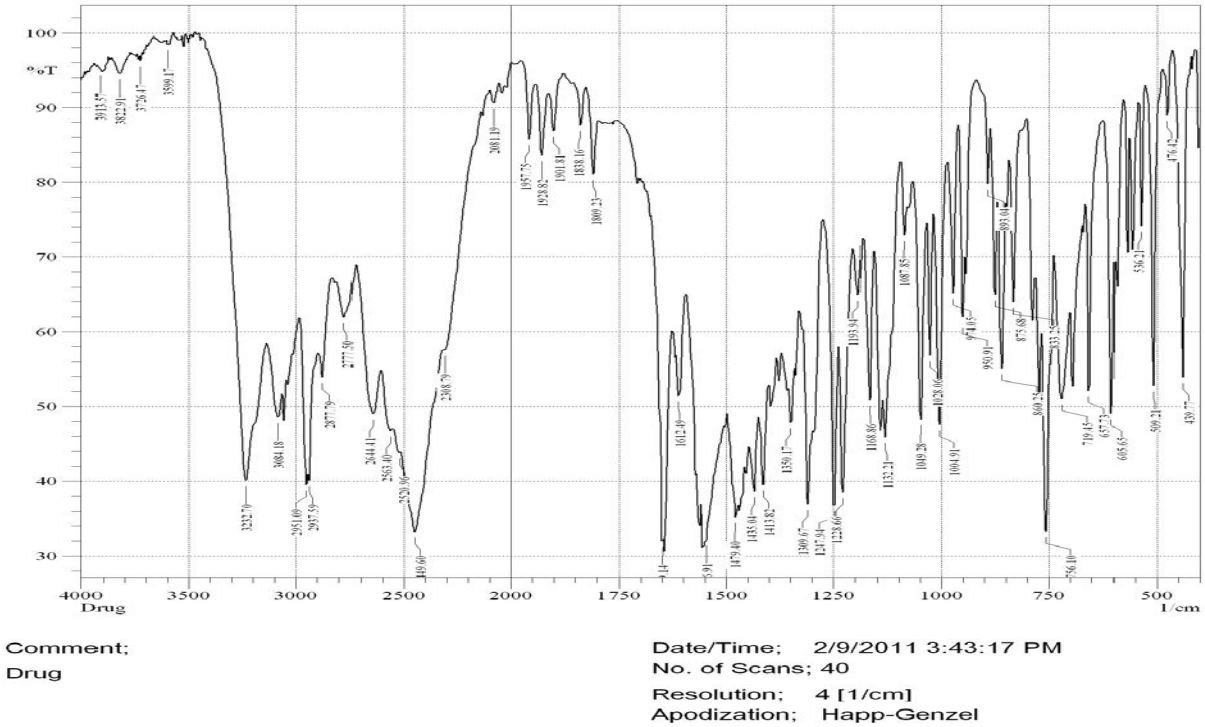

Fig 2: FTIR spectrum of Granisetron HCl pure drug

Tapped Density

Weighed quantity of blend, was transferred to a 10 ml graduated cylinder and tapped manually at specific height for a fixed number of taps (100). Average of three determinations was taken. The tapped

density was determined as the ratio of weight of sample to tapped volume (Subrahmanyam 1999).

Density = Mass/Volume

Carr's Index

The compressibility of sample blend was determined from their apparent bulk density and the tapped densities by using the following formula (Aulton 2002).

Percentage compressibility = (Tapped density – Bulk density)/ Tapped density × 100

Hausner's Ratio

Hausner's ratio is an indication of the flowability of powder and the ratio is greater than 1.25 is considered to be an indication of poor flowability. Hausner's ratio was determined by the ratio of tapped density / bulk density (Aulton 2002). Micromeritic properties are given in **Table 2**.

