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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF GRANISETRON HYDROCHLORIDE BY DRY GRNULATION METHOD

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ABSTRACT

The aim of work is to characterization and evaluation of fast dissolving tablet of Granisetron hydrochloride using three superdisintegrants like crosscarmellose sodium, crosspovidone and sodium starch glycolate. FTIR studies revealed that there was no physico-chemical interaction between granisetron hydrochloride and other excipients. The tablets were prepared by dry granulation method and all had the same amount of ingredients except, the superdisintegrant level. The prepared batches of tablets were evaluated for uniformity of weight, thickness, hardness, friability, disintegration time and *in-vitro* dissolution study. Tablet containing crosspovidone showed excellent disintegration time and drug release as compared to other formulations.

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 tolerability 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 children [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 to 14 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 dispersible tablets of Granisetron Hydrochloride and to improve its bioavailability.

MATERIALS AND METHODS: Granisetron hydrochloride was a gift from Natco Pharma Ltd. (Hyderabad, India). Crosscarmellose sodium used was procured from Loba Chemicals, Mumbai. Crosspovidone and Sodium starch glycolate used were procured from Merck Limited, Mumbai. Dibasic calcium phosphate used was procured from Vikas Pharma, Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of fast disintegrating tablets of Granisetron hydrochloride: Fast disintegrating tablets containing 2.4 mg of Granisetron hydrochloride were prepared by dry granulation method. Amount of each ingredient (mg) was added according to the **table 1**. Required quantities of Granisetron hydrochloride, mannitol and dibasic calcium phosphate were weighed and mixed in geometric progression. This blend was then forced into 12 mm die tablet press to form slugs, having hardness of about 4.0 to 4.5 kg/cm2. These slugs were then milled and screened through 22/44 mesh.

Granules retained on 44 mesh were assayed for drug content and an amount equivalent to 2.4 mg of Granisetron hydrochloride for one tablet was weighed and blended with superdisintegrants and magnesium stearate as per the table 1. Superdisintegrants and magnesium stearate were passed through being added during the lubrication step. Lubrication was done for three minutes in a plastic container. Lubricated granules were punched and evaluated.

TABLE 1: FORMULATION OF GRANISETRON HYDROCHLORIDE FDT

Formulation Code	Granulation step (mg/tablet)			Lubrication step (mg/tablet)					Total weight (mg)
	GHCl*	DCP*	Mannitol	CCS*	CP*	SSG*	AS*	MS*	
DC	2.4	20	77.6	--	--	--	3	3	100
DCS_1	2.4	20	69.1	2.5	--	--	3	3	100
DCS_2	2.4	20	66.6	5	--	--	3	3	100
DCS_3	2.4	20	64.1	7.5	--	--	3	3	100
DCS_4	2.4	20	61.6	10		--	3	3	100
DCP_1	2.4	20	69.1	--	2.5	--	3	3	100
DCP_2	2.4	20	66.6	--	5	--	3	3	100
DCP_3	2.4	20	64.1	--	7.5	--	3	3	100
DCP_4	2.4	20	61.6	--	10		3	3	100
DSG_1	2.4	20	69.1	--	--	2.5	3	3	100
DSG_2	2.4	20	66.6	--	--	5	3	3	100
DSG_3	2.4	20	64.1	--	--	7.5	3	3	100
DSG_4	2.4	20	61.6	--	--	10	3	3	100

*GHCl stands for Granisetron hydrochloride; *DCP stands for dibasic calcium phosphate; *CCS stands for crosscarmellose sodium; *CP stands for crosspovidone; *AS stands for Aspartame; *SSG stands for sodium starch glycolate; * MG stands for Magnesium stearate

The granules were evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. After evaluation of granules, the tablets were compressed with a ten-station rotary punch-tableting machine (Rimek Mini Press-1) using 6 mm flat punches set.

