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Design and Evaluation of Fast Dissolving Oral Films of Granisetron Hydrochloride

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ABSTRACT

Granisetron hydrochloride is a novel serotonin 5-HT_3 receptor antagonist used as an antiemetic to treat nausea and vomiting following chemotherapy. It is well absorbed from the gastrointestinal tract, but its oral bioavailability is low (60%) due to extensive first-pass metabolism which makes it an ideal candidate for rapid release drug delivery system. Hence, an attempt was made to prepare and evaluate fast dissolving oral films containing Granisetron hydrochloride as a model drug by solvent casting method using natural and synthetic polymers. Various formulations were developed with varying concentration of polymers like, CMC, HPMC and Pullulan. Citric acid was used as a disintegrating agent and Propylene glycol as a plasticizer. The prepared oral films were evaluated for their physicochemical and mechanical parameters such as Physical appearance, surface texture, Weight uniformity, surface pH, thickness uniformity, percentage moisture absorption, loss on drying, disintegration time, drug content uniformity, folding endurance, tensile strength, percentage elongation, *in-vitro* drug release, and stability studies. *In-vitro* release rate of Granisetron hydrochloride was studied in phosphate buffer pH 6.8. F7, F10 showed maximum release rate about 93.95% and 95.29% in 180 seconds respectively, whereas F3 showed 60.98%. The mechanism of drug release of fast dissolving oral film was found to be to be non-fickian diffusion following first order kinetics. The selected fast dissolving oral films were found to be superior to marketed conventional tablet. Short term stability studies of selected films indicated that there is no significant change with respect to physical appearance, disintegration time, drug content and *in-vitro* drug release.

Keywords: oral films, granisetron hydrochloride, HPMC, CMC, Pullulan

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INTRODUCTION

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms.

For the past two decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually[1]. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage form[2].

Mouth dissolving films, a new drug delivery system for the oral delivery of the drugs, was developed based on the technology of the transdermal patch. The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oral mucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed[5].

Among the different route of administration, the oral route of administration contains to be the most preferred route due to various advantageous including ease of administration, avoidance of pain, versatility, and most important is the patient compliance. One such relatively new dosage form is the oral strip[1, 2] Difficulty in swallowing (dysphagia) is a common problem of all groups, especially the elderly and pediatrics, because of physiological changes associated with these groups[1].

Cancer chemotherapy causes lot of adverse effects, of which nausea and vomiting is prime once. This can be clearly seen with model anticancer drug Cisplatin, which is first line drug in many types of cancers. Hence anti emetic drugs like Ondansetron, Granisetron are administered one hour prior to the administration of anticancer drug[13].Granisetron HCl is a novel serotonin 5-HT_3 receptor 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.. Granisetron HCl is well absorbed from the gastrointestinal tract, but its oral bioavailability is low (60%) due to extensive first -pass metabolism. Since oral route by passes first- pass effect, the dose of

Granisetron hydrochloride could be reduced by 50%[14].

Hence, an attempt was made to:

1. To design a fast dissolving oral film of Granisetron hydrochloride by solvent casting method.
2. To carry out drug and excipient compatibility styudies by FTIR.
3. To perform various physiochemical and mechanical parameter of the prepared films.
4. To carry out *in-vitro* evaluation studies and to analyze the data with different kinetic models.
5. To perform the stability studies of the selected formulations as per the ICH guidelines.
6. To compare with the marketed dosage forms.

MATERIALS AND METHODS:

Granisetron hydrochloride was obtained as a gift sample form Sun pharma gujurat. CMC,and HPMC E-15 were procured from Yarrow chem products Mumbai, India,and pullulan was obtained as a gift sample from DKSH India private limited, Mumbai, India. Propylene glycol was obtained from Loba-chem, Mumbai, India. citric acid, menthol and vanillin were procured from Hi-media, Mumbai, India. Ethanol was obtained from KSBCL, Mandya, India. All the chemicals were of analytical grade.

Prepartion of fast dissolving oral films of granisetron hydrochloride

Fast dissolving oral films of Granisetron hydrochloride was prepared by solvent casting method using polymers (CMC, HPMC, and pullulan).CMC polymer (250) mg was weighed accurately and it was soaked in half quantity of water for 8hr to get uniform dispersion. 10.6 mg of Granisetron hydrochloride was weighed and dissolved in water. Plasticizer (propylene glycol) was used in the range of 30% w/w of polymer concentration. This solution was added to the polymeric solution, and stirred well using a magnetic stirrer to obtain a homogenous solution, followed by the addition of vanillin and citric acid. Menthol was dissolved in 5ml of alcohol and added to the above solution and mixed well. The solution was allowed to stand for 30min to allow deareation to take place. Solution was then casted in to a petri dish having area of 64cm^2 and 1.3cm wall height. Petri dish was kept in hot air oven for 12 hr at 50ºC. After drying, films were removed with the help of sharp blade and kept in a desiccator for 24 hr before cutting in to small piece having area of 6cm^2. Films with air bubbles, cuts or imperfection were excluded from study.

Table 1: Composition of fast dissolving oral films of Granisetron hydrochloride

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Granisetron HCl	1	1	1	1	1	1	1	1	1	1	1	1
CMC	250	500	750	1000								
HPMC					250	500	750	1000				
Pullulan									500	750	1000	1250
Propylene glycol% w/w	30	30	30	30	30	30	30	30	30	30	30	30
Citricacid (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Menthol(mg)	50	50	50	50	50	50	50	50	50	50	50	50
Vanillia(mg)	55	55	55	55	55	55	55	55	55	55	55	55
Absolute alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Note: With the same procedure, various films were prepared by using various polymers (HPMC and pullulan) with different polymer concentration

Drug Excipient Compatibility Studies

FTIR can be used to investigate and predict any physicochemical interaction between different excipients. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and polymer. A physical mixture of drug, polymers and other excipients were prepared and mixed with suitable quantity of potassium bromide. It was scanned from 4000 to 400cm^{-1} in a FTIR spectrometer (FTIR 4100, Jasco).The IR spectrum of the physical mixture was compared with those of pure drug and polymer, and peak matching was done to detect any appearance or disappearance of peaks.

