Research Article

Formulation and Evaluation of Fast Dissolving Oral Films of Palonosetron Hydrochloride Using HPMC-E5

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ABSTRACT

The aim of the study was to examine various polymers considered to have fast dissolving properties for the preparation of fast dissolving oral films of Palonosetron and to evaluate the films for various physical and chemical parameters, determine compatibility between drug and polymers using FT-IR and subject the best formulation for stability studies. A number of polymers such as HPMC, NaCMC and PVP individually and Pullulan gum-Xanthan gum-HPG (1:1:1) in combination were employed as film formers for the preparation of fast dissolving oral films. Polyethylene Glycol-400 was selected as plasticizer, Tween-80 and Polaxomer-407 were selected as surfactants, Aspartame was used as sweetener and Malic acid was used as salivary stimulant. The films were made using solvent casting technique. The formulated films of Palonosetron were evaluated for parameters like thickness uniformity, weight uniformity, folding endurance, percentage moisture loss, tensile strength, percentage elongation, drug content uniformity, *in vitro* disintegration time, *in vitro* dissolution studies. The compatibility studies were carried out by using FT-IR and stability studies were carried out by storing at 40^{0}C/75RH for 3 months. HPMC-E5 (2%) and Polaxomer-407 (10%) emerged as the best film former and surfactant for the present dosage form.

Keywords: Palonosetron, HPMC-E5, PEG-400, Tween-80, Polaxomer-407.

INTRODUCTION

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity resulting in solution or suspension without the need for administration of water is known as oral fast dispersing dosage form.[1]

Oral fast dissolving films (OFDFs) evolved over the past few years from the confection and oral care markets in the form of breath strips have become a novel and widely accepted form by consumers for delivery of vitamins and personal care products. Today, OFDFs are a proven and accepted technology for the systemic delivery of APIs for **Over-The-Counter** (OTC) medications and are in the early to mid-developmental stages for prescription drugs. These are new and novel oral drug delivery systems which dissolve or disperse quickly in few seconds after placement in the mouth without drinking and chewing. When quick dispersing films are placed in the mouth, the dosage form disintegrates instantaneously or within a few seconds releasing the drugs, which dissolve or disperse in saliva. The sublingual mucosa is relatively permeable due to thin membrane and large veins. It gives rapid absorption and instant bioavailability of drugs due to high blood flow.[2]

Palonosetron hydrochloride is an antiemetic and anti nauseant agent; selective inhibitor of type 3 serotonergic (5-HT3) receptors and chemically, it is [R-(R*, R*)]-2-(1-Azabicyclo [2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one. The empirical formula is C19H24N2O.HCl, with a molecular weight of 332.87. Palonosetron hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol. It prevents acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. Palonosetron hydrochloride is being administered intravenously, as a single dose, 30 minutes before chemotherapy, or administered as a single oral capsule one hour before chemotherapy.[3]

MATERIALS AND METHODS

MATERIALS

Palonosetron hydrochloride was procured from Leo chem Pvt Ltd, Bangalore, Hydroxypropyl Methyl Cellulose (E5) was procured from

Meyers Lab, Bangalore, Polyethylene Glycol-400 was procured from Loba Chemie Pvt Ltd, Tween-80 and Aspartame were procured from Himedia Lab Pvt Ltd, Polaxomer 407 was procured from Apotex India Pvt Ltd, Malic acid was procured from S.D Fine Chemicals Pvt Ltd.

METHOD OF PREPARATION OF FAST DISSOLVING ORAL FILMS

The fast dissolving films of Palonosetron were prepared by Solvent casting technique in a circular plastic casting moulds of internal diameter of 2cm and area of 3.17cm^2 by pouring with casting solution. (Magnetic stirrer from Remi equipment's, Mumbai used for preparation of casting liquid). The casting liquid is prepared using various film formers, plasticizer, surfactants, sweetener and salivary stimulant as per details furnished in table 1.The film former was first dissolved in 20mL of water and stirred with the magnetic stirrer, the drug and the required amount of plasticizer and other additives were added to the above solution and stirred until completely dissolved. 2mL of prepared solution was transferred in to the each circular plastic casting mould and dried in an oven for 24 hours at 40^{0}C (Tempo Instruments Pvt. Ltd., Mumbai Hot air oven was used for drying of films)and films were pealed out and stored in self-sealing covers in Dessicator until further use.[4]