Evaluation of powder blends [10-13]**:**

Bulk density: Apparent bulk density (ρb) was determined by placing presieved drug excipients blend into a graduated cylinder and measuring the volume (Vb) and weight (M) "as it is".

$$\rho b = M/Vb$$

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using following formula.

$$\rho t = M/ Vt$$

Angle of repose: Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

$$\theta = \tan^{-1} h/r$$

Compressibility index: The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility that is calculated as follows:

$$C = (\rho t – \rho b) / \rho t \times 100$$

ρt - Tapped density, ρb - Untapped bulk density

Hausner's ratio: Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

$$\text{Hausner's ratio} = \rho t \backslash \rho b$$

ρt - Tapped density, ρb -Untapped bulk density

Evaluation of Granisetron Hydrochloride fast disintegrating tablets [14-16]:

Weight variation test: Weight variation test was done by weighing 20 tablets individually, by using Sartorious balance (Model CP- 224 S). Calculating the average

weight and comparing the individual tablet weight to the average weight.

Tablet thickness: The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness: The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability: The friability of the tablets was measured in a Roche Friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (Wo) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = 100 (Wo - W) / Wo$$

***In-vitro* disintegration time:** The disintegration time of tablets was determined at 37±1°C according to the method described in the British Pharmacopoeia, 1998.

***In-vitro* dissolution study:** The release rate of Granisetron hydrochloride from fast dispersible tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 as a dissolution medium, at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time interval (minutes). The samples were filtered through a 0.45µ membrane filter. Absorbance of these solutions was measured at 302 nm using a PG instrument T_{80} model UV/VIS spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Drug content estimation: Powder equivalent to 2.24 mg of Granisetron hydrochloride was dissolved in phosphate buffer pH 6.8. Sufficient dilutions were made to obtain 10 mcg/ml solution. Absorbance of the resulting solution was measured at 302 nm using a PG instrument T_{80} model UV/VIS spectrophotometer. From the absorbance values, amount of drug present in the given tablet was calculated. Procedure was repeated by using four more tablets from the same formulation and the average value of all five tablets was calculated.

