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FORMULATION, DEVELOPMENT AND EVALUATION OF ORODISPERSIBLE TABLET OF GRANISETRON HYDROCHLORIDE

Suresh Kumar Tiwari*, Ruchi Jain, Dr. R.B. Goswami

Sagar Institute of Research Technology and Science- Pharmacy, Bhopal

***Correspondence Info:**

Suresh Kumar Tiwari

Sagar Institute of Research Technology and Science-Pharmacy, Bhopal (M.P.)

Email:

Tiwarisuresh5792@gmail.com

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ABSTRACT

Granisetron hydrochloride is a novel serotonin 5-HT3 receptor used as antiemetic to treat nausea and vomiting during cancer chemotherapy but its oral bioavailability is low due to extensive first pass metabolism in liver which makes it ideal candidates for orodispersible tablet. The present work concerned with the formulation and evaluation of orodispersible tablet of granisetron hydrochloride by using three superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium. Orodispersible tablet of granisetron were prepared by the wet granulation method and blend was evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. Total nine formulations were prepared and evaluated for hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and *invitro* drug release. Pre compression studies revealed good micrometric properties of powder blend. The hardness, friability, drug content and disintegration time of orodispersible tablets were found uniform and reproducible. *In-vitro* dissolution studies are performed by using phosphate buffer pH 6.8 at 75 rpm by paddle method. Overall, the formulation F7containing of croscarmellose sodium was found to be promising and has shown a disintegration time 45±4sec. The stability studies were performed for two months (accelerated studies) as per ICH guidelines. The optimized formulation (F7) showed no significant variations for the tablets parameters and it was stable for the specified time period. The main aim of the study was to develop orodispersible tablets of granisetron hydrochloride a selective 5- HT3 receptor antagonist (antiemetic agent) for improving patient compliance, especially those of pediatric and geriatric categories with difficulties in swallowing.

Key words: Granisetron hydrochloride, Antiemetic, Wet granulation method, Sodium starch glycolate, Crospovidone, Croscarmellose sodium.

INTRODUCTION:

The advances in novel drug delivery systems for designing dosage forms like orodispersible tablets (Kuchekar et al., 2005; 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 paediatrics patients suffer in dysphagia because physiological changes associated with those groups (Lindgreen and Janzon, 1993; Bhushan et al., 2000). Generally, dysphagia is observed nearly 35% of population and associated with a number of conditions like parkinosonism, 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. These are novel dosage forms which dissolve in saliva within few seconds when put on tongue. 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 oesophagus 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. Granisetron hydrochloride undergoes hepatic first pass metabolism with a bioavailability of 60% and terminal elimination half life between 3 to 14 hrs 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 three superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium with prime objective arriving of a cost effective product and to improve its bioavailability (Bhaskran and Narmada, 2002).

MATERIAL AND METHOD

Material

Granisetron hydrochloride was a gift from Natco Pharma Ltd. (Hyderabad, India). Crospovidone, sodium starch glycolate and sodium starch glycolate was obtained from Hi-Media Laboratories Pvt. Ltd., Mumbai, India. Micro crystalline cellulose, mannitol, talc and magnesium stearate was procured from Central Drug House (P) Ltd. New Delhi. All other solvents and chemicals used were of analytical grade.

Preformulation studies

Standardization of granisetron hydrochloride by UV-Visible spectrophotometry: Accurately weighed 10 mg of drug was

dissolved in 10 ml of phosphate buffer pH 6.8 solutions in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with phosphate buffer pH 6.8 solution prepare suitable dilution to make it to a concentration range of 2-10µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+).

Drug-excipient compatibility study

FTIR spectra of pure drugs, polymers used and blends were recorded on KBr disk method using Brukers Alpha Spectrophotometer with IR solution software to confirm the compatibility between drug and excipients. Sample powder was thoroughly mixed by triturating with potassium bromide in a glass mortar with pestle and compressed into disks in a hydraulic press (Techno search Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700 to 400 cm-1 using 20 scans with 4 cm-1 resolution.

