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Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF GRANISETRON HYDROCHLORIDE USING PLANTAGO OVATE AS NATURAL SUPERDISINTEGRANTS

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ABSTRACT

The main objective of the study was to develop orodispersible tablets of Granisetron hydrochloride, a selective 5-HT3 receptor antagonist (an antivomiting agent) for improving patient compliance, especially those of paediatric & geriatric categories with difficulties in swallowing. In the wet granulation method orodispersible (ORD) tablets were prepared using natural super disintegrants plantago ovate.The prepared batches of tablets were evaluated for weight variation, hardness, friability, wetting time, *in vitro* dispersion time, drug content and *in vitro* dissolution studies. The tablet formulation batch F4 was considered as the overall best formulation (with an *in vitro* drug release study of 99.11%).Short term stability studies (at 40±2ºC/75±5% RH) on the best formulation indicated that there no significant changes in drug content. From the Fourier Transform Infrared (FTIR) spectroscopy study indicated that there are no drug excipient interactions.

Key words: Granisetron hydrochloride, Orodispersible tablets, FTIR spectroscopy, *in vitro* drug release study.

INTRODUCTION

The advances in novel drug delivery systems for designing dosage forms like orodispersible tablets (Kuchekar *et al.,* 2010; Chang *et al.,* 2000) for convenient to be manufactured and administered free side effects, offering immediate release and enhance bioavailability so as to achieve better patient compliance. Oral drug delivery systems preferably tablets are most widely used dosage forms for being compact offering uniform dose and painless delivery. But elderly and pediatric patients suffer in dysphasia because of physiological changes is associated with those groups (Lindgreen and Janzon, 1993; Bhushan *et al.,* 2000). Generally dysphasia is observed nearly 35% of population and associated with a number of conditions like parkinsonism, mental disabilities, motion sickness, unconsciousness, unavailability of water etc. To overcome such problems certain innovative drug delivery system (Sahoo *et al.,* 2011; Chein, 1992.) like mouth dissolving tablets have been developed.

The concept of orodispersible tablets emerged from the desire to provide patient with conventional mean of taking their medication. It can be disintegrated, dissolved or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric populations as well as other patients who prefer convenience of easily swallow able dosage form. Orodispersible tablets disintegrate instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating

tablets, porous tablets, rapimelts. The mouth dissolving tablets are absorbed from the mouth, pharynx and esophagus as saliva passes down into the stomach (Sahoo *et al.,* 2013). The solution containing active ingredients is absorbed through gastrointestinal epithelium to reach the target and produce desired effect. In these cases the bioavailability of drugs are significantly greater than those observed from conventional solid dosage forms such as tablets and capsules (Wilson *et al.,* 1987).

Granisetron hydrochloride is a selective 5-HT3 receptor antagonist which has effect on controlling nausea and vomiting. Its main effect is to reduce the activity of the vagus nerve which is a nerve that activates the vomiting centre in medulla oblongata. During chemotherapy induced vomiting, mucosal enterochromaffin cells release serotonin which stimulates 5-HT3 receptors. The stimulation of 5-HT3 receptors by serotonin causes vagal discharge resulting in vomiting. Granisetron blocks serotonin stimulation and is more effective than ondansetron when used in combination with dexamethasone in the prevention of acute and delayed vomiting caused by high emetogenic chemotherapy. Granisetron hydrochloride undergoes hepatic first pass metabolism with a bioavailability of 60% and terminal elimination half life between 3 to 14h after oral administration (Patil *et al.,* 2011). In the present study orodispersible tablets of granisetron hydrochloride were designed using wet granulation method using various excipients and plantago ovate as natural super disintegrants with prime objective arriving of a cost effective product (Bhaskran and Narmada, 2002).

MATERIAL AND METHODS

Granisetron hydrochloride was received as a gift sample from Suzikem Labs Pvt Ltd., cherlapally, A.P, Mannitol and Aerosil were obtained as gifts from Aurobindo labs Pvt Ltd, A.P. sodium saccharin, magnesium stearate, talc, micro crystalline cellulose,and potassium dihydrogen-o-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide, sodium lauryl sulphate and methanol were procured from Qualigens fine chemicals Mumbai.