FTIR Spectroscopy: 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 to 5.**

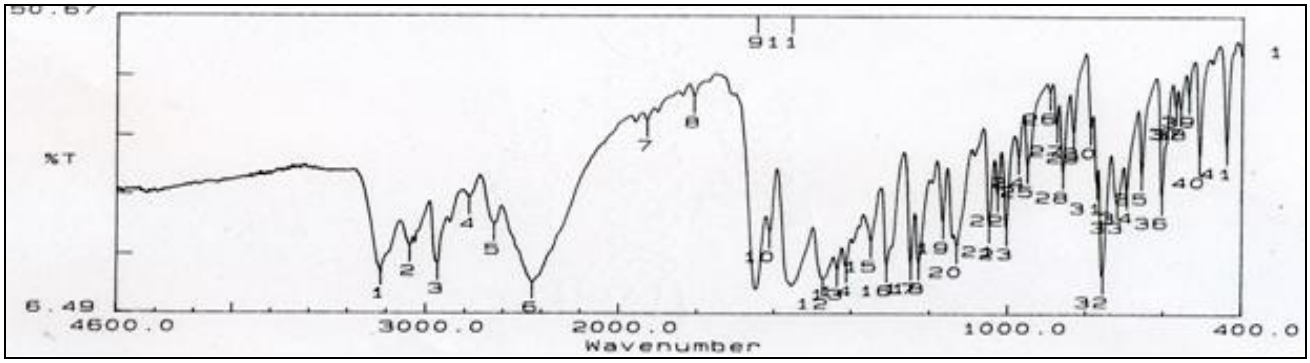

FIG. 1: FTIR SPECTRUM OF PURE GRANISETRON HYDROCHLORIDE

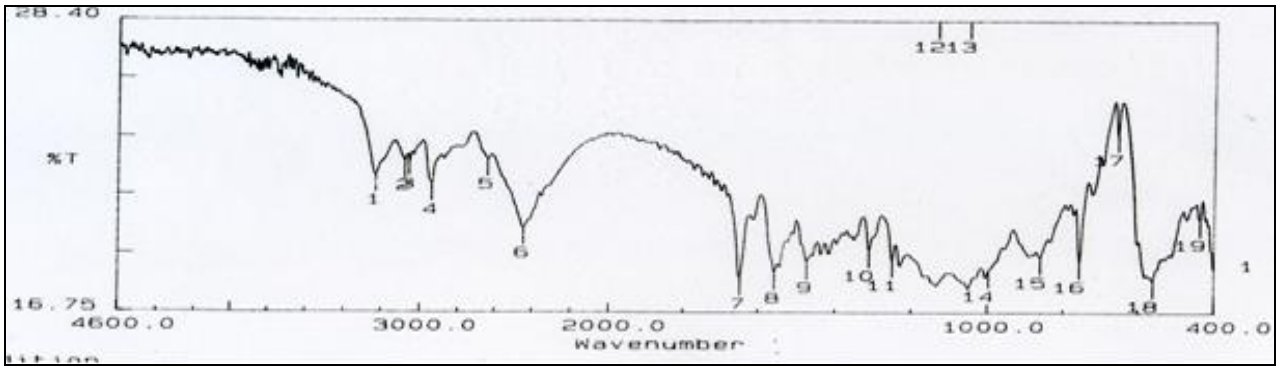

FIG. 2: FTIR SPECTRUM OF GRANISETRON HYDROCHLORIDE- DCP

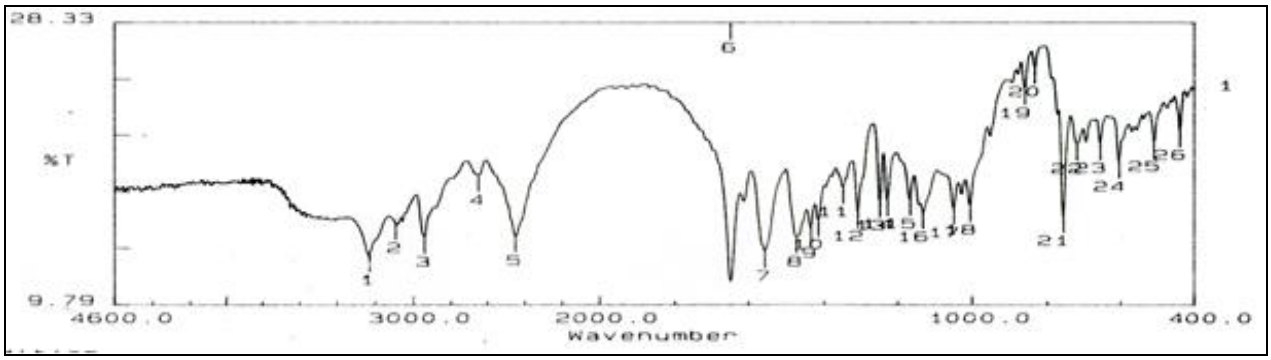

FIG. 3: FTIR SPECTRUM OF GRANISETRON HYDROCHLORIDE- CROSSCARMELLOSE SODIUM

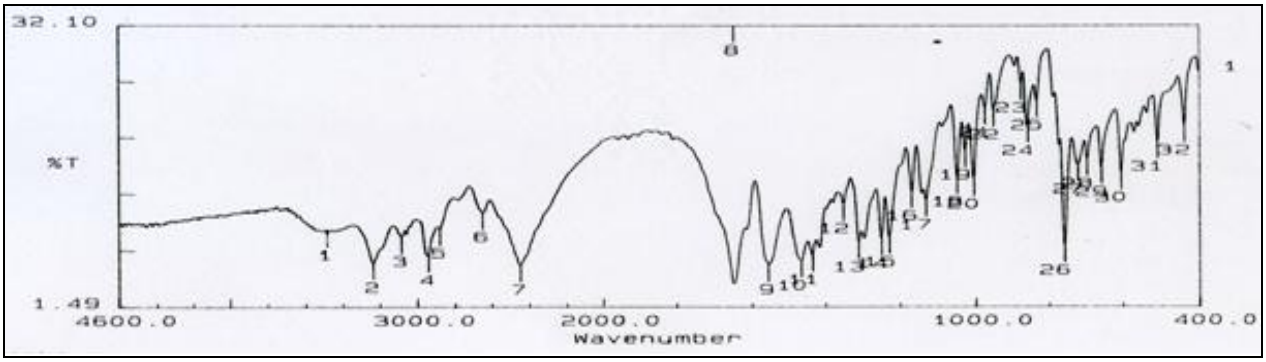

FIG. 4: FTIR SPECTRUM OF GRANISETRON HYDROCHLORIDE- CROSSPOVIDONE

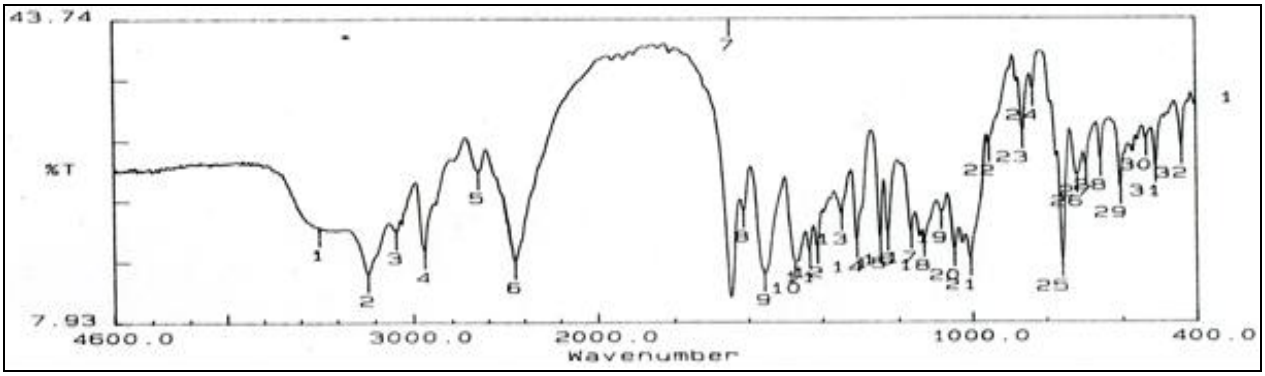

FIG.5: FTIR SPECTRUM OF GRANISETRON HYDROCHLORIDE- SODIUM STARCH GLYCOLATE

RESULTS AND DISCUSSION: FTIR studies revealed that there was no physico-chemical interaction between Granisetron hydrochloride and other excipients (Fig. 1 to 5). For each designed formulation, blend of drug and excipients was prepared and evaluated for micromeritics properties shown in **table 2**. Bulk density was found to be between 0.32±0.007 to 0.38±0.001gm/ml and tapped density between 0.35±0.002 to 0.43±0.001 gm/ml for all formulations. Hausner's ratio was found below 1.2 and Carr's compressibility index between 10- 16 for all formulations. The angle of repose is known to be a measure of flowability and the angle of repose of all formulations was found between 20.14±0.63 to 25.31±1.07 it indicate good flow properties of granules.