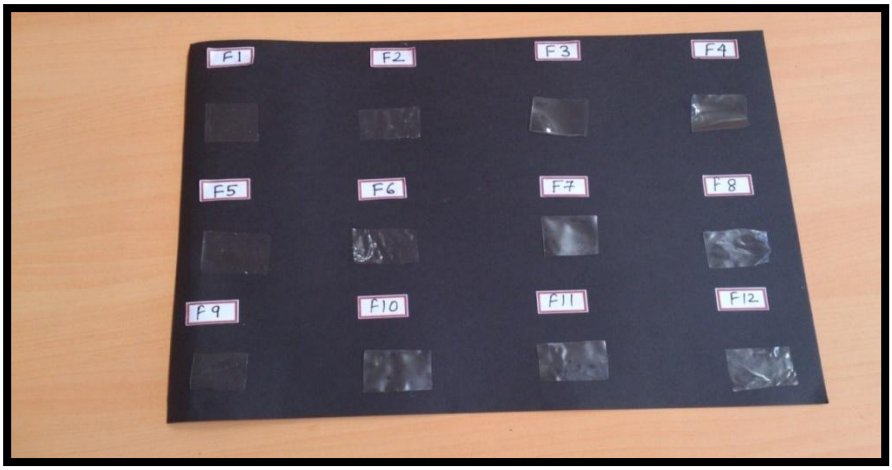

Figure1: Fast dissolving oral films of Granisetron hydorchloride

EVALUATION OF FAST DISSOLVING ORAL FILMS

Physical appearance and surface texture

This parameter was checked simply by visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of the film

The films were weighed individually using digital balance and average weight was calculated.

Surface pH

The films were allowed to swell in a closed petridish at room temperature for 30minutes in 10ml of phosphate buffer pH 6.8.Solution was placed under digital pH meter electrodes.

Thickness uniformity

Thickness of the film was measured using screw gauge with a least count of 0.01mm at different spots of the film. The thickness was measured at three different spots and average was calculated.

Percentage moisture absorption

The percentage moisture absorption test was carried out to ensure physical stability or integrity of films at high humid condition. The films were weighed and placed in a desiccator containing 100 ml of saturated solution of aluminum chloride and 75 ± 5% RH was maintained. After three days the films were taken out and reweighed. The percentage moisture absorption was calculated using the following formula.

$$\%\text{Moisture absorption} = \frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss

Percentage moisture loss was also carried to check the integrity of films at dry condition. It is determined by placing the prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using the following formula.

$$\%\text{Moisture loss} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

Loss on drying

The drying was carried out in an oven with a temperature above the temperature of solvent evaporation at atmospheric pressure. The LOD is the loss of mass expressed as percent (w/w). The weight of the films was measured until constant mass were achieved to ensure complete removal of residual solvent.

Folding endurance

The flexibility of a film can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the film was determined by repeatedly folding a small strip of

the film at the same place till it breaks. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

Tensile strength

Is the maximum stress (applied at one point) required for oral film to break. The film size 5 x 2cm^2 and free of physical imperfection was placed between two clamps held 10mm apart. The film was pulled by clamp at a rate of 5mm/min. It is calculated by the applied load at rupture divided by the cross sectional area of the strip as given in the equation below:

Tensile strength=force at break/initial cross sectional area of film in mm^2.

Percentage elongation

When stress is applied, a film sample stretches, and this is referred to as a strain. Strain is basically the deformation of film divided by the original dimension of the sample.

Percentage elongation=Increase in length /original length x 100.

***In-vitro* disintegration time**

Disintegration time is defined as the time (second) at which a film starts to breaks when brought into contact with water or saliva. It provides an indication about the disintegration and dissolution characterization of the film. It can be determined by the following method:

Slide frame method: one drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petri dish. The time until the film dissolved and caused a hole within the film was measured.

***D*rug content uniformity**

Total drug content per film was estimated by random sampling of all the prepared formulations. Film of 6sq.cm was cut and placed in 50ml volumetric flask and dissolved in phosphate buffer 6.8. Then pipette out 1 ml of solution and dilute to 10ml with buffer. The absorbance of the solution was measured at 302nm.

***In-vitro* drug release**

In-vitro dissolution study was carried out using USP Basket type apparatus using 900ml of pH 6.8 phosphate buffer. The USP dissolution apparatus was thermostated at a temperature of 37±0.5 ºC and stirred at rate of 50rpm. Aliquots of 5 ml were withdrawn at the time interval of every 30 seconds and replaced with equal volume of dissolution medium analyzed at 302nm by UV-VIS Spectrometer and cumulative amount of drug release at various time intervals were calculated.

KINETIC RELEASE STUDIES

Several theories/kinetic models describe drug dissolution from immediate and modified release

dosage form. In order to analyze the release mechanism, several release models were tested such as:

Zero order release Kinetic

To study the zero order release kinetics the release data was fitted into the following equation.

$$Q_t = Qo + K_o t$$

Where 'Q_t' is the amount of drug released at time t, 'K_o' is the apparent dissolution rate constant or zero order release rate constant and 'Qo' is the initial concentration of the drug in the solution resulting from a burst effect; in this case the drug release runs at a constant rate. The graph is plotted percentage cumulative drug release (%CDR) versus time.

