INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

FORMULATION AND EVALUATION OF ORAL FAST DISSOLVING FILMS OF GRANISETRON HYDROCHLORIDE USING DIFFERENT POLYMERS

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Article Received on: 10/09/15 Revised on: 23/09/15 Approved for publication: 01/10/15

DOI: 10.7897/2230-8407.0610141

ABSTRACT

Granisetron Hydrochloride is an orally active, highly selective $5HT_3$ receptor antagonist used in the treatment of cancer chemotherapy induced nausea and vomiting. The present work aimed at preparing quick releasing films of Granisetron Hyrochloride with the purpose of developing a dosage form providing a very quick onset of action beneficial in managing several conditions of vomiting, aiding in the enhancement of bioavailability and convenient for administration without the problem of swallowing and need of water. Oral films of Granisetron Hydrochloride were prepared using Pullulan, HPMC E5 & HPMC E15 in different concentrations by solvent casting method. Initially placebo films were prepared and evaluated on certain physical parameters to optimize the type and concentration of the polymer. Formulations containing 5 & 7.5% of Pullulan & HPMC E15 showed the optimum results. In-vitro release studies revealed that formulation containing 5% Pullulan showed the maximum release of 92% in a matter of 90sec. Thus it was concluded that of the various polymers employed Pullulan has the excellent film forming property and the formulation S1 (containing 5% Pullulan) was the best formulation. Formulation S1 was then subjected to various evaluation parameters and stability studies. All the results obtained were satisfactory. Thus, Fast dissolving films of Granisetron Hydrochloride were successfully developed.

Keywords: Granisetron Hydrochloride, Fast dissolving films, Pullulan, HPMC E5, HPMC E15

INTRODUCTION

For the last two decades, there has been an enhaced demand for more patient-compliant dosage forms[1]. The fast dissolving oral film preparation is a new drug delivery technique to provide medicines to patients with obstacles in swallowing or under emetic condition during cancer chemotherapy. The morbidity and mortality of cancer have been increasing and thus the number of patients who receive cancer chemotherapy has been elevated in the recent years. However, a number of patients who undertook cancer chemotherapy complain of side effects associated with anticancer drugs. Among them, nausea and vomiting are one of the most frequent side effects. On the other hand, disturbance in eating and swallowing associated with oral mucositis is often encountered in patients with head and neck cancer who underwent combination of chemotherapy and radiotherapy[2-5]. Therefore, the antiemetic oral medicines are inconvenient to use in such patients.

Oral disintegrating tablets[6,7] and oral jerry preparations[8] have been developed for patients with dysphagia or aphagia. The jerry preparations have an advantage of taking without choke and are useful for elderly patients but are bulky in many cases while oral disintegrating tablets are readily disintegrated but the disintegrated materials are insoluble and remain until swallowing. On the other hand, edible thin oral film preparations have been used as oral care products[9,10]. These preparations easily dissolve in saliva, thereby requiring no water to take. Therefore, the oral disintegrating thin film preparation appears to be useful for patients with eating and swallowing disturbance.

Granisetron is a highly selective $5HT_3$ receptor antagonist, 10-15 times more potent than ondansetron and probably more effective during the repeat cycle of chemotherapy. It is rapidly and extensively absorbed after oral administration. Following 2 mg oral dose, Granisetron is 60% bioavailable due to hepatic metabolism. In the present study oral fast dissolving films of granisetron hydrochloride were prepared to provide a rapid onset of action, to bypass hepatic metabolism thereby enhancing bioavailability to some extent and improve patient compliance especially in case of pediatric and geriatric population who face difficulty swallowing conventional tablets and dysphagic patients.

MATERIALS AND METHODS

Granisetron Hydrochloride was obtained as gift sample from Cipla Pvt. Ltd., Mumbai. Pullulan was received as gift sample from Hayashibara co ltd, Mumbai. HPMC E15 & HPMC E5 were received as a gift samples from Colorcon Asia Ltd.,Goa. Propylene glycol was procured from Merck Specialists Pvt. Ltd., Mumbai and Aspartame was obtained from S.D Fine Chemicals, Mumbai. All other chemicals were of analytical grade.