All batches of the tablets were evaluated for various physical parameters shown in **table 3**. The weight variation of all the tablets was within the ranges of 097±0.18 to 104±0.56 mg. The hardness of the tablets was within the range of 2.0±0.12 to 2.8±0.15 kg/cm2. The friability of all tablets below 1% and the disintegration time of different formulations are shown in **figure 6**. All the formulations had disintegration time was found between 42±1.24 to 70±1.10 seconds (crosspovidone> crosscarmellose sodium> sodium starch glycolate). The influences of superdisintegrants on the dissolution of granisetron hydrochloride from the tablets are shown in **Fig. 7 to 9**. The drug release increased with increase in the level of superdisintegrants. Out of thirteen formulations DCP_4 formulation shows best drug release 99.90% in 10 minutes.

TABLE 2: PRE COMPRESSION PARAMETERS DATA FOR GRANISETRON HYDROCHLORIDE POWDER BLEND

Formulation Code	Parameters				
	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Hausner's ratio*	Carr's index* (%)	Angle of repose* (θ)
DC	0.38±0.001	0.42±0.003	1.08±0.03	7.42±0.56	23.16±0.75
DCS_1	0.34±0.006	0.39±0.002	1.13±0.01	11.92±1.22	22.47±0.13
DCS_2	0.36±0.003	0.39±0.003	1.10±0.03	9.33±1.54	24.38±1.10
DCS_3	0.32±0.007	0.40±0.001	1.10±0.02	9.84±1.09	21.45±1.13
DCS_4	0.36±0.004	0.36±0.004	1.05±0.03	5.34±1.47	25.11±0.27
DCP_1	0.33±0.003	0.36±0.001	1.08±0.04	8.10±1.26	23.41±1.32
DCP_2	0.34±0.004	0.37±0.001	1.08±0.01	8.01±2.05	21.26±1.27
DCP_3	0.36±0.004	0.39±0.002	1.06±0.01	6.50±1.04	23.17±1.65
DCP_4	0.33±0.001	0.48±0.001	1.15±0.03	13.77±0.86	24.10±1.13
DSG_1	0.37±0.007	0.41±0.002	1.11±0.02	10.15±0.49	21.10±0.81
DSG_2	0.32±0.007	0.35±0.002	1.10±0.03	9.10±1.39	20.14±0.63
DSG_3	0.34±0.004	0.37±0.002	1.08±0.02	7.94±1.33	24.19±1.07
DSG_4	0.36±0.004	0.39±0.002	1.07±0.03	6.63±1.52	23.18±1.23

