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Research Article

NATURAL POLYSACCHARIDES AS FILM FORMER: A FEASIBILITY STUDY FOR DEVELOPMENT OF RAPID DISSOLVING FILMS OF ONDANSETRON HYDROCHLORIDE

DHAGLA RAM CHOUDHARY*[1], VISHNU A PATEL[2], USMANGANI K CHHALOTIYA[1], HARSHA V PATEL[1], ALIASGAR J KUNDAWALA[1]

[1]Indukaka Ipcowala College of Pharmacy, Anand, Gujarat 388121, [2]A. R. College of Pharmacy, Anand, Gujarat 388120, India.
Email: dhaglaram@gmail.com

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ABSTRACT

Ondansetron is a highly selective serotonin (5-HT_3) receptor blocker which inhibits serotonin to bind with serotonin 5-HT_3 receptors and hence prevent the vomiting reflex induced by serotonin. This work aimed to develop rapid dissolving films of ondansetron for the treatment of chemotherapy induced nausea and vomiting. Rapid dissolving films were prepared by solvent casting method using pullulan PI 20 as film former and PG and tween 80 as plasticizer. Bitterness of Ondansetron was masked by forming inclusion complex with HPβ-CD. The complex was evaluated by XRD, DSC and FT-IR. Optimized films were evaluated for mechanical properties, surface pH and dissolution characteristics. The combination of pullulan PI 20 and PG:tween 80 and xanthan gum exhibited excellent mechanical properties (Tensile strength 6.1 N/mm^2), drug content (96.6 %) and disintegrating time (14 sec). The research work done here suggested the exciting possibility of ondansetron as rapid dissolving Film.

Keywords: Ondansetron, Rapid Dissolving Film, Hydroxyl Propyl B – Cyclodextrin, Pullulan, Solvent Evaporation Technique.

INTRODUCTION

Rapid dissolving dosage form (RDDFs) has become increasingly important because of their unique properties. They quickly disintegrate and dissolve, and can be administered without water, making them particularly suitable for pediatrics and geriatric patients[1-2].

The rapidly dissolving dosage forms were introduced as orally disintegrating tablets (ODTs) in 1970's as an alternative to the conventional tablet and capsule which require swallowing of the dosage form. Rapid dissolving films were introduce in 2001, initially they were lunched in the market as breath fresheners and personal care products such as dental care strips and soap strips. Pfizer's Warner–Lambert's created Listerine Pocket Packs as mouth freshener in 2001 and Zengen launched chloraseptic relief strip in USA delivering Benzocaine, a local anaesthetic for the treatment of sore throat[3-4].

ODTs of many drugs are available in the market and also prepared by Margret R.et al[5] and Khan S et al[6] but these tablets have certain disadvantages as compare to films; like-1. Despite the short disintegration/dissolution times of ODT, the fear of taking solid tablets and the risk of choking persists[2], 2. For their production, many ODT requires the expensive lyophilisation process, 3. ODT are sometimes difficult to carry, store and handle (fragility and friability)[7] and 4. ODTs requires specialized and expensive packaging and processing

Now days pharmaceutical companies and consumers alike have embraced RDFs as a practical and accepted alternative to traditional over the counter (OTC) medicines, such as liquids, tablets and capsules, because of the various benefits of the films. RDFs offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without requiring the use of water or a spoon[8].

Cancer is increasing at an alarming rate globally. Chemotherapy is the primary treatment for cancer and in some cases the only resort. Most of the chemotherapeutic drugs have been found to cause release of large amounts of serotonin from enterochromaffin cells in the gut, serotonin acts on 5-HT_3 receptors in the gut and brain stem and stimulate vagal affarents to initiate the vomiting reflex. Chemotherapy induced nausea and vomiting (CINV) remains a significant problem for cancer patients, having a long lasting effect on their quality of life. 5-HT_3 receptor antagonists or serotonin antagonists suppress nausea and vomiting by inhibiting serotonin binding to the 5-HT_3 receptors[9-10].

Ondansetron is a highly selective serotonin (5-HT_3) receptor blocker which inhibits serotonin to bind with serotonin 5-HT_3 receptors and hence prevent the vomiting reflex induced by serotonin[11-12].