First order Release Kinetic

To study the first order release kinetics the release rate data are fitted into the following equation.

$$1n\ Q_t = 1n\ Qo + K_1 t$$

Where, k_1 is the first order release constant; in this case the drug released at each time is proportional to the residual drug inside the dosage form. The graph is plotted log %CDR remaining versus time.

Higuchi Release Model

To study the Higuchi release model the release rate data are fitted into the following equation.

$$Q_t = K_H\ vt$$

Where, 'Q_t' is the amount of drug released at time *t*, 'K_H' is the higuchi release rate constant; this is the most widely used model to describe drug release from pharmaceutical matrices. The graph plotted %CDR versus square root of time.

Korsmeyer and Peppas Kinetics

To study Korsmeyer and Peppas release kinetics the release rate data are fitted into following equation:

$$Q_t/Q_\infty = K_K t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism. The graph is plotted log %CDR versus time.

The value of n=0.45 for Fickian (case I) release, >0.45 but <0.89 for non-fickian (Anomalus) release and 0.89 for case II (Zero order) release and >0.89 for super case II type of release. Case II transport generally refers to the dissolution of the polymeric matrix due to the

relaxation of the polymer chain and anomalus transport (Non fickian) refers to the summation of both diffusion and dissolution controlled release

Stability studies

Short term accelerated stability studies of the selected formulation were carried out. Best formulations were stored in an amber coloured bottle with aluminum cap as a closure. It was tightly sealed and kept in the incubator maintained at 40 ± 2 °C and 75 ± 5% RH. The stability studies were carried out for 3 months. Samples were collected at 1month interval, it was observed for physic al appearance, disintegration time, drug content and *in-vitro* drug release.

RESULT AND DISCUSSION

FTIR studies

The comparison of the IR spectrum revealed that there is no appreciable change in the positions of characteristic absorption bands of groups and bonds. The spectra of these, even though slightly differ in appearance but no change is observed in the positions of the bands in the spectra. This clearly suggests that the drug remains in the same form even in its formulations indicating that there is no interaction between the drug and polymer used for the study. The results are shown in Figure 2-5.

