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Formulation Design of Fast Dissolving Tablets of Granisetron Using Effervescent Blend with Improved Efficacy

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ABSTRACT

In the present work, fast dissolving tablets of granisetron HCl were prepared by effervescent method with a view to enhance patient compliance . Croscarmellose sodium is used as a superdisintigrant along with blend of sodium bicarbonate, anhydrous citric acid and tartaric acid in different ratios (as effervescent material) were used and directly compressible mannitol (Pearlitol SD 200) to enhance mouth feel. The prepared batches of tablets were evaluated for hardnss., friability, drug content uniformity , in vitro dispersion time. Based on in vitro dispersion time (approximately 10-35 s), three formulations were selected and tested for in vitro drug release pattern (in pH 6.8 phosphate buffer) and short -term stability (at 40^0 C/ 75 % RH for 3 months) and drug-excipient interaction (IR Spectroscopy) were studied. Among the three promising formulations, the formulation containing 8% w/w of croscarmellose sodium and blend of 24% w/w sodium bicarbonate, 12 % w/w of anhydrous citric acid and 12 %w/w tartaric acid emerged as the over all best formulation ($t_{50\%}$=1.4 min) based on the in vitro drug release characteristics compared to commercial conventional tablet formulation ($t_{50\%}$= 19.3 m). Short-term stability studies on the promising formulations indicated that there were no significant changes in drug content and in vitro dispersion time($p<0.05$).

Keywords: *Granisetron HCl, Fast dissolving tablets, Croscarmellose sodium, Effervescent method.*

INTRODUCTION

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus does not comply with prescription, which results in high incidence of non -compliance and ineffective therapy. Recent advances in Novel drug delivery System (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is " Fast dissolving tablets (FDT) [1-4]. Granisetron hydrochloride [5] is a serotonin 5-HT_3 eceptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy. Its main effect is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting centre in medulla oblongata.

EXPERIMENTAL SECTION

Granisetron hydrochloride was a gift sample from Natco Pharma Ltd., Hyderabad. Croscarmellose sodium (CCS) was gift sample from Wockhardt Research Centre, Aurangabad. Directly compressible mannitol (Pearlitol SD 200) and sodium stearyl fumarate (SSF) were generous gifts from strides Acrolabs, Bangalore. All the other chemicals used were of analytical reagent grade.

Table No. 1- Composition of Different Batches of Fast Dissolving Tablets of Granisetron Hydrochloride

Ingredients*	Formulation Code									
	EC_0	EC_1	EC_2	EC_3	ET_1	ET_2	ET_3	ECT_1	ECT_2	ECT_3
Granisetron HCl	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24	2.24
Croscarmellose sodium	---	3.0	6.0	12.0	3.0	6.0	12.0	3.0	6.0	12.0
Sodium bicarbonate	18.0	9.0	18.0	36.0	9.0	18.0	36.0	9.0	18.0	36.0
Citric acid	---	9.0	18.0	36.0	---	---	---	---	---	---
Tartaric acid	18.0	---	---	---	9.0	18.0	36.0			
Citric acid + Tartaric acid (1:1)	---	---	---	---	---	---	---	9.0	18.0	36.0
Aspartame	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Flavor	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Sodium stearyl fumerate	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Mannitol (Pearlitol SD200)	98.26	113.26	92.26	50.26	113.26	92.26	50.26	113.26	92.26	50.26
Total weight	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00	150.00

*Quantities expressed are in mg/ tablet

Preparation of fast dissolving tablets by effervescent Method [6].

For the preparation of fast dissolving tablets by effervescent method. All the ingredients (except SSF 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 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 150 mg weight on a 10- station rotary tablet machine (Clit, Ahmadabad) using 7 mm round flat punches. The tablets were prepared according to the formulae shown in table-1.

Evaluation of tablets

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation [7]. Hardness and friability of the tablets were determined by using Monsanto Hardness Tester and Roche friabilator respectively. For content uniformity tests, ten tablets were weighed and powdered. The powder equivalent to 2.24 mg of GSH was extracted into distilled water and liquid was filtered (Whatmann No. 1 filter paper). The GSH content in the filtrate was determined by measuring the absorbance at 302 nm after appropriate dilution with distilled water. The drug content was determined using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations [8]. For determination of *in vitro* dispersion time, One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5^0 and the time required for complete dispersion was determined[9]. IR spectra of GSH and its formulations were obtained by potassium bromide pellet method using Perkin-Elmer FTIR series (Model 1615) spectrophotometer in order to rule out drug carrier interactions.