In above mention condition of chemotherapy induced nausea and vomiting, rapid onset of action of the drug is required. The rapid dissolving films fulfill all the requirements of potential solid dosage form for ondansetron in preventing nausea and vomiting.

Lots of research has been done using ondansetron, research like- orally disintegrating tables[5-6], fast dissolving sublingual films was prepared by Koland M[13], trandermal patch was formulated by Fatima F[14] and controlled nasal drug delivery by Eunsook Cho[15] and Bhise S B[16].

Based on scientific literature survey FDFs consisting of components like, film formers, plasticizer, saliva stimulating agents, sweetening agents and APIs. Various film formers were employed, investigated and reported[17-19]. In most of the cases, RDFs were developed by using maltodextrin[20-21], HPMC (Methocel)[22-23] or polyvinyl alcohol[24] as film former.

Earlier rapid dissolving films of ondansetron have been formulated by using maltodextrin[25] and methocel E15[26].

Present research work was attempted to investigate the film forming properties of natural gums mainly Pullulan gum. Carrageenan gum, xanthan gum, and locust bean gum were used as film modifiers. Natural gums were used as film former because of their safety, good mouth feel, better mechanical properties and water solubility[27]. Propylene glycol (PG) and polyethylene glycol 400 (PEG 400) and tween 80 were used as plasticizer to enhance the strength of the films[28-29].

Pullulan is a natural polysaccharide produced from starch by cultivating black yeast Aureobasidium pullulans. It is a white, tasteless, odorless and water soluble powder. Pullulan PI-20 grade is the deionised form of pullulan having an average molecular weight of 2,00,000 daltons and possess excellent film forming properties. RDF using pullulan can be manufactured using solvent casting, hot melt extrusion or compression moulding. Solvent casting is the most common and traditional method[30]. Films of cetirizine[31] and levocetirizine[32] were formulated using pullulan as film former by solvent casting method.

MATERIALS AND METHODS

Materials

Ondansetron Hydrochloride was obtained as gift sample from Aurobindo Pharma, Hyderabad, India. Neotame, hydroxyl propyl β-

cyclodextrin (HPβ-CD) and xanthan gum was provided by Alkem pharmaceutical Pvt Ltd. Mumbai. Pullulan gum was provided as gift sample by Gengwal Chemicals, Mumbai. Carrageenan gum, locust bean gum was purchased from Himedia, Mumbai. Propylene glycol (PG), polyethylene glycol 400 (PEG400) and tween 80 were purchased from Sigma chemicals. All other chemicals used were of analytical grade.

Methods

Preformulation Studies

Preformulation studies for drug and excipients was done by using FT-IR Spectroscopy and Differential Scanning Calorimetry (DSC)

FT-IR spectroscopy

The FT-IR of pure drug and optimized film former was measured using Fourier Transform Infra Red Spectrophotometer (Spectrum GX FT-IR, Perkin Elmer, USA). Pure drug and optimized film former 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}.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of ODS, pullulan and combination of both was carried out using DSC-PYRIS-1 (Perkin-Elmer, USA). The samples were heated from 50 to 450 °C at a heating rate of 10 °C/min in an inert nitrogen atmosphere.

Complexation of ODS with HPβ-CD

ODS– HPβ-CD inclusion complex (1:1 molar ratio) was prepared by co-evaporation method. The required quantities of ODS and HPβ-CD were dissolved in the water. The solvent was allowed to evaporate by heating at 45–50°C. The resultant solid was pulverized and then sieved through120 #. The complex formation was characterized by using X- Rray Diffraction (XRD) Studies (Xpert MPD, Philips, Holland), DSC Studies, FT-IR Spectroscopy[22].

Screening of base material for preparation of blank rapid dissolving films

Placebo films were prepared by using different concentration of pullulan ranging from 1 % to 4 % w/v. Various plasticizer like propylene glycol, polyethylene glycol 400 and tween 80 were employed at different concentrations ranging from 5 % - 15 % w/w of polymer concentration alone and in combination[33-34]. The suitable concentration of pullulan and plasticizer was evaluated depending on organoleptic evaluation and disintegrating time.