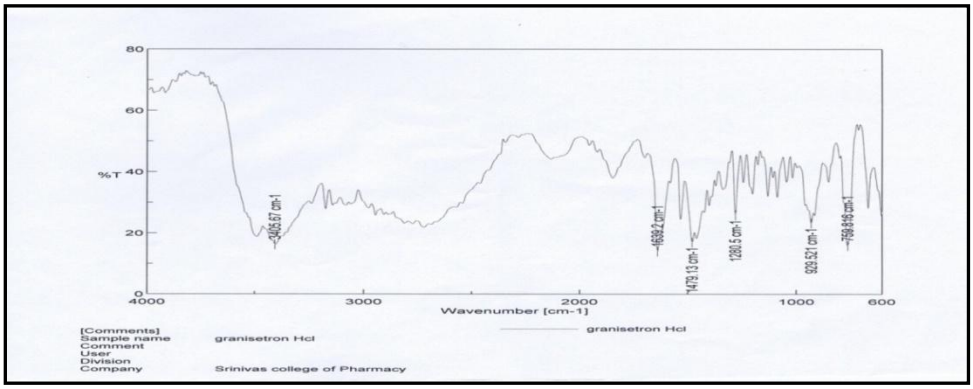

Figure 2: IR spectra of Granisetron hydrochloride

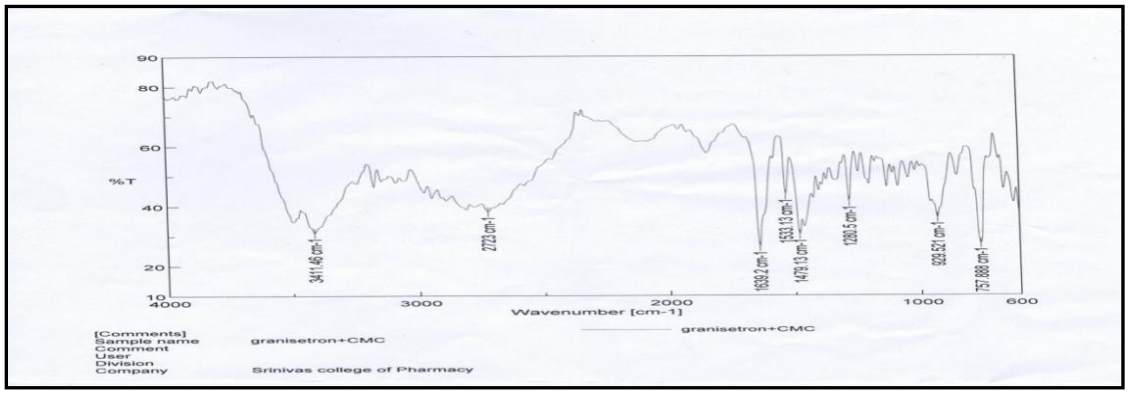

Figure 3: IR spectra of Granisetron hydrochloride and CMC

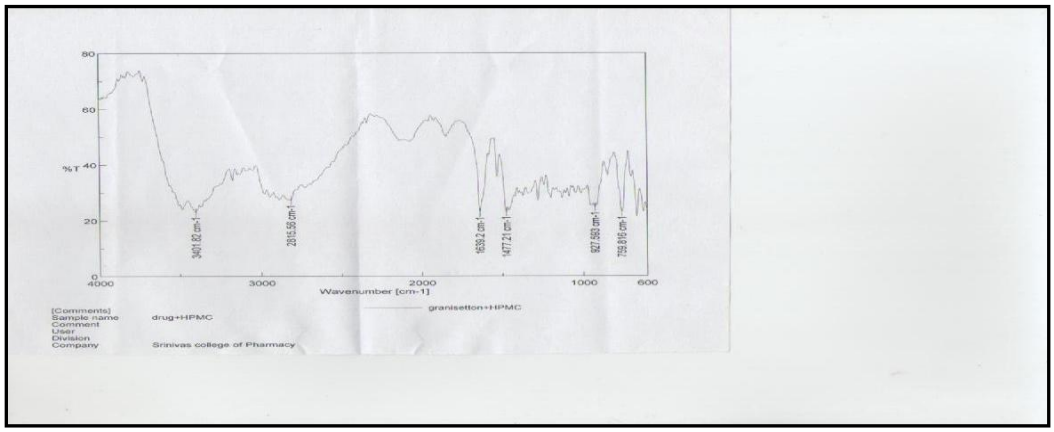

Figure 4: IR spectra of Granisetron hydrochloride and HPMC

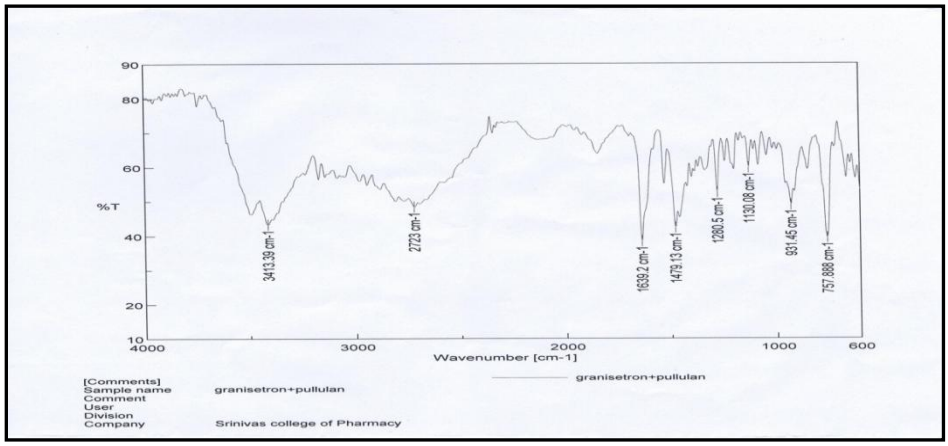

Figure 5: IR spectra of Granisetron hydrochloride and Pullulan

Table 2: Various physicochemical properties of fast dissolving oral films of Granisetron hydrochloride

Formulation code	Physical appearance	Surface texture	Weight uniformity (mg±SD)	Surface pH	Thickness (mm±SD)
F1	Transparent	Very smooth	34.1±0.072	6.67	0.0208±0.002
F2	Transparent	Very smooth	46.2±0.057	6.80	0.145±0.004
F3	Transparent	Very smooth	57.1±0.173	6.65	0.199±0.004
F4	Transparent	Very smooth	63.4±0.11	6.76	0.283±0.003
F5	Transparent	Very smooth	37.2±0.028	6.54	0.0214±0.003
F6	Transparent	Very smooth	49.4±0.112	6.80	0.148±0.005
F7	Transparent	Very smooth	60.1±0.129	6.53	0.205±0.005
F8	Transparent	Very smooth	69.1±0.086	6.66	0.291±0.001
F9	Transparent	Very smooth	55.2±0.072	6.59	0.154±0.002
F10	Transparent	Very smooth	64.1±0.158	6.71	0.209±0.004
F11	Transparent	Very smooth	73.1±0.086	6.74	0.250±0.003
F12	Transparent	Very smooth	77.0±0.144	6.50	0.299±0.005

*All values represented are mean of 4 readings (n = 4)

Physical appearance and surface texture of film

The appearance of all the films were uniform having transparent in appearance The observation

suggests that the films were having smooth surface and they were elegant enough to see. The results are shown in Table 2.and it is shown in Figure 1.

Weight uniformity

As all batches do not have uniform amount of ingredient in it, hence their weight and thickness were varied. Weight uniformity of the films were found to be between 34.1±0.072mg to 77.0±0.144mg. The results are shown in Table 2

Thickness

Thickness of the films were found to be between 0.0208±0.002mm to 0.299±0.005mm. A very low standard deviation values indicates that the method used for the formulation of film is reproducible and give film of uniform thickness and hence dosage accuracy in each film can be ensured. The results are shown in Table 2.

Surface pH

Surface pH of all films were found to be in the range of 6.53 to 6.80. All films were found to be in the range of salivary pH. The results are shown in Table 2.

Percentage moisture loss and percentage moisture absorption

The study of percentage moisture loss and percentage moisture absorption gives the idea about the stability of the film in different environmental conditions. More the moisture absorption property of the film less stable it will be. However it was found that the % moisture absorption and percentage moisture loss increased with increase in hydrophilic polymers like HPMC, CMC and Pullulan. Percentage moisture loss was found to be between 1.23 to 3.91and Percentage moisture absorption was found to be between 2.21 to 5.87 .The results are shown in Table 3.

Disintegration time

The disintegrating time limit of 30seconds or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving oral films. Although, no official guidance is available for oral fast disintegrating film, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating time for films is 5-30 sec[9]. The *in-vitro* disintegration time of the films were found to be between 10±0.31 to 58±0.45sec. Study showed that disintegration time was increased with increase in the polymer concentration. The results are represented in Table.No.3.

Drug content

Granisetron hydrochloride films prepared with various polymers were subjected to uniformity of drug content. The acceptance value of the preparation is less than 15% according to JPI5,

while in USP 27 , the content of preparation are between 85% and 115% and the relative standard deviation is less than or equal to 6.0.Drug content of the films was found to be between 97.62±0.011% to 100.01±0.063%. The observed result indicate that the drug was uniformly dispersed throughout the film. The results are shown in Table 3.