Preparation of tablets of granisetron hydrochloride

The orodispersible tablets of granisetron hydrochloride were prepared using the sodium starch glycolate, crospovidone and croscarmellose sodium as superdisintegrant, mannitol as diluent, aspartame as sweetening agent, alcoholic solution of polyvinyl pyrrolidone (PVP K-30) as binder and aerosil as flow promoter and magnesium stearate as lubricant, the composition of each batch is shown in Table 1. The raw materials were passed through a 100-mesh screen prior to mixing. The drug and other ingredients were mixed together and a sufficient quantity of alcoholic solution of PVP K-30 (10%w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules of the all formulations were then dried in a vacuum oven (Vertex, VT4810) at 60°C for 12 h resulting in localized drying. The final moisture content of the granules was found to be between 1- 2%, which was determined using an IR moisture balance. During drying, the menthol sublimed with the formation of a porous structure on the surface of the tablet. The dried granules were then blended with talc, magnesium stearate and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine (Sahoo et al., 2016).

Table 1 Formulation of various batches

F. Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	1	1	1	1	1	1	1	1	1
SSG	10	15	20	-	-	-	-	-	-
CP	-	-	-	10	15	20	-	-	-
CCS	-	-	-	-	-	-	10	15	20
Talc	10	10	10	10	10	10	10	10	10
Mg. Srearate	10	10	10	10	10	10	10	10	10
Lactose	54	49	44	54	49	44	54	49	44
Mannitol	15	15	15	15	15	15	15	15	15
Total wt.	100	100	100	100	100	100	100	100	100

Evaluation of orodispersible tablets of granisetron hydrochloride

Precompression parameters

Angle of repose (θ)

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$

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

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

LBD (Loose Bulk Density) = Mass of Powder/Volume of Packing

TBD (Tapped Bulk Density) = Mass of Powder/Tapped Volume of Packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (Pandey et al., 2019).

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light (Gautam et al., 2013; Patel et al., 2012).

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. In all the formulations the tablets weight is more than 130 mg and less than 324 mg, hence 7.5% maximum difference allowed.

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, deducted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loss more than 1% of their weight

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 5mg of drug dissolved in 10 ml phosphate buffer (pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 2 ml and Diluted up to 100 ml with phosphate buffer (pH 6.8) and the drug content was determined spectrophotometrically at 312 nm.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. A tablet placed in dissolution media (900 ml, phosphate buffer,

pH 6.8) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml phosphate buffer (pH 6.8). The samples withdrawn were assayed spectrophotometrically at 312 nm using UV visible spectrophotometer. The release of drug was calculated with the help of Standard curve of Granisetron hydrochloride.

Mathematical treatment of *in-vitro* release data: The quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

1. Zero-order kinetics: The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_o + K_o t$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

2. First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

3. Higuchi model: Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.

The simplified Higuchi model is expressed as:

$$Q = K_H \cdot t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release

pharmaceutical dosage forms such as transdermal systems and matrix tablets with water-soluble drug.

4. Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\,t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of n =0.5 for fickian diffusion and higher values of n, between 0.5 and 1.0, or n =1.0, for mass transfer following a non-fickian model. In case of a cylinder n =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as Power Law, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms [15-17].

RESULTS AND DISCUSSION

The λ_{max} of granisetron hydrochloride was found to be 312nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 10-50µg/ml. Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density, tapped density, compressibility index and Hauser's ratio of all the formulations was found to be within the range and showing that

the powder has well flow properties. The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 3.1±0.2to3.6±0.1kg/cm^2 and the friability values were less than 0.8% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 1.48±0.07 to 1.54±0.04mm. All the formulations satisfied the content of the drug as they contained 98.45±0.25 to 99.85±0.18% of granisetron hydrochloride and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control. The result in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets Table 4. The tablets were evaluated for in vitro dissolution studies in phosphate buffer pH 6.8 for 15min. The results of the optimized formulation F7 showed maximum drug release i.e. 99.12% at the end of 15 min. The results of release studies of formulations F7 was shown in Table 5. The *in vitro* drug release data of the optimized formulation F7 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Zero order was maximum i.e. 0.967 hence indicating drug release from formulations was found to follow Zero order models kinetics Table 6 & Figure 1, 2.

