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Formulation and Evaluation of Granisetron Hydrochloride Fast Dissolving Tablets by Effervescent Technique

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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 attempts were made to prepare fast dissolving tablets (FDT) of Granisetron hydrochloride by effervescent technique with a view to enhance patient compliance. sodium starch glycolate used as super disintegrant along with sodium bicarbonate, anhydrous citric acid and tartaric acid in different ratios(as effervescent material) were used. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, these results revealed that there was no interaction between dug and other excipients. The values of pre-compressional parameters were within prescribed limits and indicated good free flowing properties. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulations was less than 1. Drug content was found to be high (≥ 100.10%) and uniform in all the formulations. The tablet thickness was found to be 3.08 to 3.25 mm. The weight variation results revealed that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. The disintegration time of the tablets decreased significantly with increase in the concentration of effervescent agents. The formulations GE_4, GE_8 and GE_{12} 50 % of drug released in 3.15, 2.11, 2.61 min, and 90 % of drug released in 7.23, 7.25, 6.25 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly ($p<0.05$). The release of drug from the GE_{12} formulation was quick when compared to other formulations.
Key words: Granisetron hydrochloride, Fast dissolving tablets, Effervescent technique, Sodium starch glycolate.

INTRODUCTION

Compare to other orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiology function associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy[1]. The pediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[2] and fast-disintegrating tablets[3] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying / Lyophilization[4], tablet molding[5] and direct-compression methods[6]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity[7]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentration of active drug[2]. Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern[8]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of tablet[9]. The oral fast dissolving dosage forms, also known as fast melt, fast disintegrating dosage forms, are relatively novel dosage technology that involves rapid disintegration or dissolution of the dosage forms, into a solution or suspension in the mouth without need of water[10-14]. The dosage form begins to disintegrate immediately after coming into contact with saliva, the complete disintegration normally occurring within 30 to 50 seconds[15]. The solution containing active ingredients is swallowed, and the active ingredients are then absorbed through gastrointestinal epithelium to reach the target and to produce the desired effect[16].

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[17-19]. 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[20,21]. 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[22].

In the present work attempts were made to prepare fast dissolving tablets (FDT) of Granisetron hydrochloride by effervescent technique with a view to enhance patient compliance.

MATERIALS AND METHODS

Granisetron Hydrochloride was gift sample from Natco Pharma. Ltd. Hyderabad. (AP). Sodium bicarbonate, anhydrous citric acid, tartaric acid, microcrystalline cellulose, sodium starch glycolate, mannitol, talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

Fourier transform infrared (FTIR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Granisetron hydrochloride and excipents used in the formulation. Physcial mixtures of drug and excipents were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy. IR spectrum of pure drug and excipients was seen in between 400-4600 cm^{-1} are shown in Fig.1 to 5.