Table 3: Percentage moisture loss, Percentage moisture absorption, disintegration time and drug content uniformity of all formulation

Formulation code	% moisture loss	%moisture absorption	Disintegration time(sec±SD)	Drug content (%±SD)
F1	1.23	2.61	12±0.28	97.62±0.011
F2	1.85	3.48	18±0.34	98.04±0.022
F3	2.63	4.98	26±0.39	98.86±0.034
F4	2.95	5.01	48±0.45	99.63±0.005
F5	1.45	2.21	10±0.31	98.12±0.011
F6	1.67	4.41	16±0.35	98.65±0.005
F7	2.69	4.99	28±0.42	99.86±0.034
F8	3.11	2.45	50±0.47	100.01±0.063
F9	1.98	3.99	18±0.30	97.94±0.022
F10	3.01	4.87	22±0.36	98.13±0.017
F11	3.26	5.18	44±0.37	98.99±0.005
F12	3.91	5.87	58±0.45	99.71±0.005

Table 4: Mechanical Properties of Fast Dissolving Oral Films Of Granisetron Hydrochloride

Formulation code	Folding endurance(±SD)	Tensile strength Kg/cm^2	Percentage elongation
F1	262±2	1.27±0.021	12.5±4
F2	273±5	1.48±0.028	23.3±4
F3	272±6	1.8±0.0330	28.6±6
F4	281±3	2.3±0.0167	30.6±3
F5	265±4	1.31±0.025	16.6±6
F6	274±5	1.50±0.031	23.3±5
F7	281±3	1.86±0.035	26.6±8
F8	292±6	2.41±0.0168	33.0±5
F9	275 ±5	1.55±0.0.035	14.4±5
F10	284±6	1.71±0.032	24.7±6
F11	293±3	2.23±0.145	29.6±4
F12	301±2	2.45±0.0178	33.0±5

Mechanical properties of fast dissolving oral films of Granisetron hydrochloride:

Folding endurance

Folding endurance measurement gives an indication of brittleness of the film. The value depends on hydrophilic polymer as well as plasticizer concentrations used. Folding endurance test result indicated that the film would not break and would maintain their integrity. Folding endurance for all the formulation was found to be more than 200 which was satisfactory to

reveal good film property Folding endurance of the films was found to be between 262±2 to 301±2. The results are shown in Table 4.

Tensile strength

Tensile strength measures the ability of the film to withstand rupture. Study showed that an increase in tensile strength was observed with increase in polymer concentration. Polymers contain large number of chain of molecules and between these chains, homo polar bond and other types of bonds are possible. These bonds are either strong or feeble depending on the nature of polymer. According to the bonds formed force required to break the bonds and rupture the patch will differ. Tensile strength of the films was found to be between 1.27±0.021kg/cm^2 to 2.45±0.0178kg/cm^2.The results are shown in Table 4.

2. Percentage elongation

The Percentage elongation was found to be in the range of 12.5±4% to 33.0±5%.The results are shown in Table 4.

***In-vitro* release studies**

Dissolution study indicates the rate and extent of absorption. The *in-vitro* dissolution of Granisetron hydrochloride films were carried out using 900ml phosphate buffer of pH 6.8 using USP II basket type apparatus. *In-vitro* dissolution study for all the batches were performed for 3minutes. The results are shown in Table 5.

Table 5: *In-vitro* release studies of fast dissolving oral films of Granisetron hydrochloride

Time	Cumulative drug release											
(Sec)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
30	48.927	45.327	41.727	39.927	54.654	52.527	50.563	47.618	54.163	53.836	52.2	50.890
60	55.281	51.081	45.081	44.127	63.436	61.445	58.009	56.863	65.154	64.445	65.536	61.172
90	60.544	56.181	51.681	48.954	74.345	72.763	64.881	60.681	74.318	72.736	70.663	69.163
120	65.072	59.045	54.681	52.445	85.009	82.827	74.399	72.245	85.936	83.236	80.809	78.627
150	69.436	64.77	57.6	54.681	90.409	87.136	84.627	78.327	92.372	91.963	90.136	87.681
180	75.299	69.272	60.981	58.74	99.899	95.809	93.954	91.636	99.872	95.290	93.409	91.418

Effect of CMC:

Dissolution studies of F1 to F4 revealed that the film containing CMC has release 75.29%, 69.27%, 60.98%, 58.74% respectively of drug in 180 seconds. The low release rate of CMC was due to high molecular weight of the polymer. Dissolution rate decrease with increase in molecular weight of polymer. The results are shown in Figure 6.

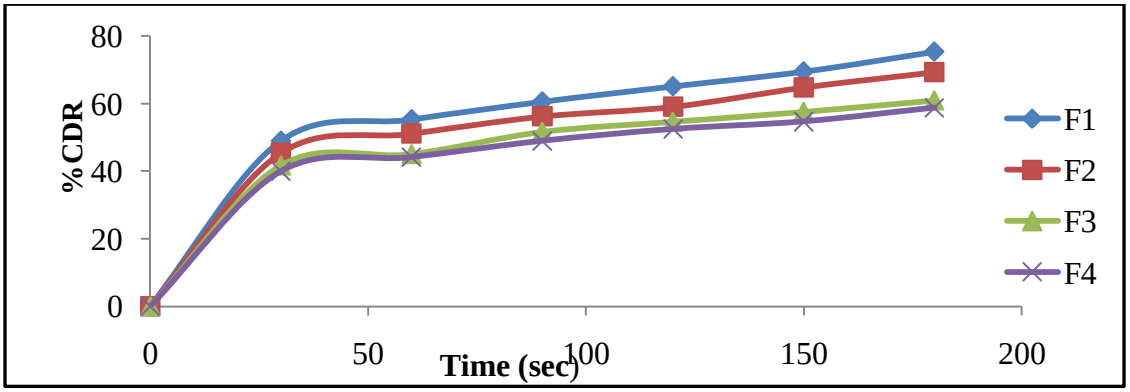

Figure 6: *In-vitro* release pattern of F1-F4 containing CMC(250,500,750&1000mg)

Effect of HPMC:

Dissolution studies of F5 to F8 revealed that the film containing HPMC E-15 has release 99.89%, 95.89%, 93.95%, 91.63% respectively of drug in 180 seconds. The results are shown in Figure 7.

