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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF GRANISETRON HYDROCHLORIDE ORODISPERSIBLE TABLETS

Sunita Dahiya[1]*, Sachin Asati[2] and Vivek Mallurwar[2]

[1]*Department of Pharmaceutics, Bhopal Institute of Technology and Science - Pharmacy, Bhojpur Road, Bhopal-462 045, Madhya Pradesh, India*
[2]*R & D, Aristo Pharmaceuticals, Mandideep-462 046, Bhopal, Madhya Pradesh, India*

**E-mails*: sunitadahiya73@rediffmail.com, asatisachin@rediffmail.com
Tel.: +91-9009484272.

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The object of the present work was to formulate and evaluate orodispersible tablets of granisetron hydrochloride, a highly water soluble, tasteless, antiemetic drug employing superdisintegrants explotab, crospovidone, Ac-Di-Sol. The mix powder blends of varying compositions were prepared and evaluated for micromeritic properties and then subjected to tablet preparation by direct compression method. The prepared tablets were evaluated for physical parameters, wetting time, disintegration time, content uniformity and *in vitro* dissolution. The physical parameters were found satisfactory and the disintegration time of tablets was found between 19 to 35 seconds which is well below the limit of disintegration time by European Pharmacopoeia *i.e.* 3 minutes where as wetting time was found between 26-34 sec. Tablets prepared with crospovidone at 5% level (F4) was found to be the best formulation as it exhibited satisfactory physical parameters, least disintegration and wetting time and highest percent drug release (99.45%) at 10 min. Furthermore, F4 showed good stability at accelerated conditions (40°C±75% RH). The studies aid in the judicious selection of type and concentration of superdisintegrants in order to formulate a cost effective and patient friendly dosage form.

Key words: Granisetron hydrochloride, Superdisintegrants, Orodispersible tablets, Antiemetic.

INTRODUCTION

Difficulty in swallowing (Dysphagia) is a common problem in all age groups, especially the elderly and pediatrics, because of physiological changes associated with these age groups. It is common to see those afflicted carrying a small device with them, which is used for crushing tablets, enabling easy ingestion. Other categories that experience problems using conventional oral dosage forms include the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack and coughing. Sometimes, it may be difficult to swallow conventional products due to unavailability of water especially during traveling. These problems led to the development of a special type of solid oral dosage form called orodispersible tablets, which disintegrate and dissolve rapidly in saliva without the need of water. They are also known as mouth dissolve tablets, fast dissolving tablets, melt-in-mouth tablets, rapimelts, porous tablets, quick dissolving or rapidly disintegrating tablets. A number of researchers reported various aspects of orodispersible tablets (Seager, 1998; Panigrahi *et al* 2010; Reddy and Ghosh, 2002; Biradar *et al* 2006; Bandari *et al* 2008; Shukla *et al* 2009). Granisetron hydrochloride is the antagonist of serotonin 5-HT3 receptors, located peripherally on vagal nerve terminals, enteric neurons in the GI tract, and centrally in the chemoreceptor trigger zone. During chemotherapy, mucosal enterochromaffin cells from the small intestine release serotonin

which stimulates the 5-HT3 receptors. This evokes vagal afferent discharge, inducing vomiting. Granisetron hydrochloride is potent; freely water soluble, possesses longer half life ($t_{1/2}$) and acceptable taste, and is currently not available in market in form of orodispersible tablet (ODT). So, present work was undertaken to develop ODT of granisetron hydrochloride employing superdisintegrants using cost effective direct compression method. Superdisintegrants *i.e.* sodium starch glycolate, cross povidone and croscarmelose sodium were used in formulation of ODT because of their high swelling indices and greater solubilization potential.

MATERIALS AND METHODS

Materials

Granisetron hydrochloride and Pearlitol SD 200 was obtained from Aristo Pharmaceuticals, Mandideep, Bhopal. Explotab (Sodium starch glycolate), Crospovidone (crosslinked polyvinyl pyrrolidone), Ac-Di-Sol (croscarmelose sodium), Starch 1500 were obtained from Colorcon, India. Avicel PH 102 was obtained from Arihant Chemicals, Mumbai. All other chemicals used were of analytical grade. Double distilled water was used throughout the studies.