Dissolution study [10]

In vitro dissolution of GSH fast dissolving tablets was studied in USP XXIII type-2 dissolution apparatus (Electro lab, Model-TDT 06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37 ± 0.5^0 as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 302 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of GSH released was calculated and plotted against time. The studies were carried out in triplicate.

Stability Testing

Short-term stability studies on the selected promising formulations (EC_3, ET_3 and ECT_3) were carried out by storing the tablets in amber colored vial with rubber stopper at 40^0/ 75 % RH over a 3 month period(as per ICH guidelines). At an intervals of one month, the tablets were visually examined for any physical changes, changes in drug content and *in vitro* dispersion time.

RESULTS AND DISCUSSION

Fast dissolving tablets of GSH were prepared by effervescent method employing CCS as super-disintegrant along with blend of sodium bicarbonate, anhydrous citric acid and tartaric acid in different ratios.Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to enhance mouth feel. A total of nine formulations and a control formulation EC_0 (without super-disintegrant) were designed. As the blends were free flowing (Angle of repose$<30^0$, and Carr's index <15%) tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below ±7.5%. Drug content was found to be in the range of 98.00 to 99.48%,which in within acceptable limits. Hardness of the tablets of the tablets were found to be 3.0 to 3.5 kg/ cm^2. friability below 1% was an indication of good mechanical resistance of the tablets. Among all the designed formulations,three formulations, viz., EC_3 , ET_3 and ECT_3 were found to be promising and displayed an *in vitro* dispersion time ranging from 10 to 35 s, which facilitates their faster dispersion in the mouth.

Overall, the formulation ECT_3 containing 8% w/w of croscarmellose sodium along with blend of sodium bicarbonate 24% w/w anhydrous citric acid 12% w/w of was found to be promising and

has shown an *in vitro* dispersion time of 10 s, when compared to control formulation (EC_0) which shows 95 s, for *in vitro* dispersion (Tablet 2).

Table No. 2-Evaluation of fast Dissolving Tablets of Granisetron Hydrochloride

Parameters	Formulation Code									
	EC_0	EC_1	EC_2	EC_3	ET_1	ET_2	ET_3	ECT_1	ECT_2	ECT_3
Hardness±SD* (kg/cm^2)	3.30±0.26	3.50±0.10	3.36±0.32	3.43±0.05	3.33±0.32	3.16±0.57	3.43±0.05	3.50±0.10	3.36±0.32	3.00±0.03
Thickness (mm)	2.85	2.90	2.78	2.70	2.85	2.80	2.85	2.74	2.56	2.78
Friability (%)	0.51	0.50	0.43	0.41	0.52	0.42	0.40	0.43	0.53	0.42
In vitro Dispersion time ±SD(%)*	95.45±0.37	55.56±1.63	41.76±1.52	35.17±1.76	52.29±1.86	38.12±1.74	33.12±1.73	35.36±1.02	16.54±1.30	10.74±1.52
Drug content ± SD*(%)	98.42±0.38	98.91±0.41	99.48±0.10	98.09±0.10	98.61±0.05	99.21±0.38	98.42±0.35	98.09±0.10	98.61±0.05	99.37±0.19
Weight variation	(147-155 mg) within the IP limits of ±7.5%									

* Average of three determinations. Formulations EC_3, ET_3 and ECT_3 were selected as the best and used for further studies.