EVALUATION OF FAST DISSOLVING ORAL FILMS

The prepared formulations were evaluated for the Drug-Polymer compatibility using FT-IR, Thickness uniformity, Weight uniformity, Folding endurance, Percentage moisture loss, Drug content and Content uniformity, Tensile strength, Percentage Elongation, *in vitro* Disintegration time, *in vitro* Dissolution, Stability studies.

a) Thickness uniformity of the film

Three films were taken from each formulation and the thickness of the film was determined by screw gauge at different positions by placing the film in between two glass slides of known thickness, Mean thickness and standard deviation were calculated.[4] (Screw gauge from Micro Co., Mumbai was used for thickness measurement).

b) Weight uniformity of the film

Three films of each formulation were took and weighed. The weight of each film was recorded, Mean weight and standard deviation were calculated.[5] (Sartorius CE212 digital balance was used for weighing)

c) Folding Endurance

The folding endurance is expressed as the number of folds (number of times a film is folded at the same plane) required to break the film or to develop visible cracks. This gives an indication of brittleness of the film. Three films from each formulation were selected and cut into 5mmx20mm size and subjected to this test by folding the film at the same place repeatedly several times until visible cracks were seen. Mean folding endurance, standard deviations were calculated.[6]

d) Percentage moisture loss

Percentage moisture loss test was carried to check the integrity of films in dry condition. Three films were weighed accurately and kept in desiccator containing fused anhydrous Calcium chloride. After 72 hours the films were removed and weighed. Percentage moisture loss was calculated using below mentioned formula and Mean percentage moisture loss from the three films was found out; standard deviation were calculated.[4]

Table 1: Formulation details of Fast Dissolving Oral Films of Palonosetron Hydrochloride

Formulation	Drug (mg)	Water (ml)	HPMC-E5 (%w/v) of water	PEG400 (%w/w) of polymer	Tween-80 (%w/w) of polymer	Polaxomer 407 (%w/w) of polymer	Aspartame (%w/w) of polymer	Malic Acid (%w/w) of polymer
F1	12.5	50	2	10	5		5	5
F2	12.5	50	2	10	10		5	5
F3	12.5	50	2	10		5	5	5
F4	12.5	50	2	10		10	5	5
F0	12.5	50	2	10			5	5

Note: "F0" is the formulation made without the added surfactant

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

e) Drug content and content uniformity

- **Drug content**

10 films from each formulation were taken and dissolved in 50mL of Phosphate buffer pH 6.8 to give 100µg/mL solution. From the above solution 1, 1.5, 2mL were taken and made up to 10mL with pH 6.8 Phosphate buffer to give 10, 15, 20 µg/mL solutions respectively. The absorbance of each solution was measured at the 256nm (λmax of Palonosetron), mean and standard deviations were recorded. (Shimadzu-UV1800 UV-Visible Spectrophotometer used for absorbance measurements).

- **Drug content uniformity**

Three films from each formulation were took and dissolved in 50mL of Phosphate buffer of pH 6.8 to give 10µg/mL solution. The absorbance of each solution was recorded at 256nm (λ max of Palonosetron), mean and standard deviations were calculated.[7] (Shimadzu-UV1800 UV-Visible Spectrophotometer was used for absorbance measurements).

f) Tensile strength

Three films from each formulation were took and cut in to 5mm width and 10mm length. Breaking force of each film was determined using Tensile strength apparatus and Tensile strength was calculated. Mean and Standard deviation were calculated.[8] (H1KS Tensile strength apparatus (HTE-500N) used for tensile strength measurement).

$$\text{Tensile strength} = \frac{\text{Breaking force}}{\text{Area of cross section}}$$