Formulation of placebo oral films

Initially placebo films were prepared using Pullulan, HPMC E5 & HPMC E15 as film forming agents and propylene glycol as plasticizer by solvent casting method. Clear viscous polymeric solutions were prepared by dissolving 2.5, 5, 7.5 & 10 gm. Pullulan, HPMC E15 & HPMC E5 in sufficient quantity of water (70%) with continuous stirring resulting into 2.5, 5, 7.5 & 10% polymeric solutions respectively (Solution I). Solutions were kept aside for few minutes to attain defoaming. A sufficient quantity of propylene glycol was dissolved in small amount of water (30%) with continuous stirring (Solution II). With continuous stirring solution II was slowly added to solution I. The resulting solution was casted as a film into

petriplates and allowed to dry in oven at 45-60˚C. Films were then cut into pieces of the desired size.

Table 1: Compositions of various oral films formulated by varying the type and concentration of polymer

Formulation Code	Pullulan (gm)	HPMC E15 (gm)	HPMC E5 (gm)	Propylene gycol (ml)	Water (qs)
F1	2.5	-	-	1	100
F2	5	-	-	1	100
F3	7.5	-	-	1	100
F4	10	-	-	1	100
F5	-	2.5	-	1	100
F6	-	5	-	1	100
F7	-	7.5	-	1	100
F8	-	10	-	1	100
F9	-	-	2.5	1	100
F10	-	-	5	1	100
F11	-	-	7.5	1	100
F12	-	-	10	1	100

Evaluation of placebo films: Films were then evaluated on the basis of certain physical parameters so as to optimize the type and concentration of the polymer to be used in the formulation of oral fast dissolving films.

Weight determination: Three films of each formulation were randomly selected and weighed individually then the mean weight of films of each batch was calculated.

Thickness measurement: The thickness of polymer films was determined by using screw gauge. The thickness of each film at different places was determined and the standard deviation was calculated[11].

Disintegration time: The disintegration time of fast-dissolving films prepared using different polymers was determined visually in a beaker of 30 ml distilled water with swirling every 10 s. The disintegration time is the time when a film starts to break or disintegrates[12]. Optimum disintegration time of fast dissolving films is less than 60 seconds.

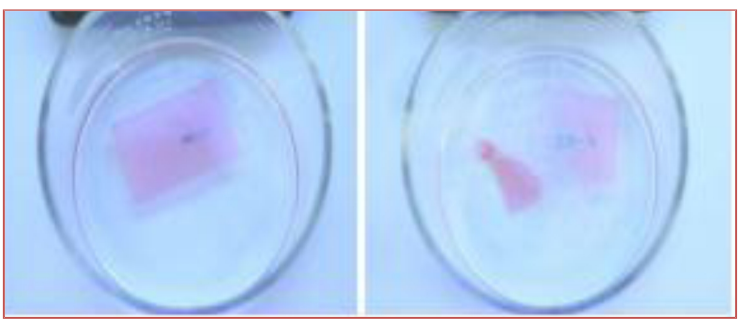

Figure 1: Visual determination of dissolution profile of oral films

Folding endurance: Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking was computed as the folding endurance value[13].

Visual appearance: Appearance of strip was evaluated by visual observation such as transparent and semitransparent nature of strip
The results of various evaluation parameters are shown in Table 2.