Table 2 Results of pre-compression parameters of granisetron hydrochloride

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.312	0.425	26.59	1.362	43^0
F2	0.325	0.436	25.46	1.342	43^0
F3	0.319	0.421	24.23	1.320	44^0
F4	0.327	0.436	25.00	1.333	43^0
F5	0.331	0.445	25.62	1.344	45^0
F6	0.336	0.452	25.66	1.345	44^0
F7	0.337	0.458	26.42	1.359	44^0
F8	0.346	0.465	25.59	1.344	43^0
F9	0.325	0.436	25.46	1.342	44^0

N=3 mean ±S.D

Table 3 Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.2±0.2	0.565±0.045	102±3	1.52±0.02	98.45±0.25
F2	3.4±0.3	0.754±0.065	98±2	1.54±0.04	98.74±0.32
F3	3.6±0.1	0.685±0.023	103±2	1.53±0.02	98.86±0.14
F4	3.3±0.4	0.674±0.041	96±4	1.52±0.03	99.12±0.26
F5	3.2±0.3	0.698±0.023	98±3	1.51±0.04	98.95±0.42
F6	3.4±0.2	0.745±0.032	100±5	1.53±0.06	98.86±0.18
F7	3.5±0.3	0.658±0.047	104±6	1.52±0.05	99.85±0.18
F8	3.4±0.1	0.745±0.033	102±2	1.53±0.03	98.65±0.19
F9	3.1±0.2	0.632±0.033	99±3	1.48±0.07	98.74±0.22

Table 4 Results of *In vitro* disintegration time of all formulations

Formulation code	Disintegration Time (sec.)
F1	85±5
F2	73±4
F3	65±3
F4	80±2
F5	75±4
F6	63±2
F7	45±4
F8	78±3
F9	69±3

N=3 mean ±S.D

Table 5 *In-vitro* drug release data for optimized formulation F7

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.000	0.000	55.65	1.745	44.35	1.647
5	2.236	0.699	75.32	1.877	24.68	1.392
10	3.162	1.000	85.45	1.932	14.55	1.163
15	3.873	1.176	99.12	1.996	0.88	-0.056

N=6 mean±S.D

Table 6 Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F7	0.967	0.857

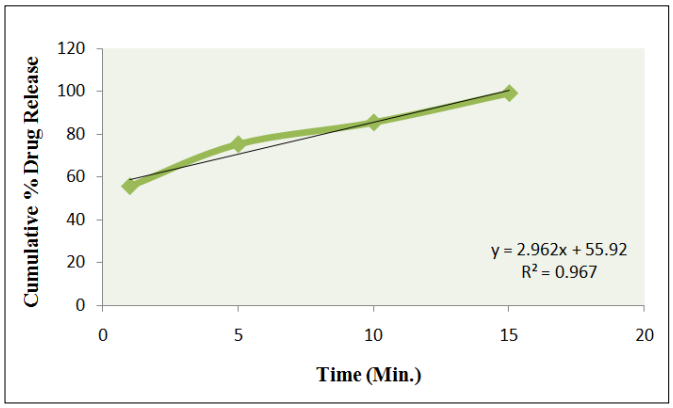

Figure 1 Graph of zero order release Kinetics of formulation F7

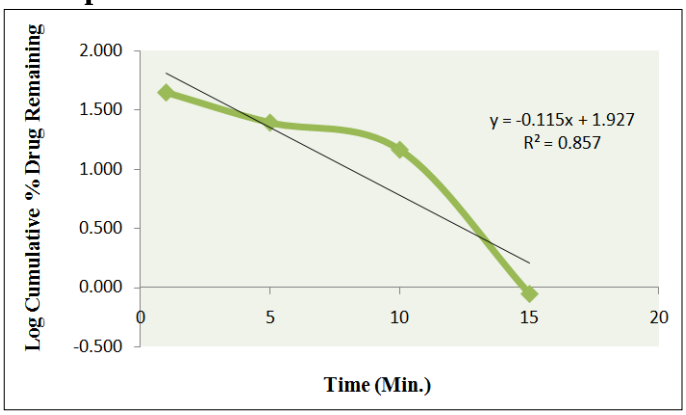

Figure 2 Graph of first order release kinetics of formulation F7

CONCLUSION

The study clearly demonstrates that orodispersible tablets of granisetron hydrochloride could be successfully prepared by wet granulation method in a cost effective manner using three superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium. It was evident from the results that rate of drug release can be optimized using disintegrates for orodispersible formulations. From the developed formulations the release of granisetron hydrochloride was best in F7 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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