Methods

Preparation and evaluation of different blends

For formulation designing, super-disintegrating agents were used at lower, medium and higher concentrations. Eight formulations were designed using sodium starch glycolate used in concentration of 5%, 7.5%, crospovidne 2.5%, 5%, Ac-Di-Sol 5%, 7.5%. Avicel pH 102 (Microcrystalline cellulose pH102) was used at level of 7.5%, 10%. Each formulation was composed of drug, Pearlitol SD 200 as diluents, starch 1500 as dry binder (**Table 1**). This design technique was used to optimize and obtain a better formulation with respect to dispersion time. Lubricated blends of all formulations were examined for angle of repose, bulk and tapped density, Carr's index, Hausner's ratio.

Preparation of tablets

After evaluation, each powder blend was subjected to direct compression using single 8.0 mm standard concave punch on six station D tooling compression machine.

Table 1. Composition plan of different formulation blends

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Granisetron hydrochloride	1.12	1.12	1.12	1.12	1.12	1.12	1.12	1.12
Sodium starch glycolate	7.5	11.25	-	-	-	-	-	-
Crospovidone	-	-	3.75	7.5	-	-	-	-
Croscarmelose sodium	-	-	-	-	7.5	11.25	-	-
Avicel pH102	-	-	-	-	-	-	11.25	15
Pearlitol SD 200	111.88	108.13	115.63	111.88	111.88	108.13	108.13	104.38
Starch 1500	20	20	20	20	20	20	20	20
Flavor peppermint premium	3	3	3	3	3	3	3	3
Sucralose	3	3	3	3	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil 200	2	2	2	2	2	2	2	2
Total weight (mg)	150	150	150	150	150	150	150	150

Evaluation of tablets

Weight variation, hardness and friability test:

Twenty tablets were selected randomly from the lot and weighted individually to check for weight variation. Hardness or tablet crushing strength (f_c) is the force required to break a tablet in a diametric compression and was measured using Monsanto tablet hardness tester. Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Wetting time:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. The water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$dl/dt = r\Upsilon\cos\theta/(4\eta l)$

Where l is the length of penetration, r is the capillary radius, Υ is the surface tension, η is the liquid viscosity, t is the time, and θ is the contact angle. A piece of double folded tissue paper was placed in a petri plate (internal diameter is 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C (Gohel *et al* 2004).

Content uniformity test:

Twenty tablets were powdered and 1mg equivalent of granisetron was weighed and further dissolved in 50 ml phosphate buffer pH 6.8. One ml of this solution was transferred in a 100 ml volumetric flask, diluted to 100 ml with phosphate buffer pH 6.8 and the content of drug was determined spectroscopically at 301nm (Shimadzu 1700, Japan).

In vitro drug dissolution studies:

The drug release was studied using USP Type 2 Paddle apparatus at 50 rpm in 500 ml of phosphate buffer pH 6.8 as dissolution medium. The samples were withdrawn after predetermined time intervals, filtered, suitably diluted and amount of drug dissolved from tablets was determined spectrophotometrically at 301 nm against suitably constructed calibration curve (Patel and Patel, 2008).

Packaging and labeling:

Compressed tablets were packed in Alu Alu strip packing and labelled.

Stability study:

Selected formulations were subjected to stability studies as per ICH Guidelines at 30°C/65% RH and 40°C/75% RH analyzed at a time interval of 30 days till a period of 3 months.

Taste evaluation studies:

A taste evaluation study was carried out by panel method on 10 healthy human volunteers.

RESULTS AND DISCUSSION

The formulated blends were evaluated for parameters like angle of repose, tapped density, bulk density, % compressibility and Hausner ratio and found satisfactory with respect to pre-compression parameters (**Table 2**).