Drug excipient studies

The FTIR spctroscopy allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the FTIR spectroscopy study it can be concluded that the major peaks of drug remains intact and no interaction was found between the drug and excipients.

Preparation of orodispersible tablets

Accurately weighed quantities of ingredients mentioned in table I were passed through sieve no. 12. and *plantego ovate* was passed through sieve no.20. All the ingredients lubricant magnesium stearate and talc (glidant) were manually blended homogenous by way of geometric dilution. The mixture was moistened with aqueous solution and granulated with sieve no.20 and placed in hot air oven at 50ºC for sufficient 3-4h. Then dried granules passed through sieve no.12 and blended with magnesium stearate and talc. The homogenous mixture were placed into tablet punching machine (10 station rotary tablet machine Clint India) getting tablet weight 190mg each using deep concave punch.

Evaluation of granules

Pre compression parameters of orodispersible tablets

Angle of repose

The angle of repose (Aithal *et al.,* 2006.) of granules blend was determined by the fixed funnel method. The accurately weighed quantity of granules was taken in a funnel. The height of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equation

$$\tan\Theta = h/r$$
$$\Theta = \tan^{-1}(h/r)$$

Where Θ is the angle of repose,h is the height of cone in cm and r is the radius of the cone base in cm.

Bulk density (e_b)

Bulk density was determined by pouring the granules into a graduated cylinder. The bulk volume (V_b) and mass (m) of the granules was determined. The bulk density was calculated (Sahoo *et al.,* 2015)by using the following formula.

$$\text{Bulk density } (e_b) = \frac{\text{Mass of granules(m)}}{\text{Bulk volume of granules}(V_b)}$$

Tapped density (e_t)

The measuring cylinder containing known mass of granules blend was tapped 1000 times for a fixed time. The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) was measured. The tapped density was measured (Satyanarayana *et al.,* 2015) by using the following formula.

$$\text{Tapped density } (e_b) = \frac{\text{Mass of granules(m)}}{\text{Tapped volume of granules}(V_b)}$$

density (e_t)= Mass of granules(m)/Tapped volume of granules(V_b)

Compressibility index (Carr's index)

The compressibility index (Danagi *et al.,* 2006.) [14] determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure of the potential powder arch and stability. The Carr's index can be calculated by the following formula.

$$\%\text{Carr's index} = \frac{e_t - e_b}{e_t} \times 100$$

Where e_t is the tapped density of granules and e_b is bulk density of granules

Hausner's ratio

Hausner's ratio is used for the determination of flow properties of granules (Sahoo *et al.,* 2015). The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Post compression parameters of orodispersible tablets

Thickness

The thickness of individual tablets is measured by using vernier calliper (Sahoo *et al.,* 2012) which gives the accurate measurement of thickness. It provides information of variation of thickness between tablets. Generally the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is ±5%.

Hardness

The hardness of prepared tablets was determined by using Monsanto hardness tester (Shishu *et al.,* 2007) and measured in terms of kg/cm^2. Test was done in triplicate.

Friability

Friability (Malke *et al.,* 2007) of tablets was performed in a Roche friabilator. Ten tablets were initially weighed (W_0) together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W). The percentage of friability was calculated using the following equation.

$$\%\text{Friability} = F = \left(1 - \frac{W_0}{W}\right) \times 100$$

Where, W_0 and W are the weight of the tablets before and after the test respectively. The limit for percentage of friability is between 0.5-1%.

Weight variation

The weight variation test [19] 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.

Disintegration test

Six tablets along disc were introduced in each tube of basket of disintegration (Jain *et al.,* 2009) test apparatus (Lab care instruments). The basket was positioned into a beaker containing 900mL of distilled water and operated at 37±2°C. The time of disintegration of tablet was recorded. The average time and standard deviation were calculated. Three trails were performed.