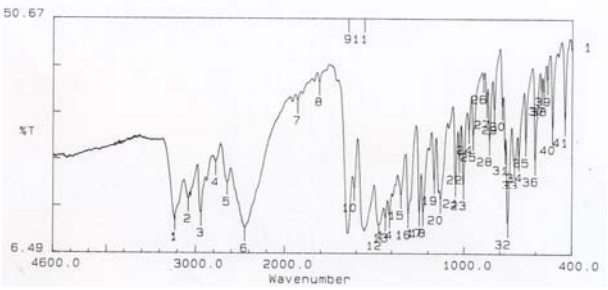

Fig. 1: IR spectrum of Granisetron hydrochloride

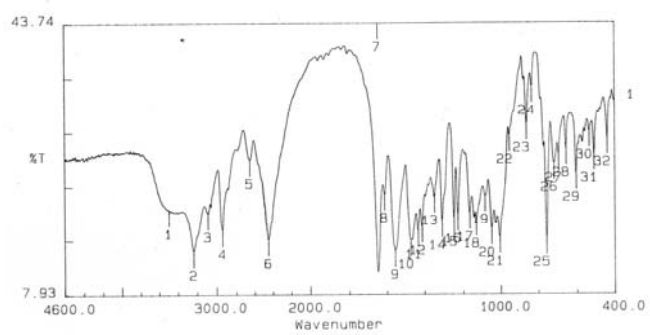

Fig. 2: IR spectrum of Drug + SSG

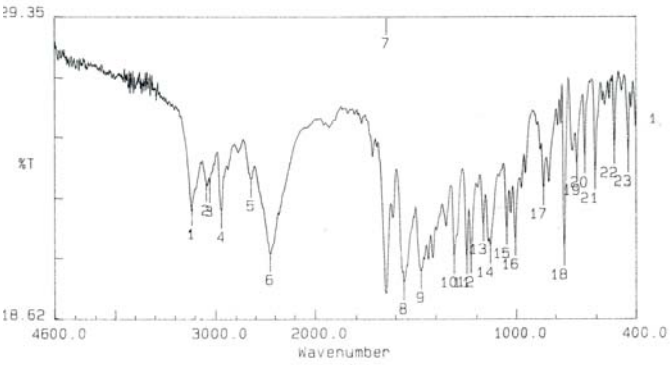

Fig. 3: IR spectrum of Drug + Sodium bicarbonate

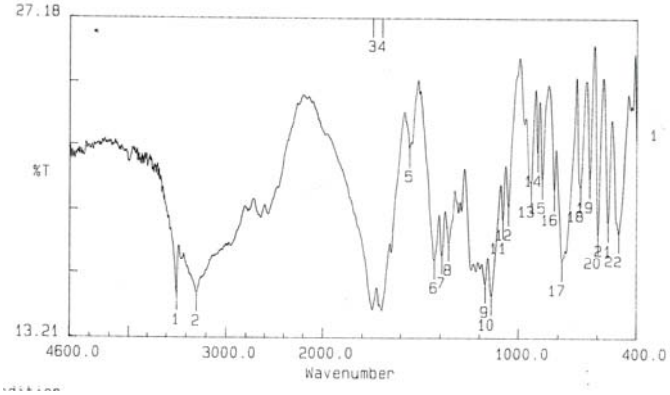

Fig. 4: IR spectrum of Drug + Citric acid

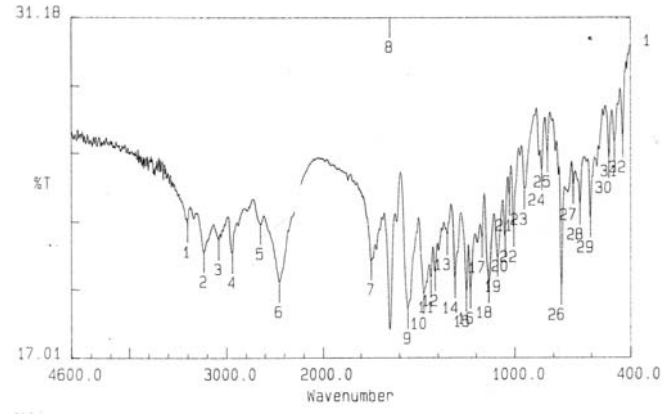

Fig. 5: IR spectrum of Drug + Tartaric acid

Table 1: Formulation of Granisetron hydrochloride FDT

Ingridents (mg)	Formulation code											
	GE_1	GE_2	GE_3	GE_4	GE_5	GE_6	GE_7	GE_8	GE_9	GE_{10}	GE_{11}	GE_{12}
Granisetron hydrochloride	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
SSG	6	6	6	6	6	6	6	6	6	6	6	6
Sodium bicarbonate	3	6	9	12	3	6	9	12	3	6	9	12
Citric acid	3	6	9	12	-	-	-	-	1.5	3.0	4.5	6
Tartaric acid	-	-	-	-	3	6	9	12	1.5	3.0	4.5	6
Aspartame	5	5	5	5	5	5	5	5	5	5	5	5
Mannitol	48.6	42.6	36.6	30.6	48.6	42.6	36.6	30.6	48.6	42.6	36.6	30.6
MCC	30	30	30	30	30	30	30	30	30	30	30	30
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium state	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