Table 2. Summary of evaluation of the formulation blends

Batch code	Bulk density	Tapped density	Angle of repose (°)	Carr's Index	Hausner's Ratio
F1	0.46	0.54	25.28	14.81	1.17
F2	0.44	0.53	24.35	16.91	1.20
F3	0.47	0.56	26.18	16.07	1.19
F4	0.45	0.53	24.53	15.09	1.17
F5	0.43	0.50	23.73	14.00	1.16
F6	0.46	0.52	25.80	15.38	1.13
F7	0.43	0.51	26.32	15.68	1.18
F8	0.42	0.50	25.21	16.00	1.19

All tablet formulations were appeared white to off white, round shaped biconvex and uncoated tablets with plain surfaces on both sides. All the formulations complied with weight variation, hardness, friability and content uniformity (**Table 3**).

The effect of the superdisintegrants on disintegration time is shown in **Table 4**. The disintegration time obtained for formulation F1 to F8 was within 19-35 sec and wetting time was within 26-34 sec (**Figure 1-3**). It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. The results suggested that Ac-Di-Sol exhibited the lowest disintegration time as compared to other superdisintegrants.

Table 3. Evaluation of physical parameters of Granisetron hydrochloride ODT

Batch code	Wt. variation	Thickness (mm)	Hardness	Friability (%)	DT[a] (sec)	WT[b] (sec)	Assay (%)	*In vivo* dispersion time (sec)	Water absorption ratio
F1	Pass	2.93	2.2	0.21	35	34	98.62	31	72.92
F2	Pass	2.96	2.4	0.22	27	31	99.06	29	75.83
F3	Pass	2.91	2.3	0.24	25	32	98.78	28	73.13
F4	Pass	2.30	2.1	0.28	24	31	100.21	27	76.48
F5	Pass	2.98	2.2	0.30	21	30	99.39	25	77.9
F6	Pass	3.0	2.6	0.31	22	33	99.88	30	78.31
F7	Pass	3.1	2.3	0.33	20	29	100.03	27	75.39
F8	Pass	2.95	2.4	0.39	19	26	99.98	23	75.82

[a]disintegration time, [b]wetting time

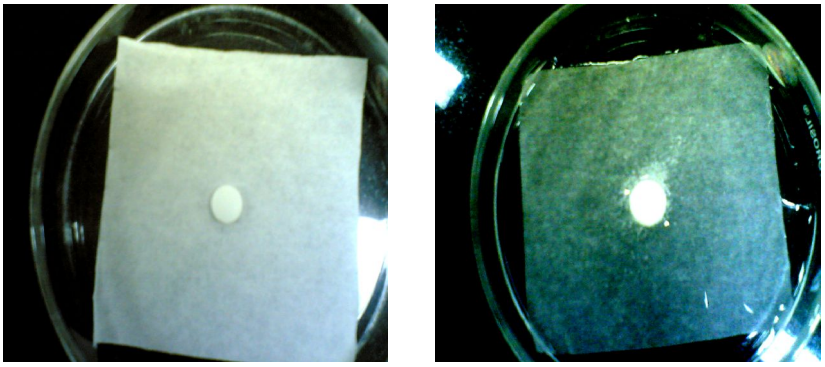

Fig. 1. Wetting time of granisetron hydrochloride ODT

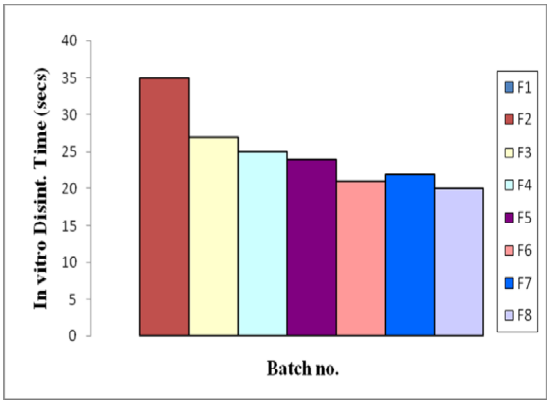

Fig. 2. Comparison of disintegration time of batches F1 to F8

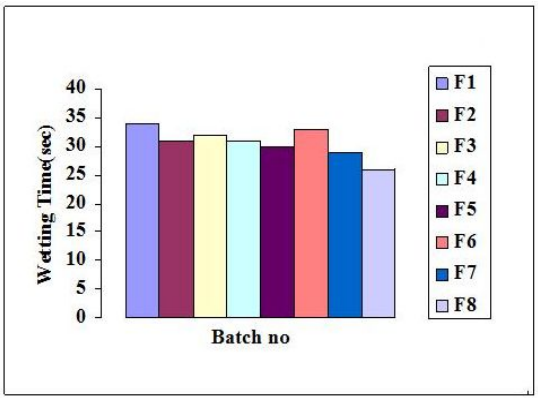

Fig. 3. Comparison of wetting time of batches F1 to F8

The drug release studies of formulated ODT suggested that all the formulations showed 85% drug release within 4 min and almost complete drug release within 10 min of drug dissolution studies (**Table 4**).