Area of Cross section (mm^2) = width of the film X thickness of the film, Breaking force (N), Tensile strength (N/mm^2)

g) Percentage Elongation

Percentage elongation was determined for three films of each formulation by measuring the increase in length of the films after tensile measurement by using the following formula; mean and standard deviation were calculated.[9] (HTE-500N was used for Percentage Elongation measurement).

$$\textbf{Percent Elongation} = [L - L_0] \times 100 / L_0$$

L = Final Length, L_0= Initial Length

h) *in vitro* Disintegration time

Three films from each formulation were took and performed disintegration test by placing the films in the petridish of size 6.3cm^2 area and wall height of 1.3cm containing pH 6.8 Phosphate buffer. The time at which film disintegrated is noted. Mean and standard deviation were calculated.[10]

i) *in vitro* Dissolution studies

An in-vitro dissolution study was performed for the films of selected formulations for 3 minutes in USP basket apparatus using pH 6.8 Phosphate buffer solution. Dissolution medium was kept at 37º C ± 0.5º C and 50rpm. The samples (5 mL) withdrawn after every 30 sec and replaced with fresh pH 6.8 Phosphate buffer solution. 5mL samples then diluted up to 10 ml in a volumetric flask. The samples were determined for the drug content using U V spectrophotometer at λ max 256nm.[11] (Electro Lab Ltd Dissolution Apparatus used for dissolution studies)

j) Compatibility study using FT-IR spectroscopy

Pure drug and drug combined with polymers were separately mixed with IR grade KBr and converted into KBr pellet by hydraulic press and scanned over a range of 4000 to 400 cm^{-1}.[12] (Shimadzu-FTIR 8400 FT-IR spectrophotometer used for compatibility study).

k) Stability Study

Short term accelerated stability studies were performed for optimized films placed in plastic containers and exposed to 40˚C / 75 % RH (ICH guidelines) for a period of 3 months. Different film properties such as *in vitro* disintegration time and drug content were determined at intervals of one month.[13] (Stability Chamber from Remi Instruments Ltd used for stability studies).

RESULTS

Table 2: Evaluation of fast dissolving oral films of Palonosetron Hydrochloride

Sl no.	Film Parameters	Formulation				
		F0 (mean±SD*)	F1 (mean±SD*)	F2 (mean±SD*)	F3 (mean±SD*)	F4 (mean±SD*)
1	Thickness uniformity (mm)	0.03±0.009	0.023±0.0057	0.013±0.0057	0.026±0.0115	0.026±0.005
2	Weight uniformity (mg)	27.1±0.12	27.1±0.12	32.53±0.95	58.56±0.20	44.26±0.26
3	Folding endurance (no. of pressings)	64.66±3.51	81.66±1.52	83.33±2.51	54.33±3.05	46.66±3.21
4	Percentage moisture loss (%)	2.45±0.83	3.18±1.07	7.16±2.16	4.2±2.85	5.58±0.25
5	Tensile strength (N/mm^2)	12.39±1.44	13.43±1.18	14.94±2.87	8.13±0.28	9.62±0.11
6	Percentage Elongation (%)	11.53±0.33	14.89±0.32	18.55±0.32	10.36±1.24	9.37±0.32
7	Drug content (%)	96.46±0.35	95.36±0.4	91.8±0.65	93.73±0.49	93.6±0.26
8	Drug content uniformity (%)	96.05±0.7	95.63±0.28	92.45±0.81	93.32±0.26	92.48±0.28
9	in vitro Disintegration time (sec)	41±2.64	31.66±2.88	27.33±2.07	28±3.0	19.33±2.07
10	in vitro Dissolution studies (CDR at 180 sec) (%)	86.9074	91.47996	95.8918	93.0677	96.75088