Table 2: Micromeritic properties of precompressional powder blend

Code	Bulk density* (gm/cm^3)	Tapped density* (gm/cm^3)	Angle of repose* (θ)	Carr's Index* (%)	Hausner's Ratio*
F1	0.53±0.12	0.59±0.43	13.64±0.15	10.16± 0.31	1.11±0.02
F2	0.41 ± 0.11	0.47± 0.33	19.43±0.17	12.76± 0.25	1.14±0.03
F3	0.47 ± 0.13	0.55 ± 0.36	15.93±0.15	14.54± 0.13	1.17±0.01
F4	0.54 ± 0.12	0.63 ± 0.42	23.12±0.15	14.28± 0.11	1.16±0.03
F5	0.44±0.15	0.51±0.63	15.08±0.23	13.72±0.18	1.15±0.01
F6	0.47±0.18	0.53± 0.42	14.31±0.17	11.32±0.12	1.12±0.03
F7	0.52±0.15	0.59±0.52	18.04±0.12	11.86±0.16	1.13±0.02
F8	0.55±0.17	0.49±0.35	16.13±0.19	14.28±0.28	1.16±0.01

*Average of 3 determinations, □□SD.

Evaluation of tablets

General appearance

Morphological characters like shape, color and texture were determined visually.

Thickness and Diameter

Thickness and diameter of prepared tablets (10) were tested using vernier calipers.

Hardness

The hardness of prepared tablets (5) was determined by using Monsanto hardness tester and measured in terms of kg/cm^2 (USP 2000).

Friability

The test was performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for testing the friability of prepared fast dissolving tablets. 10 tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions (USP 2000). The tablets were de-dusted and reweighed. Friability (F) was calculated using the following formula.

$$F = (1- W_0/W) \times 100$$

Where, W_0 and W are the weight of the tablets before and after the test respectively.

Weight variation

The weight variation test was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications (USP 2000).