The results of all studied parameters suggested that formulation prepared with crospovidone at low concentration level (F4) exhibited the lowest disintegration and wetting time with complete drug release at 10 min even at lowest concentration, hence was ranked as the best among the four superdisintegrants. F4 was subjected to stability studies as per ICH guidelines for a period of three months and found stable with respect to hardness, drug content and *in vitro* dissolution.

Table 4. Dissolution data of formulations

S. No.	Time (min)	% Drug dissolved							
		F1	F2	F3	F4	F5	F6	F7	F8
1	2	77.22	79.23	88.25	89.25	81.22	89.41	82.41	84.41
2	4	93.72	94.79	92.01	95.01	91.72	94.88	93.69	94.25
3	6	96.33	96.29	95.13	97.13	93.33	97.30	94.30	96.32
4	8	97.73	96.88	97.35	98.35	96.73	98.73	97.73	96.99
5	10	98.03	97.71	98.11	99.45	98.70	99.05	98.91	99.02

The effects of temperature and time on the physical characteristics of the tablets were evaluated. The different parameters studied were hardness, drug content (%), *in vitro* disintegration time, wetting time, in vitro dissolution studies. The results suggested no significant changes in any parameter of tablets and therefore found stable under test conditions. Tablet taste evaluation studies suggested that all the formulated tablets were acceptable in taste (**Table 5**). The tablets were packed in strips and labeled (**Figure 4**).

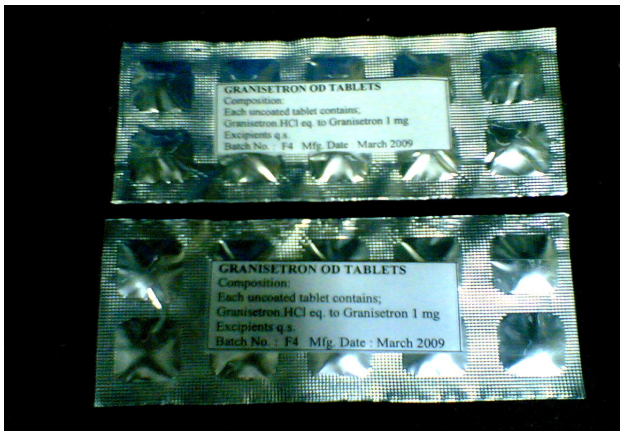

Fig. 4. Strip package of granisetron hydrochloride ODT

Table 5. Tablet taste evaluation studies

Volunteer No./ Formulation	1	2	3	4	5	6	7	8	9	10
Drug	0	0	0	0	0	0	0	0	0	0
F1	1	2	1	2	1	2	2	1	1	1
F2	3	2	1	2	2	1	1	1	1	2
F3	1	2	1	2	1	2	2	1	2	2
F4	3	3	3	3	3	2	3	2	3	3
F5	1	1	2	1	2	2	1	2	1	2
F6	1	2	2	1	1	2	1	2	2	1
F7	2	1	1	1	1	1	2	1	1	2
F8	1	1	1	2	1	2	1	2	1	1

Bitterness sensation scale: 0 – Tasteless, 1 - Acceptable, 2 - Moderately acceptable, 3 - Highly acceptable.

CONCLUSION

The orodispersible tablets of granisetron hydrochloride were successfully prepared using different superdisintegrants. Among all the superdisintegrants, crospovidone was found to be the best as it was effective even at least concentration level. The results of studies aid in the judicious selection of superdisintegrants and other adjuvants to formulate simple, convenient, cost effective and patient friendly dosage form.

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