*SSG = Sodium starch glycolate, MCC = Microcrystalline cellulose

Preparation of tablet

For the preparation of fast dissolving tablets by effervescent method. All the ingredients (except magnesium sterate and purified talc) were accurately weighed and sifted through # 44 mesh separately, sodium bicarbonate, anhydrous citric acid and tartaric acid were pre-heated at a temperature of 80^0 C to remove adsorbed /residual moisture and were thoroughly mixed in a mortar to get a uniform powder and then added to other ingredients. The ingredients after sifting through # 44 mesh were thoroughly mixed in a tumbling cylindrical blender (fabricated in our laboratory). The blend thus obtained was directly compressed into tablets of 100 mg weight on using 6 mm 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 tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus using 900 ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper, wetting time study, a piece of tissue paper folded twice was kept in culture dish containing 6 ml of distilled water. A tablet having small amount of amaranth powder on upper surface was kept on tissue paper. A time required to develop a red color on upper surface of tablet was recorded as the wetting time. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 2.4 mg of Granisetron hydrochloride was taken and dissolved in phosphate buffer 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 302 nm. Using 900 ml of buffer monitored *in vitro* dissolution of Granisetron hydrochloride from tablets at 37 ± 0.5^0C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 min time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 302 nm. The stability study of the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40 ± 2^0 C / 75 ± 5% RH for 3 months

RESULTS AND DISCUSSION

The compatibility of drug with other ingredients was checked by FTIR studies, these results revealed that there was no interaction between drug and other excipients. The flow properties of the powder mixture are important for the uniformity of mass of tablets, the flow of powder mixture was before compression of tablets. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post compressional parameters results are shown in table 3 and 4.

Table 2: Precompressional parameters of Granisetron hydrochloride FDT

Formulation code	Angle of repose* (degree) ±SD	Bulk density* (g/cc) ± SD	Tapped density* (g/cc) ± SD	Carr's index* (%)± SD	Hausner's Ratio*± SD
GE_1	27.29 ± 1.27	0.50 ± 0.06	0.61 ± 0.01	17.95 ± 1.23	1.21 ± 0.03
GE_2	25.43 ± 1.19	0.51 ± 0.06	0.62 ± 0.01	17.47 ± 1.02	1.21 ± 0.02
GE_3	28.33 ± 1.30	0.49 ± 0.06	0.57 ± 0.01	13.79 ± 1.03	1.16 ± 0.03
GE_4	24.09 ± 1.01	0.53 ± 0.06	0.63 ± 0.02	14.82 ± 1.25	1.17 ± 0.03
GE_5	26.51 ± 1.45	0.51 ± 0.06	0.59 ± 0.01	14.47 ± 1.36	1.16 ± 0.03
GE_6	28.59 ± 1.56	0.49 ± 0.06	0.60 ± 0.02	17.13 ± 1.29	1.20 ± 0.03
GE_7	25.42 ± 1.20	0.52 ± 0.06	0.63 ± 0.01	16.56 ± 1.89	1.19 ± 0.03
GE_8	29.21 ± 1.15	0.51 ± 0.06	0.62 ± 0.02	16.85 ± 1.56	1.20 ± 0.03
GE_9	25.11 ± 1.29	0.51 ± 0.06	0.61 ± 0.02	15.66 ± 1.57	1.18 ± 0.02
GE_{10}	24.31 ± 1.49	0.54 ± 0.06	0.63 ± 0.01	14.63 ± 1.49	1.17 ± 0.03
GE_{11}	26.10 ±1.23	0.51 ± 0.06	0.61 ± 0.01	16.35 ± 1.69	1.19 ± 0.03
GE_{12}	29.19 ± 1.14	0.49 ± 0.06	0.57 ± 0.01	13.28 ± 1.75	1.15 ± 0.03