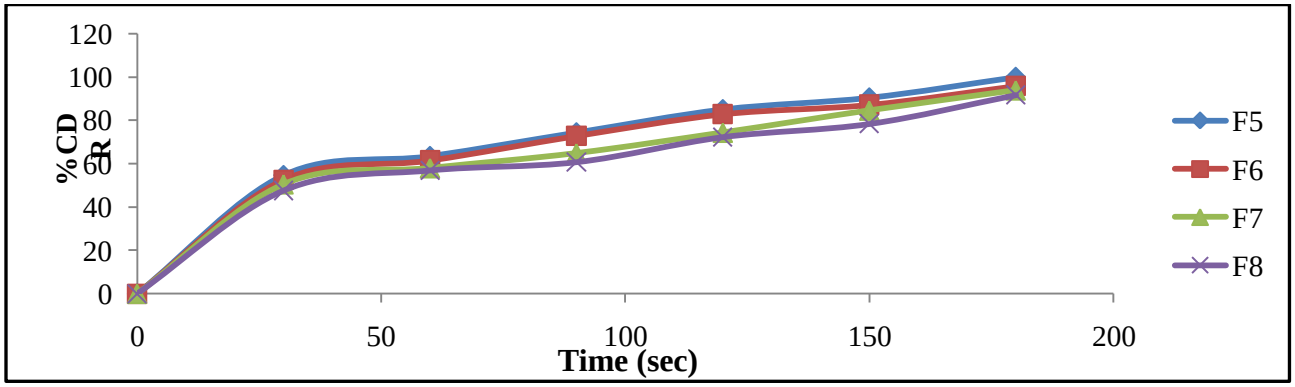

Figure 7: *In-vitro* release pattern of F5-F8 containing HPMC(250,500,750&1000mg)

Effect of Pullulan*:*

Dissolution studies of F9 to F12 revealed that the film containing Pullulan has release 99.87%, 95.29%, 93.40%, 91.41% respectively of drug in 180 seconds. The results are shown and Figure 8.

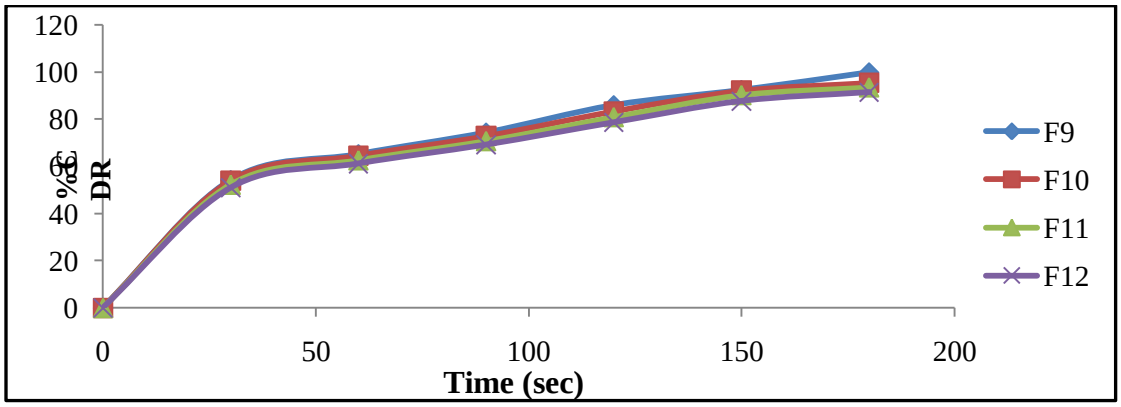

Figure 8: *In-vitro* release pattern for F9-F12 containing Pullualn(500,750,1000&1250mg)

It was found that increase in the polymer concentration significantly decreased the drug release. The slow drug release mechanism for higher polymer concentration can be explained by reduction in permeability due to change in the morphology of the polymer. Increased polymer concentration may have provided the matrix with higher tortuosity and poor water porosity for diffusion of drug. Moreover, higher polymer concentration would have resulted in viscous environment of the system inhibiting movement of water into the matrix for easy diffusion of the drug into the surroundings.