SD*=Standard deviation, n=3

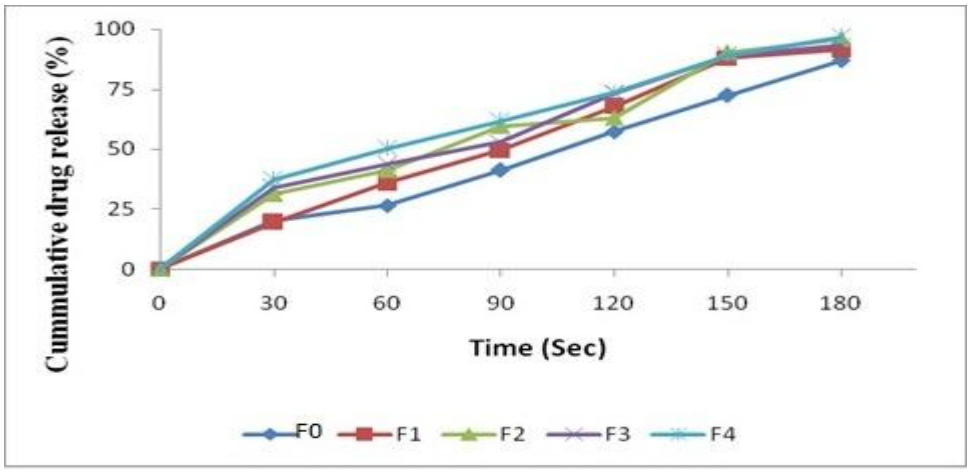

Fig. 1: *in vitro* Dissolution studies of formulation A, F1, F2, F3, F4

Compatibility study using FT-IR spectroscopy

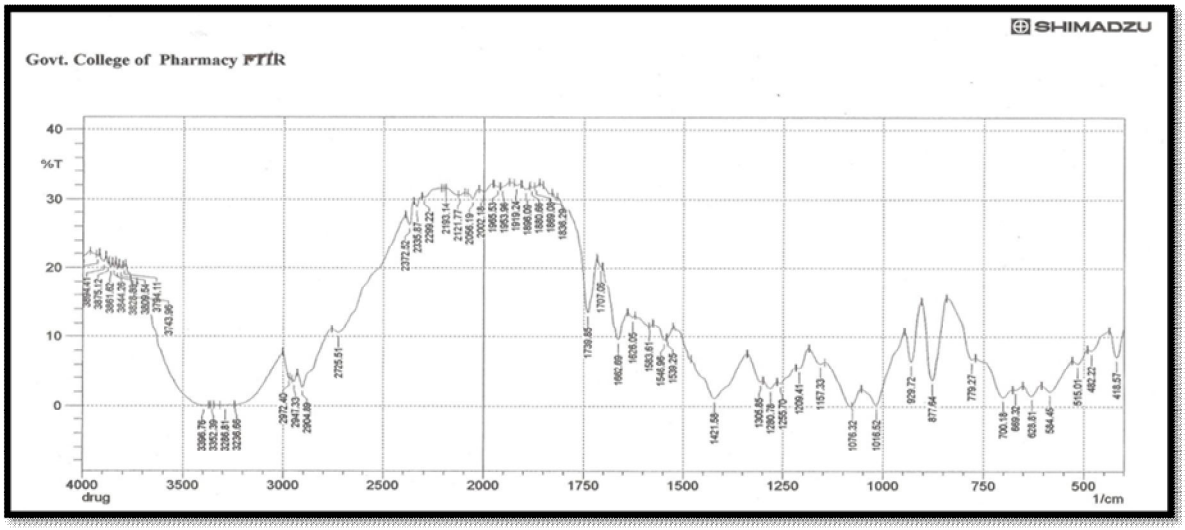

Fig. 2: IR Data of pure drug Palonosetron Hydrochloride

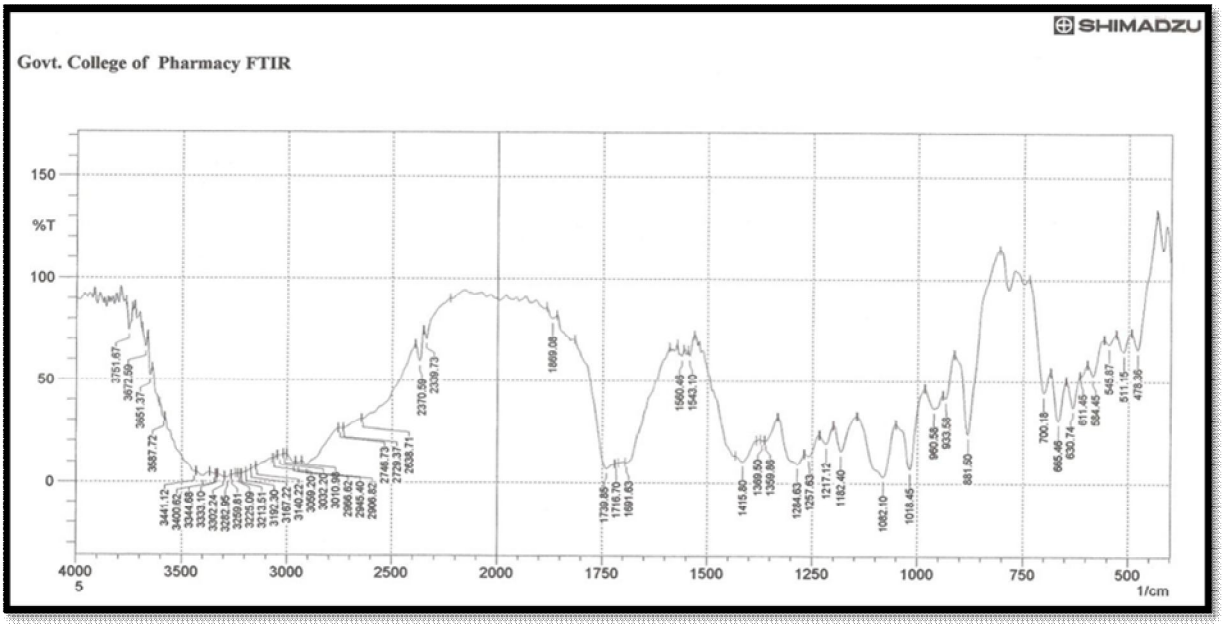

Fig. 3: IR Data of Palonosetron Hydrochloride+ Polaxomer (408) +HPMC (E5) + PEG (400) +Aspartame + Malic acid

Table 3: Stability Studies data for formulation F4

Time in months	Formulation F4 stored at 40^0 C/75%RH	
	In vitro Disintegration time (mean ± SD)sec	Drug content (mean ± SD)%
1	20±1.6	96.03±0.15
2	20±2.43	95.76±0.31
3	21±1.56	95.3±0.43

DISCUSSION

The films of all formulations showed uniformity in thickness, weight and drug content with minor deviation and all these factors were within the prescribed limit. Formulation F2 containing Tween-80(10%) revealed high degree of folding endurance, more percentage moisture loss, high tensile strength and more percentage elongation and it was also noticed that the increase in the concentration of Tween-80 increased the folding endurance, percentage moisture loss, tensile strength and percentage elongation, but in formulations with Polaxomer-408 there was decrease in folding endurance and percentage elongation and slight increment in tensile strength and percentage moisture loss when compared with the formulation F0. The formulation with Polaxomer-408(10%) showed lesser *in vitro* disintegration time and more cumulative drug release and it was found that the increase in the surfactant concentration decreased the *in vitro* disintegration time and increase in the cumulative drug release when compared with the formulation without surfactant. The FT-IR studies of formulation F4 revealed that there was no interaction between the polymers and drug, the formulation F4 was stable at subjected stability condition as it showed negligible variations in the *in vitro* disintegration time and drug content at time intervals of one month.

CONCLUSION

From the above results, it was concluded that the increase in the concentration of surfactants will surely affect the properties of the films and the formulation F4 showed lesser *in vitro* disintegration time and more cumulative drug release when subjected to *in vitro* dissolution and good performance in respect other parameters. The FT-IR revealed that drug Palonosetron and the polymers used for formulation F4 were compatible and the formulation F4 was stable with negligible variations in the subjected stability conditions. F4 was considered as the best formulation for Palonosetron.

ACKNOWLEDGEMENT

Authors are thankful to the AAGCP for extending financial support in part for the research work. The authors are thankful to the Principal, Government College of Pharmacy, Bangalore, for extending the laboratory facilities to carry out the Research work.

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