* Average of three determinations

Table 3: Post-compressional parameters of Granisetron hydrochloride FDT

Formulation Code	Hardness*(Kg/cm^2) ± SD	Thickness*(mm) ± SD	Friability(%)	Weight variation* (mg) ± SD
GE_1	3.5 ± 0.10	3.13 ± 0.10	0.51	101 ± 1.02
GE_2	3.0 ± 0.15	3.08 ± 0.02	0.67	100 ± 1.35
GE_3	2.5 ± 0.19	3.14 ± 0.10	0.81	98 ± 0.60
GE_4	2.5 ± 0.20	3.08 ± 0.20	0.72	97 ± 1.39
GE_5	2.8 ± 0.11	3.10 ± 0.14	0.38	99 ± 0.30
GE_6	3.0 ± 0.17	3.05 ± 0.19	0.45	100 ± 1.57
GE_7	3.0 ± 0.23	3.03 ± 0.12	0.40	102 ± 0.78
GE_8	3.5 ± 0.25	3.10 ± 0.25	0.37	99 ± 1.29
GE_9	3.1 ± 0.30	3.17 ± 0.30	0.35	101 ± 0.40
GE_{10}	3.2 ± 0.32	3.25 ± 0.09	0.29	100 ± 1.49
GE_{11}	3.3 ± 0.27	3.15 ± 0.05	0.60	99 ± 1.30
GE_{12}	2.9 ± 0.12	3.11± 0.10	0.58	99 ± 1.50

* Average of three determinations

Table 4: *In vitro* disintegration time, wetting time, water absorption ratio and drug content Granisetron hydrochloride FDT

Formulation Code	*In vitro* disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Water absorption ratio* ± SD	Drug Content* (%) ± SD
GE_1	72 ± 1.56	112 ± 1.25	80 ± 1.20	98.80 ± 0.75
GE_2	68 ± 2.36	108 ± 1.37	82 ± 1.53	99.75 ± 0.40
GE_3	64 ± 1.36	104 ± 1.53	81 ± 1.39	99.60 ± 0.53
GE_4	59 ± 1.59	99 ± 1.54	84 ± 1.98	100.10 ± 1.02
GE_5	52 ± 1.28	92 ± 1.35	82 ± 1.69	98.40 ± 1.90
GE_6	41 ± 1.53	80 ± 1.23	80 ± 1.30	99.30 ± 1.20
GE_7	44 ± 1.29	84 ± 2.09	84 ± 1.93	99.20 ± 1.17
GE_8	30 ± 1.44	74 ± 2.45	83 ± 1.62	98.10 ± 0.97
GE_9	34 ± 1.46	70 ± 2.03	81 ± 1.29	98.35 ± 1.31
GE_{10}	39 ± 2.04	79 ± 2.26	89 ± 1.49	99.03 ± 1.47
GE_{11}	37 ± 2.31	77 ± 0.29	87 ± 1.53	99.09 ± 0.64
GE_{12}	24 ± 1.34	64 ± 2.56	84 ± 1.63	98.50 ± 0.56