PREPARATION OF DRUG LOADED FILMS

On the basis of evaluation parameters mentioned in Table 2, four formulations were selected and drug was incorporated into these formulations. Films were prepared using solvent casting method as described earlier. The composition of drug loaded films is given in Table 3

Table 3: Composition of drug loaded films

Formulation Code	Pullulan (gm)	HPMC E15 (gm)	Drug (mg)	Propylene glycol (ml)	Aspartame (mg)	Flavor (ml)	Water (q.s)
S1	5	-	1.2	1	40	0.6	100
S2	7.5	-	1.2	1	40	0.6	100
S3	-	5	1.2	1	40	0.6	100
S4	-	7.5	1.2	1	40	0.6	100

In-Vitro Release Studies: Formulations S1, S2, S3 & S4 were subjected to invitro release studies to optimize one of the two polymers i.e. Pullualn or HPMC E15. In-vitro drug release was carried out in a beaker containing 30 ml of Phosphate Buffer pH 6.8 as a dissolution medium with revolution speed set at 50 rpm. Temperature of the dissolution medium was maintained at 37˚±0.5ºC. Samples of 5ml were withdrawn at every 15 seconds interval, filtered (through 0.45µ) and replaced with 5ml of fresh dissolution medium. The samples were suitably diluted and estimated spectrophotometrically at 302 nm using UV-VIS 1700 (SHIMADZU) double beam Spectrophotometer[14]. The dissolution experiments were

conducted in triplicate. The cumulative % drug release profile of all the formulation batches has been shown in Table 4.

Characterization of Fast Dissolving Films of Granisetron Hydrochloride:

Tensile strength measurement: The instrument which was designed in our laboratory was used for the measurement of tensile strength (Figure 2). The strip was clamped at the static end and was attached to the movable rod on railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the film was cut. The weight required to break the film was noted as the break force[15]. The tensile strength was calculated using ;

Tensile strength = Force at break (N) / Initial cross sectional area of the film (mm^2)

Tensile strength of the prepared films was found to be 673.47 ± 0.14 gm/mm^2

Figure 2: Tensile strength measuring apparatus

Drug content: Method to determine drug content was developed in-house to find out amount of drug present in 1 strip. Strip was dissolved in water in 100ml volumetric flask. Volume was made up to 100ml and the solution was sonicated for 10-30 min. 5ml of above solution was then diluted with water to 50ml. The resulting solution was filtered (through 0.45µ) and absorbance was measured spectrophotometrically at 302nm.

Moisture loss studies[16]: The percent moisture loss studies were carried out to check the physical stability and integrity of the films. In the present study the moisture loss capacity of the films was determined by placing the known weight and predetermined size of films in dessicator containing anhydrous calcium chloride (inside the dessicator) for three days. The films were removed and reweighed, and the percentage moisture loss of the films was measured by using the formula.

Percent moisture loss = Initial weight – Final weight × 100 / Initial weight

Surface pH study: The surface pH of fast dissolving strip was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. The film to be tested was placed in a petridish and was moistened with 0.5 ml of distilled water and kept for 30sec. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min[15]. Films were also evaluated for weight, Thickness, Disintegration time and Folding Endurance using the methods as described earlier.

RESULTS AND DISCUSSION

Evaluation of Placebo films: From the data presented in Table 2 it was concluded that:-

- Pulluan and HPMC E15 showed the desired film forming capacity
- Since the formulations F9, F10, F11 & F12 resulted in semitransparent films, it indicates that HPMC E5 has an average film forming capacity and thus cannot be considered as a good film former.
- Formulations F2, F3, F6 & F7 showed the desired results i.e formulations containing 5% & 7.5% Pullulan and 5% & 7.5% HPMC E15 were the optimized formulations. Drug was then incorporated in these four optimized formulations

Table 2: Evaluation parameters of placebo oral films

Formulation Code	Weight (gm)	Thickness (mm)	Disintegration Time (sec)	Folding Endurance	Visual Appearance
F1	0.016±0.003	0.11 ±0.02	4.13±0.03	11±1	Transparent
F2	0.022±0.001	0.32 ±0.01	7 .21±0.02	73±2	Transparent
F3	0.037±0.004	0.55±0.02	11 .07±0.02	51±2	Transparent
F4	0.051±0.013	0.73±0.01	21.17±0.01	27±1	Transparent
F5	0.025±0.003	0.07±0.01	13.33±0.03	14±3	Transparent
F6	0.033±0.003	0.34 ±0.03	37.24±0.02	86±3	Transparent
F7	0.048±0.002	0.53 ±0.02	58.11±0.02	57±1	Transparent
F8	0.057 ±0.004	0.68 ±0.01	111.42±0.4	29±1	Transparent
F9	0.021 ±0.001	0.13 ±0.03	17.27±0.02	13±2	Semitransparent
F10	0.030 ±0.005	0.37 ± 0.05	49.15±0.02	77±3	Semitransparent
F11	0.043 ±0.003	0.49 ±0.01	76.31±0.04	58±1	Semitransparent
F12	0.055 ±0.002	0.67 ±0.02	102.19±0.03	31±4	Semitransparent