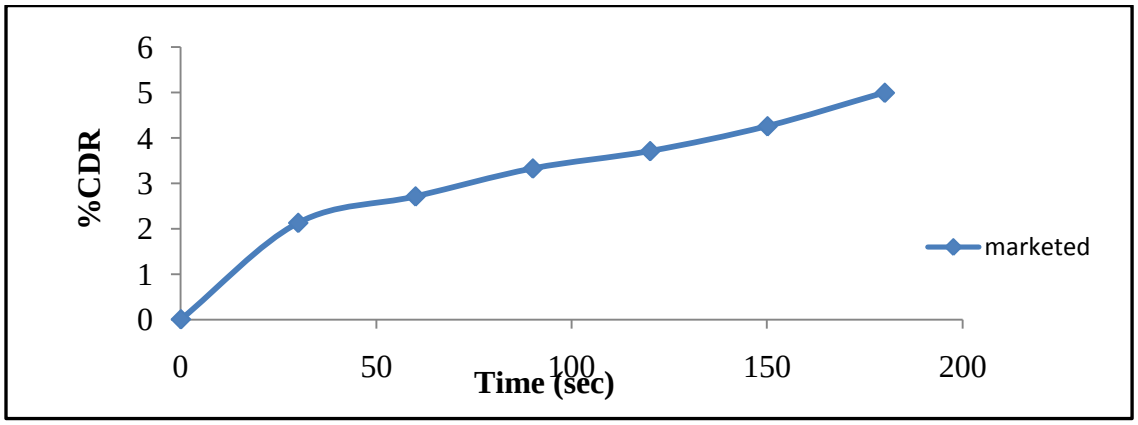

Figure 9: *In-vitro* release of marketed Granisetron hydrochloride tablet

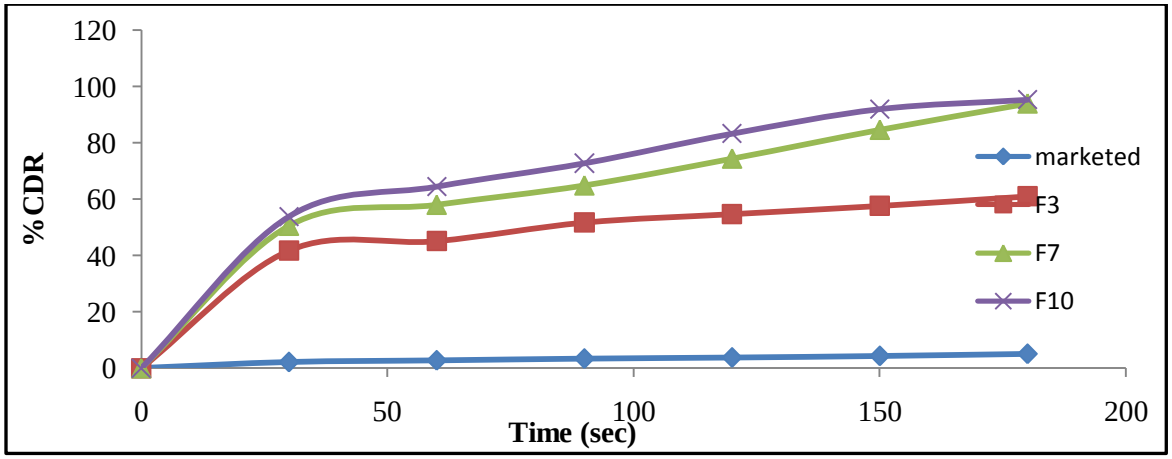

Figure10: Comparative study of *in-vitro* release pattern for F3,F7,F10 &marketed tablet

Table 7: *In-vitro* release studies of marketed Granisetron hydrochloride tablet

Time (Sec)	%Cumulative drug released
0	0
30	2.126
60	2.709
90	3.257
120	3.708
150	4.256
180	4.995

Kinetic study

Kinetic model fitting was carried out for all the formulation F1 to F12 to understand the order and release pattern. The data was subjected to various kinetic equations and plotted according to zero order, first order, Higuchi and korsemeyr's equations. The first order plot was found to be fairly linear as indicated by their high regression value between (0.950 to 0.988). The data was fitted with Higuchi equation which yielded almost linear plots with their high regression co-efficient between (0.912 to 0.980) indicating the mechanism of drug release was diffusion. To know precisely whether fickian or non fickian diffusion existed the data was further plotted according to korsmeyer's peppas equation. The plot showed linearity with their 'n' values between (0.723 to 0.830). The observations showed that mechanism of drug release for all the formulation was non-fickian diffusion following first order release. Data is given in Table 6

Table 6: Kinetics study of fast dissolving oral films of Granisetron hydrochloride

Formulation code	Zero Order	First order	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	n
F1	0.719	0.968	0.927	0.937	0.830
F2	0.717	0.965	0.925	0.938	0.824
F3	0.694	0.974	0.914	0.936	0.802
F4	0.691	0.955	0.912	0.936	0.793
F5	0.827	0.979	0.978	0.953	0.821
F6	0.821	0.950	0.977	0.953	0.791
F7	0.844	0.978	0.976	0.954	0.723
F8	0.845	0.974	0.973	0.955	0.803
F9	0.827	0.953	0.980	0.954	0.825
F10	0.812	0.976	0.974	0.952	0.817
F11	0.819	0.984	0.976	0.953	0.795
F12	0.819	0.988	0.976	0.953	0.761

Stability study

The selected formulation (F3, F7, and F10) was evaluated for stability studies which was stored at 40ºC at 75%RH tested for 3month and were analyzed for physical appearance, disintegration time, drug content and *in-vitro* release rate at 1 month interval. It was found that films retained its physical appearance and there was no much significant change in the values of disintegration time, drug content and *in-vitro* release studies. The results are shown in Table 8-10.1 & Figure 11-13. This indicates that the oral films are stable at 40ºC at 75%RH.

Stability studies

Table 8: Stability study data for F3 formulation

Time in month	F3 formulation stored at 40ºC/75%RH		
	Physical appearance	Disintegration time	Drug content
1	Transparent	27	99.41
2	Transparent	26	99.23
3	Transparent	26	99.01

Table 8.1: % CDR during stability studies for F3 formulation

Time(Sec)	1st Month	2nd Month	3rd Month
	F3	F3	F3
0	0	0	0
30	41.534	41.190	41.007
60	45.690	45.230	44.993
90	50.991	50.437	49.022
120	54.337	53.982	53.643
150	57.02	56.97	56.58
180	60.31	60.14	59.90

Table 9: Stability study data for F7 formulation

Time in month	F7 formulation stored at 40ºC/75%RH		
	Physical appearance	Disintegration time	Drug content
1	Transparent	28	99.23
2	Transparent	27	99.15
3	Transparent	27	99.07

Table 9.1 %CDR during stability studies for F7 formulation

	1st Month	2nd Month	3rd Month
Time(Sec)	F7	F7	F7
0	**0**	**0**	**0**
30	50.563	50.341	50.196
60	58.001	57.95	57.88
90	64.741	64.513	64.217
120	74.367	74.121	74.098
150	84.210	84.099	83.930
180	93.891	93.397	93.005