* Average of three determinations

TABLE 3: EVALUATION OF GRANISETRON HYDROCHLORIDE FDT

Formulation Code	Formulation parameters					
	Weight Variation*	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	Disintegration time* (sec)	% Drug release (10 min)
DC	102±1.45	2.98 ±0.41	2.1 ± 0.42	0.81	265±1.22	12.31
DCS_1	103±1.62	3.05 ±0.17	2.3 ± 0.15	0.69	58±1.16	88.26
DCS_2	098±1.73	3.00 ±0.45	2.3 ± 0.20	0.75	49±2.35	96.34
DCS_3	104±1.69	3.01 ±0.26	2.5 ± 0.05	0.59	32±1.57	98.00
DCS_4	101±0.96	3.20 ±0.18	2.2 ± 0.10	0.58	30±1.11	98.50
DCP_1	100±1.85	3.17 ±0.09	2.8 ± 0.15	0.73	61±0.56	81.56
DCP_2	097±0.18	3.11 ±0.01	2.1 ± 0.24	0.77	52±1.28	93.57
DCP_3	099±1.50	3.03 ±0.23	2.1 ± 0.10	0.60	54±1.50	97.02

DCP_4	103±1.21	3.16± 0.20	2.3 ± 0.21	0.58	43±0.38	99.90
DSG_1	097±1.93	3.10± 0.11	2.2 ± 0.15	0.66	71±1.10	72.12
DSG_2	098±0.65	3.11± 0.13	2.3 ± 0.10	0.62	59±0.21	87.19
DSG_3	100±1.97	3.19± 0.09	2.2 ± 0.18	0.58	48±1.29	89.99
DSG_4	104±0.56	2.97± 0.14	2.0 ± 0.12	0.56	42±1.24	96.38