*Values expressed as mean ± S.D (n=3)

In-vitro release studies: The release pattern as shown in Figure 3 and data presented in Table 4 revealed that the drug release from formulation S1 was faster than the S2, S3 and S4 formulation. Moreover, formulation S1 released about 92% drug while release rate was slow in case of formulation S2, S3 and S4 i.e. 81%, 79% and 74% respectively. Thus, it was concluded that 5% Pullulan has an excellent film forming property among the three polymers employed and formulation S1 containing 5% Pullulan was the best and the final formulation.

Table 4: Percentage cumulative drug release from various formulations

TIME (sec)	%CDR			
	S1	S2	S3	S4
0	0	0	0	0
15	14.5±0.2	10.15±0.03	2.15± 0.04	1.9±0.1
30	29.3±0.11	23.45±0.03	9.8±0.21	9.5±0.3
45	47.71±0.03	42.8±0.1	22.8±0.1	21.7±0.2
60	61.95±0.02	59.63±0.020	39.55±0.03	37.66±0.03
75	75.33±0.21	71.58±0.01	51.25±0.02	50.2±0.11
90	84.21±0.11	78.7± 0.11	66.6±0.2	59.75±0.03
105	86.18±0.02	81.63±0.03	77.9±0.13	65±2
120	86.42±0.23	81.55±0.01	79.6±0.2	74.85±0.01
135	86.23±0.11	81.37±0.02	79.5±0.2	74.75±0.01
150	86.11±0.2	81.72±0.02	79.4±0.1	74.6±0.2

*Values expressed as mean ± S.D (n=3)

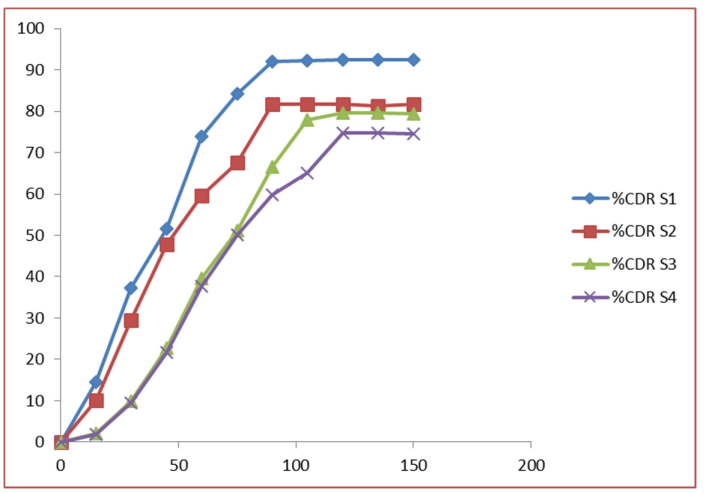

Figure 3: Percentage cumulative drug release from various formulations

Characterization of oral fast dissolving films of Granisetron Hydrochloride: Average weight of the films was found to be in the range 0.027-0.051 gm. No significant difference in thickness was observed among the films indicating that the films were uniform. Thickness of the films was found to be 0.32-0.42 mm. The observed disintegration time of the films lies in the range 13.40 -13.64 sec. indicating that the films disintegrate rapidly providing a rapid onset of action. All the films showed good folding endurance i.e. 71-77 folds indicating that the films have good flexibility. Tensile strength of the prepared films was found to be 673.33- 673.61 gm/mm^2 indicating an optimum strength and integrity of the films. No significant difference in the drug content (97.85%-100.65%) among the films indicated good content uniformity. Oral fast dissolving films of Granisetron Hydrochloride showed a moisture loss of 0.31%-0.37% which is in the acceptable limits as per British pharmacopoeia. This indicates good physical stability of the films. Surface pH of the films was found to be 6.71- 6.75, which is close to the neutral pH indicating that films have less potential to irritate the oral mucosa and thus more acceptable by the patients.