Wetting time

The Wetting time (Bhardwaj *et al.,* 2010) of the tablets can be measured using a simple procedure. Five circular tissue papers of 10cm diameter are placed in petri dish with a 10cm diameter. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small petri dish containing 6mL of simulated saliva pH 6.8, and the time for complete wetting was measured. Five tablets from each batch were used.

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5mL of distilled water. A tablet was placed on the tissue paper. The wetted tablet was weighed. The test was done in triplicate. The water absorption (Swamy *et al.,* 2007) ratio(R) was determined according to the following equation,

$$\text{Water absorption} = \frac{Wa - W_b}{W_a} \times 100$$

Where, W_a is the weight of the tablets before the test and W_b is the weight of the tablet after water absorption.

Drug content

Drug content for ORD tablet was done by the assay method (Bi *et al.,* 1999; Bhagwati *et al.,* 2005). First the prepared tablet (2mg API) was crushed and added to 10mL of phosphate buffer pH 6.8. After 30min the solution was filtered and from 10mL solution 1mL solution was withdrawn diluted upto 20mL with phosphate buffer pH 6.8 (10µg/mL). This solution concentration for the drug content of formulations were calculated using calibrated standard curve equation y=0.033x+0.018.The drug content was determined at λmax302 nm by UV-spectrophotometer (ELICO164) against blank.

In vitro dissolution studies

The release rate of Granisetron hydrochloride (Aithal *et al.,* 2006; Desai *et al.,* 2006). Orodispersible tablets was determined using United States pharmacopeia (USP) dissolution testing apparatus type 2 (paddle method). The dissolution test was performed using 900mL of Phosphate buffer pH 6.8, at 37°±0.5°C and 50rpm. In specified time intervals (0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5min) an aliquot of 5mL samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of 0.45µm. Absorbance of these solutions were measured at λmax 302nm using a UV/Visible Spectrophotometer (ELICO164). The drug release was plotted against time to determine the release profile of various batches.

In vitro dispersion time

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. *In vitro* dispersion (Chaudhari *et al.,* 2005) time was measured by dropping a tablet in a measuring cylinder containing 6mL of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was measured.

Stability studies

Tablets were stored at 40±2ºC/75±5% RH for a storage period of 0 days, 30 days, 60 days and 90 days for short term stability study (Patil *et al.,* 2011). The post compression parameters of tablets were tested during the storage period. The changes of dissolution and drug content were compared for stability study.

RESULTS AND DISCUSSION

Drug excipient studies

The FTIR spectroscopy allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the FTIR spectroscopy study it was found that there was no interaction between peaks of drug as well as other ingredients. So from the study it can be concluded that the major peaks of drug remains intact and no interaction was found between the drug and disintgrants. Hence drug and excipients are compatible to each other.

Pre-compression parameters of ORD formulations

All the compressible excipients (Table I) with drug by wet granulation method was

Table I. Composition of granisetron hydrochloride orodispersible tablets containing natural superdisintegrants

Ingredients(mg)	F1	F 2	F 3	F 4	F 5	F 6
GSH	2	2	2	2	2	2
Plantago Ovate	4	6	8	10	12	14
Micro Crystalline Cellulose	126	124	122	120	118	116
Mannitol	50	50	50	50	50	50
Aerosil	2	2	2	2	2	2
Sodium Saccharin	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Total weight(mg)	190	190	190	190	190	190

Where Θ is the angle of repose,h is the height of cone in cm and r is the radius of the cone base in cm.

Table II. Relationship between powder flowability and angle of repose

Angle of repose(Θ)	Observation
$<25^0$	Free flowing granules
$>40^0$	Poorly flowing granules

Table III. Relationship between powder flowability and % compressibility range

%Compressibility index	Flow type
5-15	Excellent flow(free flowing granules)
12-16	Good
18-21	Fair(powdered granules)
23-28	Poor(very fluidpowders)
28-35	Poor(fluid cohesive powders)
35-38	Very poor(fluid cohesive powders)
>40	Extremely poor(cohesive powders)

prepared using *Plantago Ovate* along with magnesium stearate and talc. This granules were evaluated for pre-compressionparameters (Table V) such as bulk density, tapped density,angle of repose and Carr's index.