* Average of three determinations

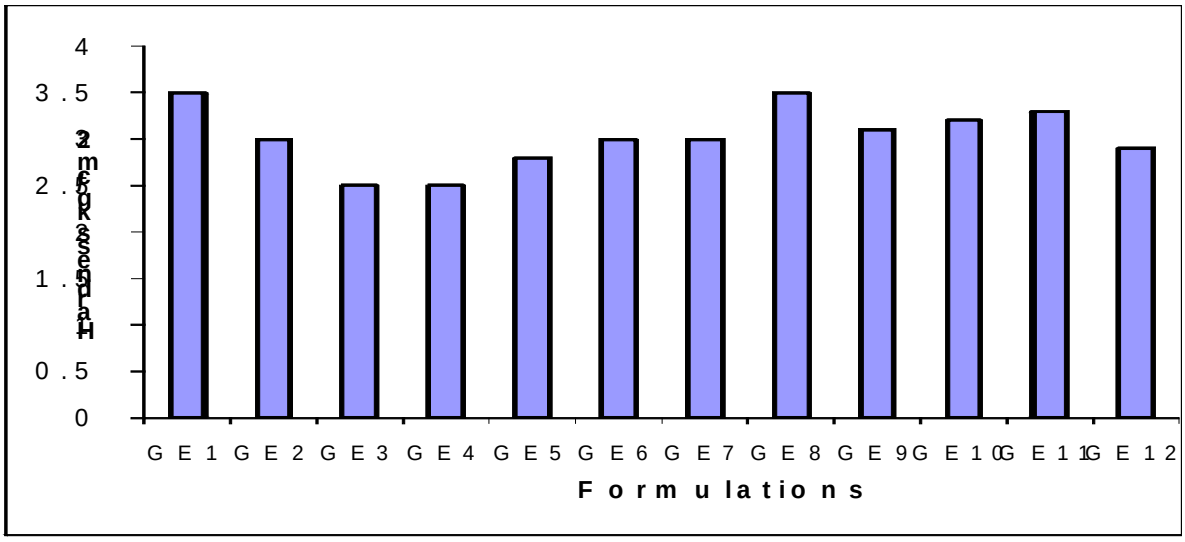

Fig. 6: Comparison of hardness of formulations

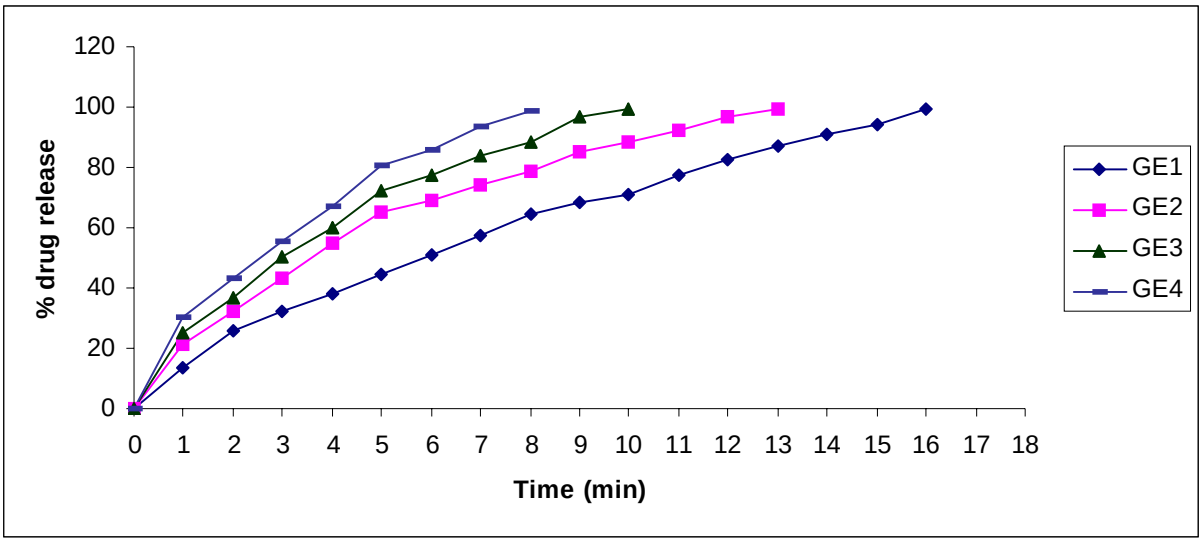

Fig. 7: Dissolution profile of formulations GE_1-GE_4

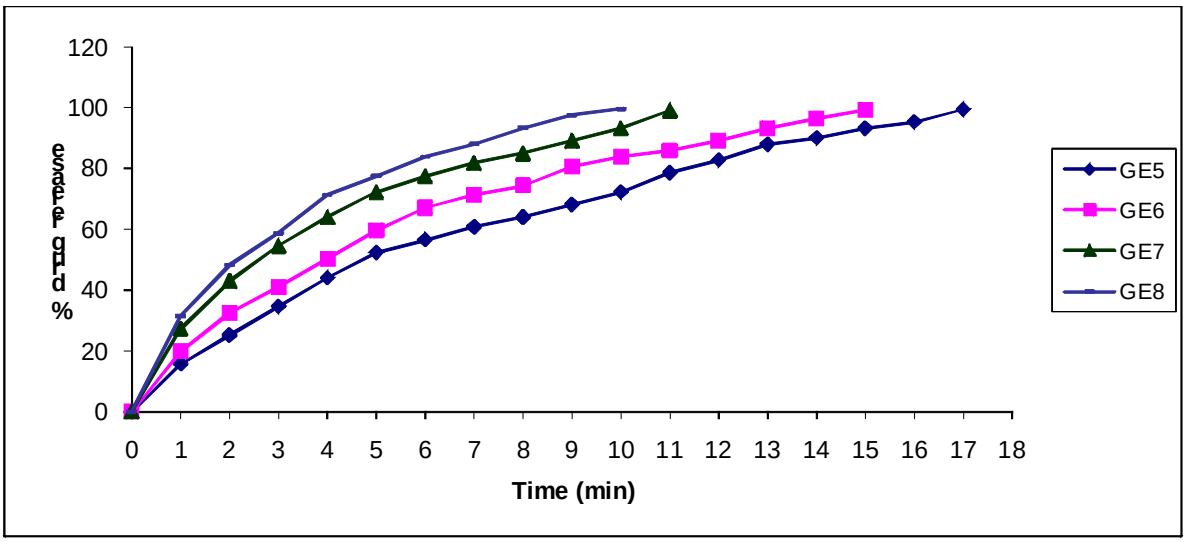

Fig. 8: Dissolution profile of formulations GE_5-GE_8

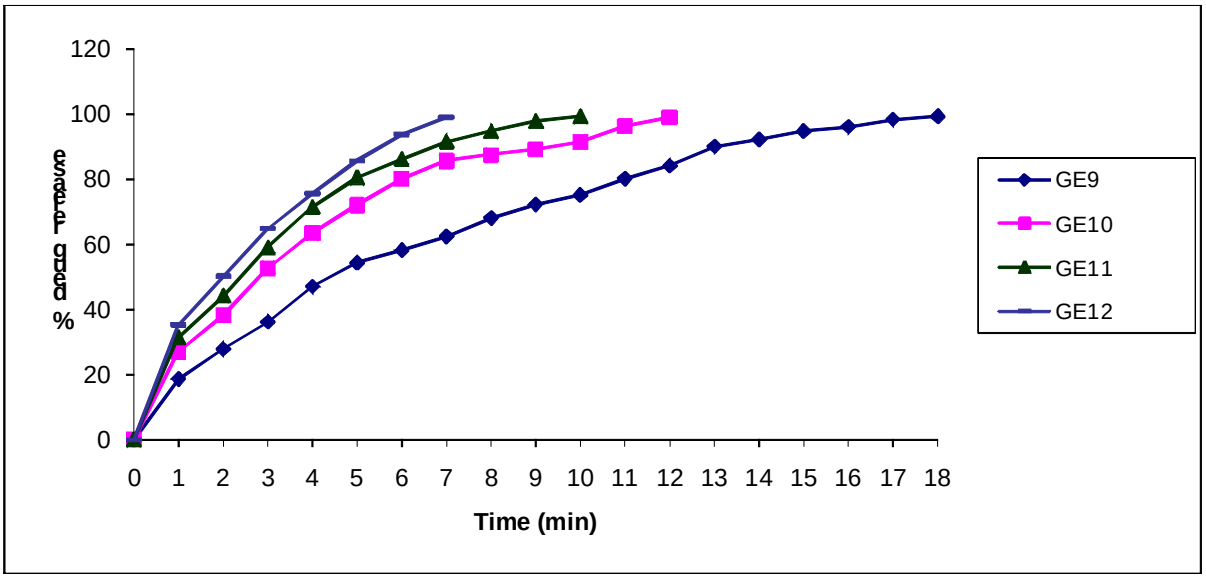

Fig. 9: Dissolution profile of formulations GE_9-GE_{12}

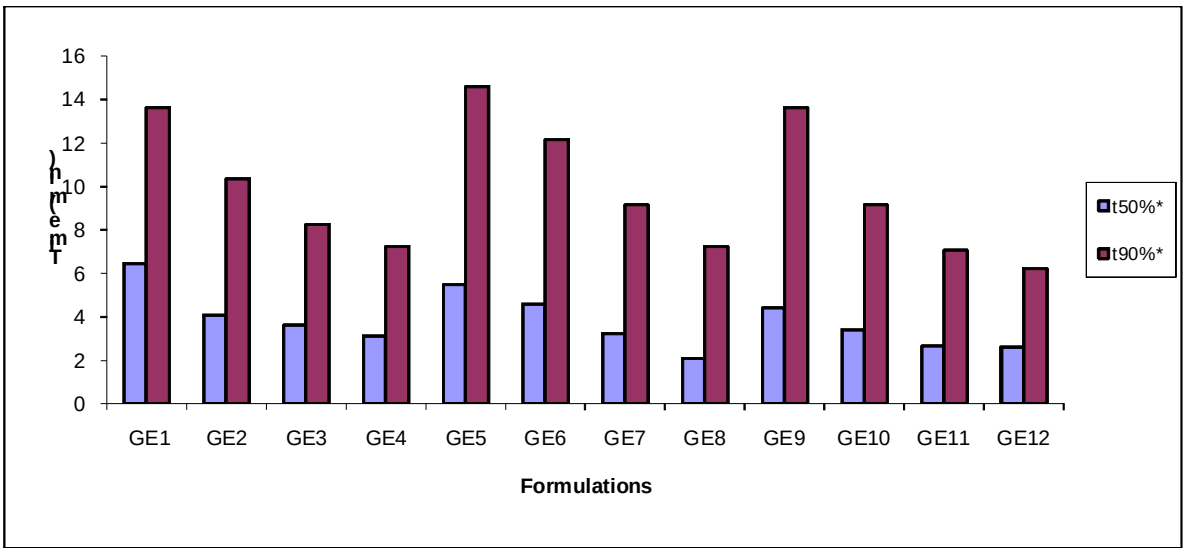

Fig. 10: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different formulations

In all the formulations the hardness test indicates good mechanical strength. The hardness of tablet decrease with increase in amount of effervescent component is shown in Fig. 6. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be high (≥100.10 %) and uniform in all formulations. The tablet thickness was found to be 3.08 to 3.25 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The disintegration time of decreased significantly with increase in