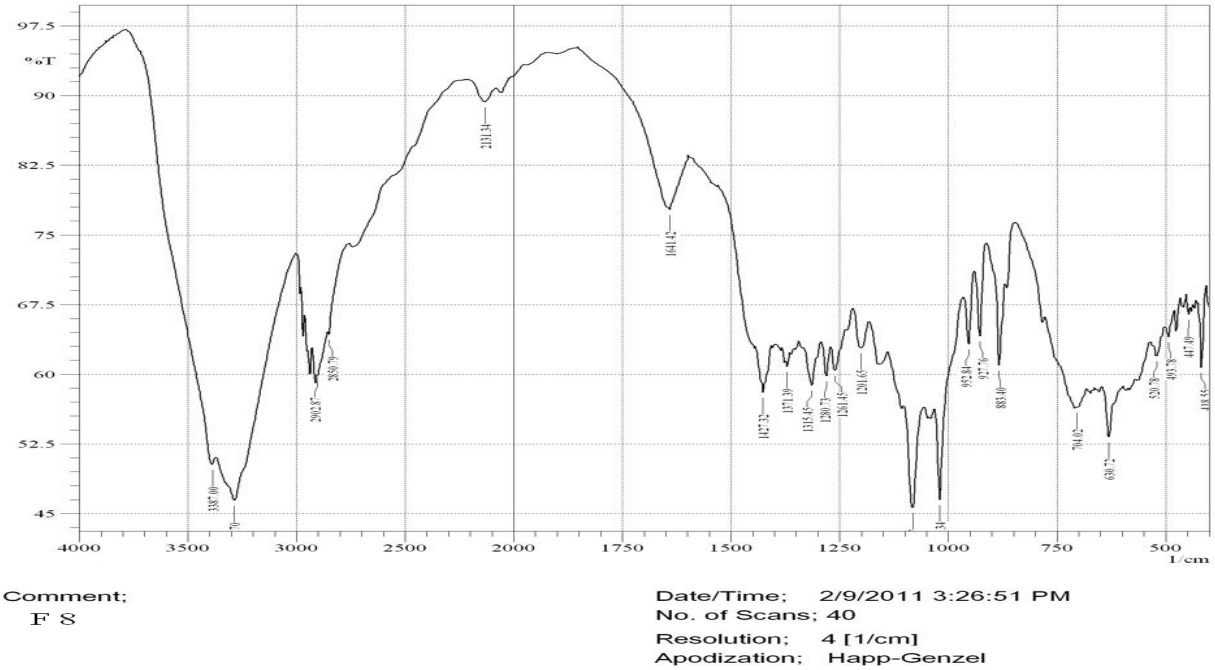

Fig 3: FTIR spectrum of formulation (F8)

Table 3: Physico-chemical Evaluation of fast dissolving tablets

Code	Thickness** (mm)	Hardness test* (kg/cm²)	Weight variation*** (%)	Friability**	Drug content* (%)
F1	4.32 ± 0.03	4.0±0.34	198.48±1.74	0.41±0.02	99.28 ± 0.65
F2	4.30 ± 0.05	3.9±0.30	200.64±1.43	0.44±0.01	99.83 ± 0.73
F3	4.31 ± 0.01	4.1±0.24	201.55±1.50	0.32±0.03	99.34 ± 0.34
F4	4.28 ± 0.02	4.2±0.28	198.48±1.56	0.49±0.01	99.56 ± 0.68
F5	4.28 ± 0.03	4.0±0.55	195.58±1.32	0.34±0.03	99.38 ± 0.78
F6	4.35 ± 0.01	3.8±0.35	200.64±1.46	0.36±0.01	99.57 ± 0.92
F7	4.25 ± 0.04	4.1±0.43	196.45±1.28	0.42±0.04	99.66 ± 0.33
F8	4.33 ± 0.06	4.2±0.28	201.68±1.53	0.33±0.01	99.85 ± 0.32

All values are expressed as mean ± SD, n=5/10**/20***

Drug content

Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of powder equivalent to 2 mg of Granisetron HCl was taken into 50 ml volumetric flask, dissolved in phosphate buffer of pH 6.8 and the solution was filtered through Whatman filter paper no.41. The filtrate was collected and suitably diluted with phosphate buffer of pH 6.8. The drug content was determined at 302 nm by UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) against blank. All physico-chemical evaluation parameters of tablets are given in **Table 3**.

Table 4: Comparison of wetting time and disintegration time of tablets

Code	Wetting time* (sec)	Disintegration time* (sec)
F1	29.16 ± 1.3	32.05 ± 1.4
F2	25.08 ± 1.4	29.14 ± 1.1
F3	22.28 ± 1.3	27.14 ± 1.2
F4	18.10 ± 1.1	22.35 ± 1.8
F5	24.23 ± 1.1	27.58 ± 1.5
F6	20.11 ± 1.2	24.18 ± 1.3
F7	17.05 ± 1.6	22.12 ± 1.1
F8	13.18 ± 1.8	17.10 ± 1.2

*Average of 3 determinations, □□SD.

Disintegration test

Six tablets along disc were introduced in each tube of basket of disintegration test apparatus (Lab care instruments). The basket was positioned into a beaker containing 900 ml of distilled water and operated at 37 ± 0.5° C. The time of disintegration of tablet was recorded (USP 2000). The average time and standard deviation were calculated.

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured. Disintegration test and wetting time data are given in **Table 4**.

In vitro dissolution

In vitro drug release for prepared fast disintegrating tablets were carried out using USP XXIV (Type II) dissolution apparatus at 37± 0.5°C and 50 rpm speed using 900 ml of phosphate buffer pH 6.8 as dissolution medium. At a predetermined interval of time 5 ml of sample was withdrawn and replaced with fresh medium. After filtration and appropriate dilution, the samples were analyzed at 302 nm for Granisetron HCl by UV-visible spectrophotometer against blank. The amounts of drug present in samples were calculated (**Table 5**).