* Average of three determinations

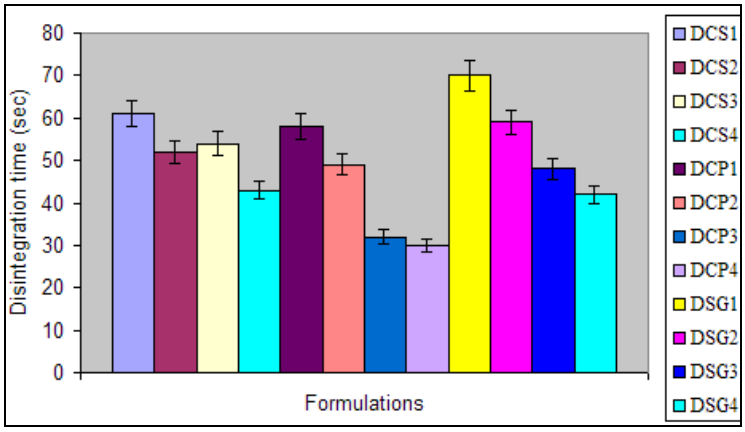

FIG. 6: DISINTEGRATION TIME OF VARIOUS GRANISETRON HYDROCHLORIDE FDT FORMULATIONS

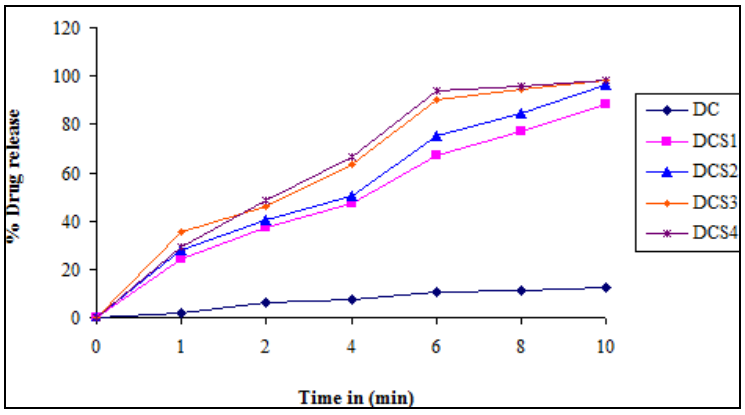

FIG. 7: DRUG RELEASE PROFILE OF FORMULATIONS CONTAINING CROSSCARMELLOSE SODIUM

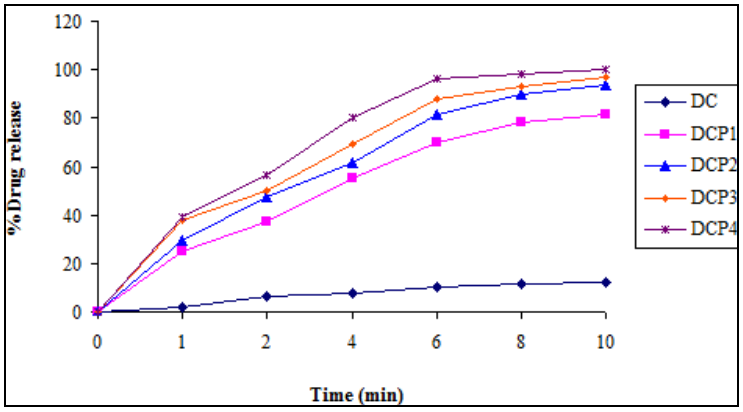

FIG. 8: DRUG RELEASE PROFILE OF FORMULATIONS CONTAINING CROSSPOVIDONE

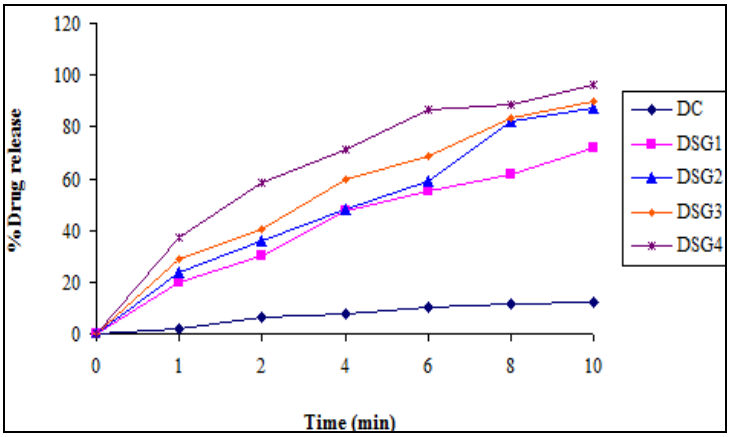

FIG.9: DRUG RELEASE PROFILE OF FORMULATIONS CONTAINING SODIUM STARCH GLYCOLATE

CONCLUSION: It can be concluded that disintegration time and dissolution rate of granisetron hydrochloride can be enhanced to a great extent by dry granulation technique with the addition of superdisintegrants. Further investigations are needed to confirm the *in-vivo* efficiency.

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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. Martin A. Diffusion and Dissolution. In: Physical pharmacy. 3rd ed. Philadelphia: Lea and Febiger; 1983; 399-444.
11. Fiese EF, Hagen TA. Preformulation. In: Lachman L, Lieberman HA, Kanig JL. Editors. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987; 182-184.
12. Ansel HC, Popovich NG, Allen LV. Pharmaceutical dosage forms and drug delivery system. 8th Ed. New Delhi. B.I. Waverly Pvt. Ltd., 1995; 189-194, 235-236.
13. Staniforth JN, Aulton ME. Powder flow In: Aulton's Pharmaceutics: the design and manufacturing of medicines. 3rd ed. Hungary: Harcourt publisher ltd.; 2007; 175-179.
14. Banker GS, Anderson NR. In: Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987; 293-399.
15. Mohapatra A, Parikh RK, Gohel MC. Formulation, development and evaluation of patient friendly dosage forms of metformin, Part-I: Orally disintegrating tablets. AAPS. 2009; 167-171.
16. United State Pharmacopoeia Convention. NF Asian edition; 2004; 74-75.

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