The bulk density of pre-compression blends was found to be in the range of 0.52 to 0.68g/mL, tapped density in the range of 0.56 to 0.74g/mL, the Carr's index values were in the range of 12 to 20%, angle of repose in the ranges from 23 to 29 degrees and the hausner's ratio was in the range between 1.07 to 1.17.

Post-compression parameters of ORD formulations

The post compression parameters such as hardness, weight variation, drug content uniformity, friability and thickness have given below (Table VI). The other parameters such as wetting time, disintegration time and *in vitro* dispersion time have given below (Table VII).

The hardness of the tablet formulations was found to be in the range of 3.85to3.94kg/cm^2. The friability values were found to be in the range of 0.49 to 0.57%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed USP limits. The average weight of one tablet was found to be in range 189 to 190mg. The percent drug content of all the tablets was found to be in the range of 99.1 to 99.9% of the expected drug content, which was within the acceptable limits.

The disintegration time was in range 17 to 27s, wetting time was found be in range 14

Table IV. Relationship between powder flowability and Hausner's ratio

Hausner's ratio	Flow type
1.2	Free flowing granules
>1.6	Poorly flowing granules

Table V. Pre-compression parameters of ORD formulations

Formulation code	Bulk density (gm/mL) ±S.D	Tapped density (gm/mL) ±S.D	Angle of repo se (degree) ±S.D	Carr's index (%)±S.D	Hausner's Ratio±S.D
F1	0.56±0.02	0.66±0.08	23.0±0.03	15.15±0.02	1.17±0.08
F2	0.68±0.11	0.74±0.09	25.0±0.12	8.1±0.13	1.08±0.12
F3	0.54±0.13	0.68±0.11	24.0±0.11	20.58±0.01	1.2±0.125
F4	0.58±0.14	0.66±0.02	26.0±0.13	12.12±0.01	1.13±0.01
F5	0.52±0.15	0.56±0.02	27.0±0.01	7.1±0.14	1.07±0.09
F6	0.53±0.11	0.58±0.14	29.0±0.09	8.62±0.11	1.09±0.11

Table VI. Post-compression parameters of ORD formulations

Formulation code	Hardness (kg/cm^2) ±S.D	Friability (%)±S.D	%Drug Content ±S.D	Average wt. of 1tablet(mg)±S.D	Thickness (mm) ±S.D
F1	3.9±0.02	0.49±0.11	99.2±0.01	191±0.1	4±0.10
F2	3.89±0.01	0.52±0.01	99.4±0.02	190±0.1	4±0.11
F3	3.85±0.02	0.57±0.02	99.3±0.03	190±0.1	4±0.14
F4	3.94±0.05	0.51±0.10	99.9±0.04	189±0.1	4±0.13
F5	3.85±0.01	0.52±0.01	99.4±0.02	190±0.1	4±0.10
F6	3.85±0.02	0.53±0.04	99.1±0.02	189±0.1	4±0.10

Table VII. Post-compression parameters of ORD formulations

Formulation code	Disintegration time(s) ±S.D	*In vitro* dispersion time(s) ±S.D	Wetting time(sec) ±S.D	Water absorption ratio±S.D
F1	27±1.01	34±1.02	24±1.1	68.23±1.3
F2	24±1.05	30±1.02	20±1.02	71.50±1.8
F3	22±1.11	26±1.02	17±1.06	78.51±1.2
F4	17±1.23	20±1.02	14±1.07	80.48±1.6
F5	19±1.12	27±1.01	22±1.02	72.50±1.8
F6	24±1.04	30±1.02	19±1.02	66.23±1.3

to 24s, *in vitro* dispersion time was in range 20 to 34s and the water absorption ratio was between 66.23 to 80.48. The results are shown in table VII.