concentration of effervescent agent. Faster wetting time of tablets was decreased with increase in the concentration of the effervescent agent. The wetting time of all formulations were found to be in the range of 64 to 112 sec. The dissolution profiles of all formulations are shown in Fig. 7 to 9. Out of twelve formulations, the formulation (GE_{12}) shows faster drug release within 7.00 min. *In vitro* release profile of different formulations are shown in Fig. 10 and in table 5.

Table 5: Release profile of Granisetron hydrochloride fast dissolving tablets prepared by sublimation method

Formulation Code	$t_{50\%}$*	$t_{90\%}$*
GE_1	6.48 ± 0.12	13.63 ± 0.29
GE_2	4.10 ± 0.21	10.35 ± 0.32
GE_3	3.61 ± 0.39	8.28 ± 0.56
GE_4	3.15 ± 0.51	7.23 ± 0.18
GE_5	5.48 ± 0.54	14.60 ± 0.27
GE_6	4.61 ± 0.45	12.18 ± 0.34
GE_7	3.25 ± 0.43	9.13 ± 0.54
GE_8	2.11 ± 0.29	7.25 ± 1.25
GE_9	4.40 ± 0.43	13.63 ± 0.59
GE_{10}	3.40 ± 0.39	9.13 ± 1.03
GE_{11}	2.65 ± 0.16	7.05 ± 0.22
GE_{12}	2.61 ± 0.38	6.25 ± 0.18

* Avserage of three determinations

The $t_{50\%}$ and $t_{90\%}$ values changed with changing concentration of effervescent agent. The formulations GE_4, GE_8 and GE_{12} 50% of drug released in 3.15, 2.11, 2.61 min, and 90 % of drug released in 7.23, 7.25, 6.25 min. The stability studies results revealed that, the disintegration time, wetting time was decreased significantly (Table 6).

Table 6:Results of stability study

Formulation Code	*In vitro* disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Drug Content* (%) ± SD
GE_4	56 ± 1.20	96 ± 1.40	98.02 ± 1.05
GE_8	28 ± 1.30	74 ± 1.10	98.16 ± 0.70
GE_{12}	24 ± 1.01	63 ± 1.47	98.14 ± 1.25

* Average of three determinations

CONCLUSION

The release of drug from the GE_{12} formulation was quick when compares to other formulations. It may be concluded that fast dissolving tablets of Granisetron hydrochloride showing enhanced dissolution rate with increasing concentration of effervescent agents.

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