Table 5: *In vitro* release data of Granisetron HCl from the tablets containing natural superdisintegrants

	Cumulative release data (%)							
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
0.5	2.67	5.35	10.71	14.73	4.01	9.37	13.39	20.08
1	12.67	16.68	22.04	30.08	15.34	20.70	26.06	34.09
1.5	22.11	27.49	34.21	43.63	27.48	32.87	39.59	50.35
2	31.60	39.69	49.13	61.28	39.68	47.78	57.22	66.70
2.5	39.81	50.62	60.11	76.35	50.61	60.09	69.59	83.13
3	52.02	61.61	72.49	88.82	61.60	73.81	87.38	99.16
3.5	64.41	74.00	83.60	98.68	72.65	86.27	99.91	-
4	76.82	85.11	97.45	-	83.76	98.79	-	-
4.5	87.95	96.29	-	-	98.95	-	-	-
5	97.80	-	-	-	-	-	-	-

Results and Discussion

In the present study pure Granisetron HCl 25µg/ml in a medium containing phosphate buffer of pH 6.8 was scanned over a range of 200-400 nm to determine its λ max. The peak was observed at 302 nm for Granisetron HCl. The obtained results revealed that the maximum absorbance appeared at 302 nm which confirms identification of Granisetron HCl in phosphate buffer of pH 6.8. The comparison of the IR spectrum of the formulation F8 with that of pure drug revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. Even though slightly differ in appearance but no change is observed in the positions of the bands in the spectra, this clearly suggests that the drug remains in the same form even in its formulations indicating that there is no interaction between the drug and polymer used for the study. Plain Granisetron HCl exhibited angle of repose (40.10 ± 0.26^{o}) indicating extremely poor flow property. It was further supported by high Carr's index value (20.46 ± 0.25%) and Hausner's ratio (1.45 ± 0.02). Hence it was necessary to use directly compressible vehicles like spray dried mannitol and MCC to improve the flow property of Granisetron HCl. Then the powder blend was compressed into tablets by direct compression on 10 station rotary punching machine. Further the tablets were subjected for physico-chemical evaluation. Tablets were obtained of uniform weight due to uniform die fill with acceptable variation as per IP specification i.e. below 7.5 %. Hardness of the tablets was between 3.8 to 4.2 kg/cm^2 for all the formulations. The thickness was ranged from 4.25 to 4.35 mm. Weight variation was found in between 195.58 to 200.64, Friability was found in between 0.32 to 0.49. The value below 1 % was an indication of good mechanical resistance of the tablet. The drug content was found to be 99.28 to 99.83 % which was within the acceptable limits. There is a good relation between wetting time and disintegration time. The disintegration time is short with quick wetting properties at the core of the tablet (Jacob 2007). The wetting time decreased with increasing the concentration of plantago ovata irrespective presence of the directly compressible vehicle used. The wetting time of formulation F8 was found 13.18 sec. The disintegrating time of the tablets decreased with increase in the concentration of plantago ovata. It showed that dissolution of tablets was proportionate with superdisintegrant concentration (Aly 2005). Also the results indicated that the dissolution profiles of tablet containing plantago ovata and agar are in agreement with disintegration time. The release profiles of tablets containing 2-5% w/w of superdisintegrants were observed. As the concentration of superdisintegrants increased the release of the drug was also increased. The selected formulations F8 have released 99.66% in 3 min. The investigated superdisintegrants can be ranked based on overall *in-vitro* release profile of Granisetron HCl FDT tablet plantago ovata > agar. The results of dissolution profile of FDT were in accordance with that of disintegration data.

Conclusion

The present research work revealed that the natural superdisintegrants plantago ovata showed better disintegrating and dissolution property than the agar in the formulation of fast disintegrating tablets.

Acknowledgements

The authors are thankful to Natco Pharma Ltd. Hyderabad (India) for providing gift sample of Granisetron HCl.

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