In vitro dispersion time

This test was performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. Among all formulations F4 formulation was found to be best. The dispersion time was found to be 20s (Figure 1).

In vitro drug release study

In vitro drug release studies were performed in pH 6.8 phosphate buffer, on the above promising formulation (F4) gives maximum amount of drug release comparing to other formulations. The percentage of drug release of F4 was best giving 99.11% in 3min comparing to other batches F1 (93.92%in 4.5min), F2 (95.43 in 4min), F3 (97.32in 3.5min), F5 (96.23 in 4.5min) and F6 (95.26 in 4.5min). The dissolution profiles of the above formulations are depicted in figure 2.

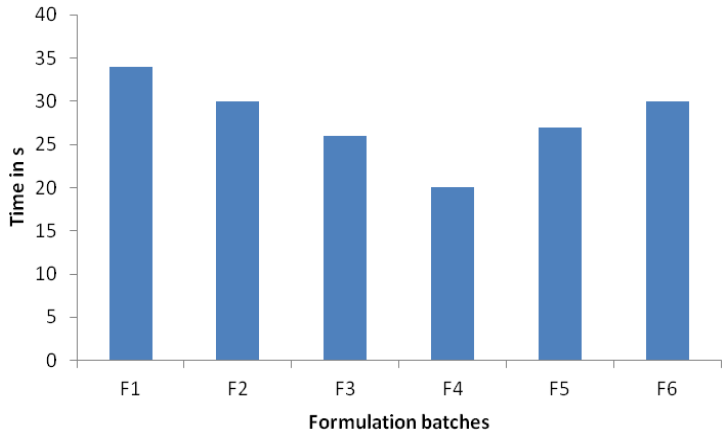

Figure 1. *In vitro* dispersion time of orodispersible tablets

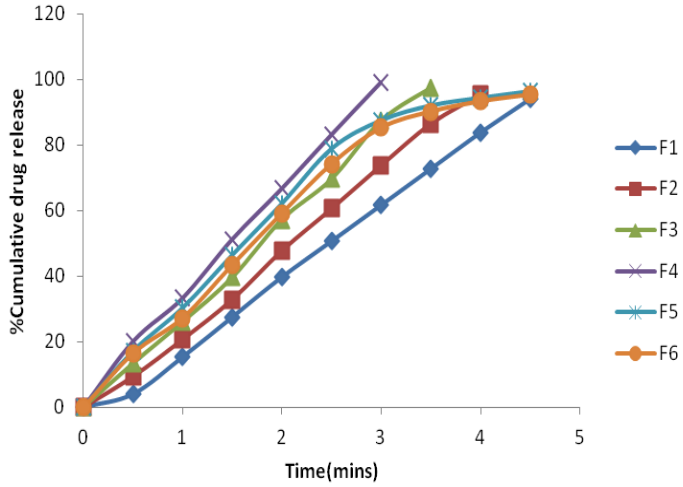

Figure 2. Comparative *in vitro* drug release study of GSH batches.

Short-term stability studies

Short-term stability studies on the above promising formulation (at 40±2°/75±5% RH for 3 months) have shown no significant changes in physical appearance, drug content and *in vitro* dispersion time. Statistical analysis ('t'-test) of drug content data gives 't' value of 1.91 for F4 formulation which is much less compared to the table value of 4.3 ($p<0.05$). There are no appreciable changes in *in vitro* dispersion time up on storage at 40±2°/75±5% RH for 3 months period.

CONCLUSION

The study clearly demonstrates that orodispersible tablets of granisetron hydrochloride could be successfully prepared by wet granulation method in a cost effective manner employing plantego ovate. It was evident from the results that rate of drug release can be optimized using disintegrants for orodispersible formulations. From the developed formulations the release of granisetron hydrochloride was best in F4 formulation i.e in-vitro study and *in vitro* dispersion time study. From the FTIR spectroscopy study, it was confirmed that the drug and excipients in the formulations were compatible with each other. Hence the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance providing rapid onset of action.

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