Table 3: *In vitro* Dissolution Parameters in pH 6.8 Phosphate Buffer

Formulation code	D_5(%)	D_{10}(%)	D_{15}(%)	DE_{10} min(%)	$t_{50\%}$(min)	$t_{70\%}$(min)	$t_{90\%}$(min)
EC_0	12.00	21.00	25.00	29.04	>30	>30	>30
EC_3	52.00	73.00	82.00	34.64	4.00	9.20	22.00
ET_3	56.00	78.00	94.00	33.65	3.00	8.20	13.40
ECT_3	63.0	99.00	--	31.61	1.40	6.00	8.40
CCF	17.00	32.00	46.00	26.84	19.30	>30	>30

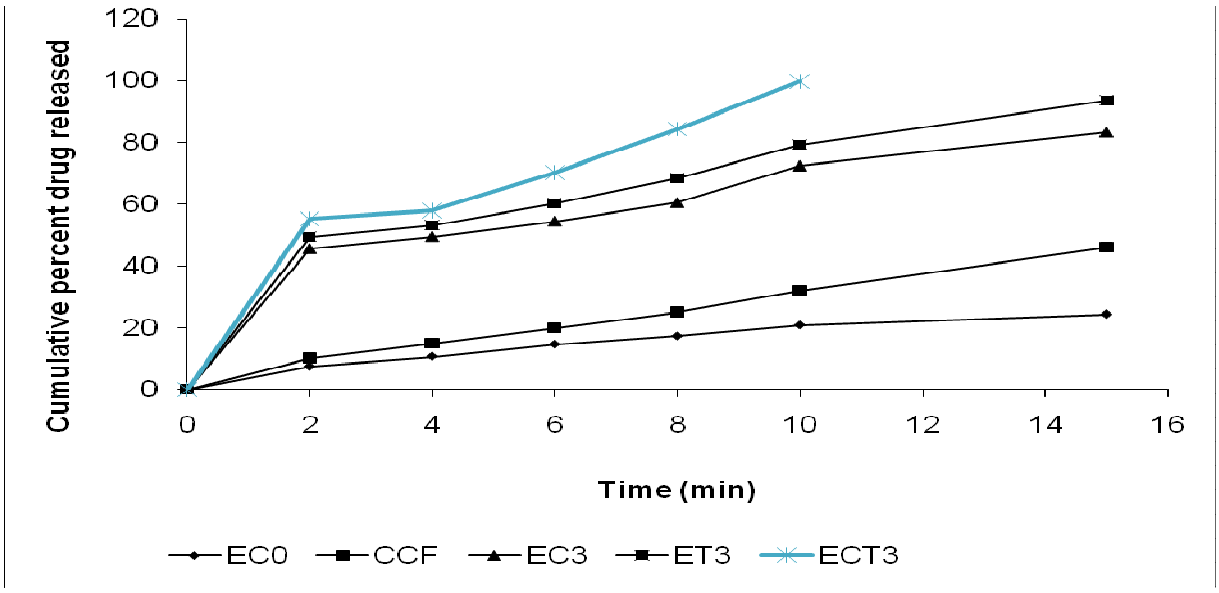

Fig. 1 *In vitro* cumulative percent drug release versus time plots of promising formulations in pH 6.8 phosphate buffer.

Plot showing percent cumulative release of promising granisetron HCl formulations.

In vitro dissolution studies on the promising formulations (EC_3 , ET_3 and ECT_3), the control (EC_0) and commercial conventional formulations (CCF) were carried out in pH 6.8 phosphate buffer, and the various dissolution parameter values viz., percent drug dissolved in 5 m, 10 min and 15 min (D_5, D_{10} and D_{15}), dissolution efficiency at 10 m ($DE_{10\ min}$) [11], $t_{50\%}$, $t_{70\%}$ and $t_{90\%}$ are shown in table 3, the dissolution profiles depicted in fig.1. This date reveals that overall, the formulation ECT_3 has shown nearly fourteen –fold faster drug release ($t_{50\%}$ 1.4 min) when compared to the commercial conventional tablet formulations of GSH ($t_{50\%}$ 19.3min) and released nearly 5-times more drug than the control formulation in 10 m.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of ECT_3 showed all the characteristic peaks of GSH pure drug, thus confirming that no interaction of drug occurred with the components of the formulation. Short-term stability studies of the above formulations indicated that there were no significant changes in drug content and *in vitro* dispersion time at the end of 3 months period ($P<0.05$).

CONCLUSION

The present study conclusively indicates that formulation ECT_3 is very much promising as fast dissolving (fast disintegrating) tablets formulation of granisetron hydrochloride with an *in vitro* dispersion time of 10 s.

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