Table 10: Stability study data for F10 formulation

Time in month	F10 formulation stored at 40ºC/75%RH		
1	Physical appearance	Disintegration time	Drug content
	Transparent	28	99.30
2	Transparent	27	99.21
3	Transparent	26	99.04

Table 10.1: %CDR during stability study for F10 formulation

Time(Sec)	1st Month	2nd Month	3rd Month
	F10	F10	F10
0	0	0	0
30	53.836	53.661	53.310
60	64.430	64.194	63.971
90	72.561	72.191	72.146
120	83.129	83.010	82.95
150	91.910	91.730	91.231
180	95.117	95.054	94.989

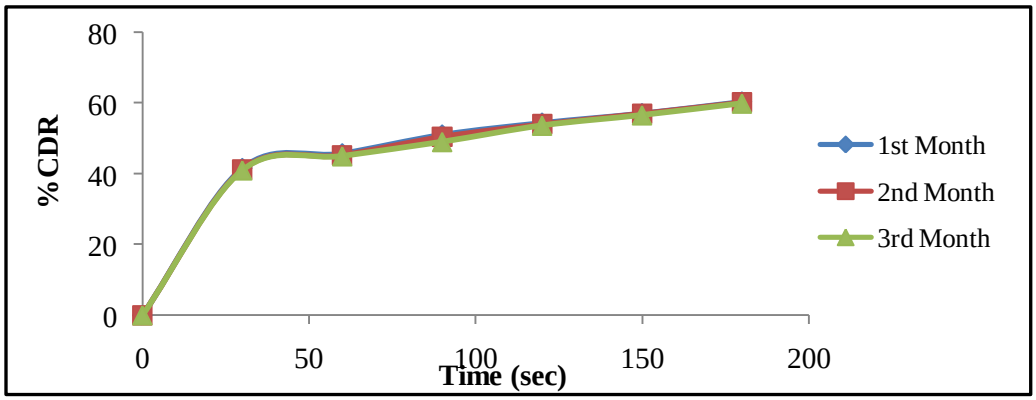

Figure 11: %CDR during stability studies for F3 formulation

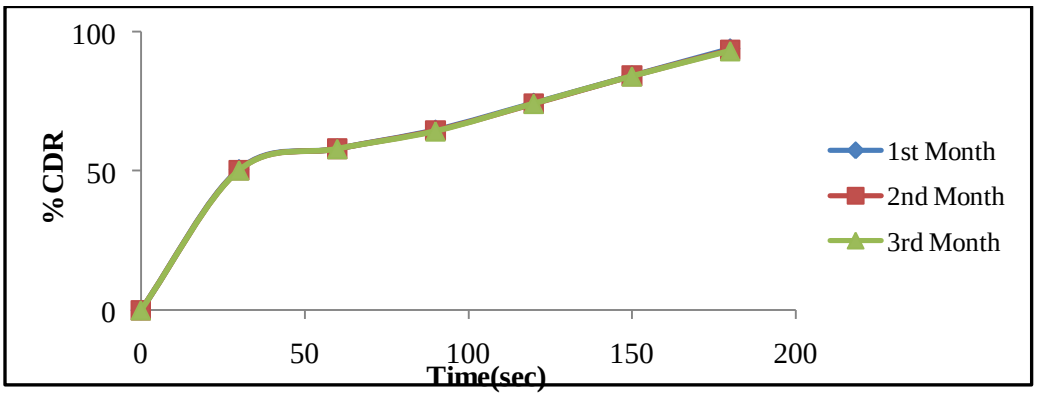

Figure 12: %CDR during stability studies for F7 formulation

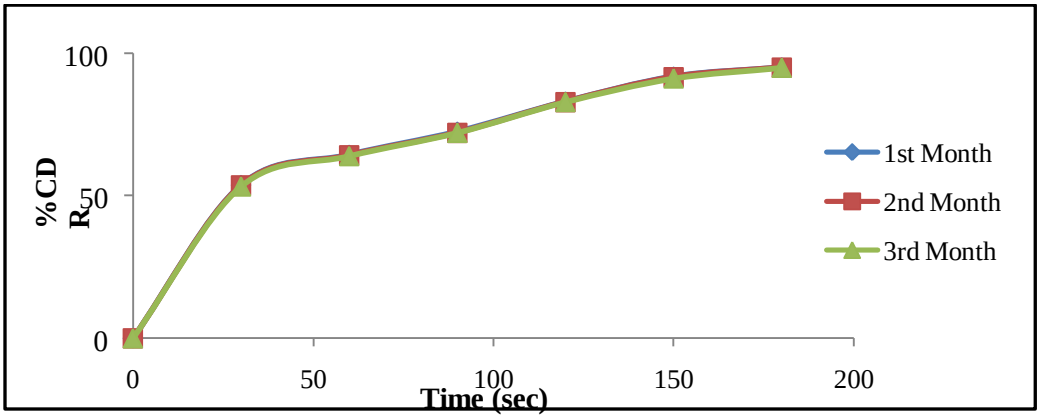

Figure 13: %CDR during stability studies for F10 formulation

CONCLUSION

It can be concluded that fast dissolving oral films of Granisetron hydrochloride can be formulated using CMC, HPMC E-15 and Pullulan as a film forming polymer. Increase in polymer concentration was found to influence in all the aspects of physicochemical and mechanical properties of the films. The release pattern followed non-fickian diffusion with first order release. FTIR studies revealed that there is no interaction between drug and excipients. Therefore Granisetron hydrochloride can be conveniently administered orally in the form of films which can improve its bioavailability. Since the films showed promising results and there exist a scope for *in-vivo* evaluation using suitable animal models.

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