STABILITY STUDIES

A Stability study of the prepared films was carried out by storing films in an aluminium package for 30 days at 4˚C/ 75% RH, 30˚C/75% RH and 40°C/ 75% RH. The films were observed for physical change (form and color), disintegration time and drug content. Fast dissolving films of Granisetron Hydrochloride were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics (no discoloration & no change in shape), disintegration time and drug content under all the storage conditions.

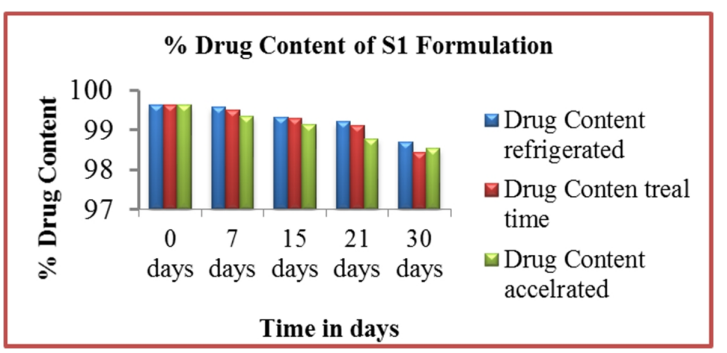

Figure 4: Percentage Drug Content of S1 Formulation during Stability Studies

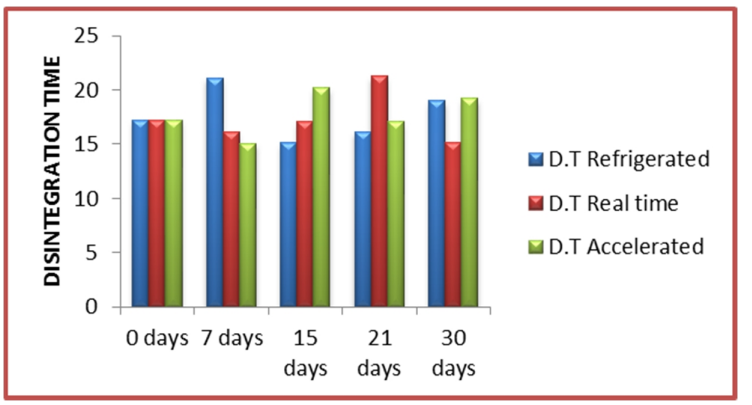

Figure 5: Disintegration time of formulation S1 during stability studies

CONCLUSION

We prepared for the first time a fast dissolving oral thin film containing Granisetron Hydrochloride. The preparation revealed excellent uniformity and stability of Granisetron under all conditions. Based on the encouraging results fast dissolving films of granisetron hydrochloride can be considered clinically useful for cancer patients with disturbance in eating and swallowing who receive radiotherapy and/or high- to moderate emetogenic anticancer drugs and other conditions of vomiting where a quicker onset of action for a dosage form is desirable along with ease of administration. The method of preparation was found to be simple requiring minimum excipients thus making the product cost effective.

ACKNOWLEDGMENT

The authors are thankful to the Director and Teachers of Rayat Institute of Pharmacy, Railmajra (India) and Chandigarh University, (Punjab, India) for providing the facilities to carry out this work.

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Cite this article as:

Aggarwal Jyoti, Jindal Keshav, Singh Gurpreet. Formulation and evaluation of oral fast dissolving films of Granisetron hydrochloride using different polymers. Int. Res. J. Pharm. 2015; 6(10):724-728
http://dx.doi.org/10.7897/2230-8407.0610141

Source of support: Nil, Conflict of interest: None Declared