Film modifiers like - xanthan gum, carrageenan gum and locust bean gum were employed in different concentrations ranging from 0.2 to 0.6 % w/w. All these placebo films of different concentrations were investigated for their suitability as film modifier by evaluating different parameters like-film forming ability, peelability, integrity, uniformity, thickness and disintegrating time. All the properties were evaluated on the basis of grading system, A was for excellent, B for average and C for poor results[32].

Preparation of RDFs

Film former pullulan gum and modifier- xanthan gum, carrageenan gum and locust bean gum were soaked in half the quantity of water separately for 8 hours to get uniform dispersion and mixed both the solution with stirring. ODS – HPβ-CD complex was dissolved in a portion of water. This solution was added to polymeric solution and mixed well to obtain homogenous solution followed by addition of plasticizers, neotam and citric acid. The solution was mixed well to get uniform dispersion. Solution was then casted into petridishes having surface area of 64 cm^2 and 1.3 cm wall height. Petridishes were kept in hot air oven for 8 hours at 50. After drying films were removed with the help of sharp blade and kept in desicator for 24 hrs before cutting into small pieces having area of 6 cm^2 for each film. Films with air bubbles, cuts or imperfections were excluded from further study. Selected films were subjected for different evaluation parameters.

Evaluation Parameters

Appearance

All prepared films were checked for their appearances either they are transparent or opaque.

Weight Variation and Thickness

Films were evaluated for its weight variation and thickness. Weight variation was evaluated by using electronic balance (Shimadzu Corp. Japan. Type AX200) and thickness was measured using Digital Vernier Calipers[23].

Mechanical properties

Various mechanical properties like tensile strength, % elongation, elastic modulus and folding endurance were evaluated for prepared films[35-36].

Tensile strength

It was measured using Shimadzu AG-100kNG (Winsoft tensile and compression testing). The film of size 5×2 cm^2 and free of physical imperfections was placed between two clamps held 10 mm apart. The film was pulled by clamp at a rate of 5mm/min. Whole experiment was carried out in triplicate[23].

Percentage elongation

Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.

Percentage Elongation = $[L-L_0]$ X 100 / L_0

Where, L = Final length, L_0 = initial length.

Elastic modulus

Elastic modulus was calculated by following formula

$$Elastic\ Modulus = \frac{Force\ at\ corresponding\ strain}{Cross\ sectional\ area\ (mm^2)} \times \frac{1}{Corresponding\ strain}$$

Folding endurance

A film of 6 cm^2 was repeatedly folded and unfolded at the same place till it breaks. The number of times, the film could be folded at same place, without breaking was recorded as the value of folding endurance. This gives an indication of brittleness of the film[20].

Morphology study of film

Morphology of the prepared films was observed under a scanning electron microscope (SEM) (ESEM TMP with EDAX, Philips, Holland) The sample was attached to the slab surface with double sided adhesive tapes and the scanning electron photomicrograph was taken at 2000 x magnification[37].

Surface pH

The surface pH of rapid dissolving films 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[20]. The films were allowed to swell in closed petridish at room temperature for 30 minutes in 1ml of distilled water. Solution was placed under digital pH meter (Elico, India) to determine the surface pH.

Uniformity of drug content

The drug content of optimized films were assayed by random sampling of the 5 films of 6 cm^2 from one petridish (64 cm^2), each film was dissolved in 50 ml volumetric flask containing water. Solution was subjected to centrifugation for 15 min at 2500 rpm. The supernatant liquid was diluted to obtain 10 µg/ml solution and passed through whatman filter paper. Filtered solution was analyzed by double beam UV Spectrophotometer at 210 nm against 6.4 buffer solution as blank[32].

In-vitro disintegration time

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The require size of film (6 cm^2) of selected formulations was placed in a glass petridish (9 cm diameter and 1.3 wall height) containing 10 ml of distilled water and left undisturbed. The time was noted down till film was completely converted into small pieces. Test was performed 3 times on each formulation[24].

In-vitro dissolution studies

An in-vitro dissolution study was performed for the films of selected formulations for 3 minutes in USP paddle apparatus using pH 6.4 buffer solutions. Dissolution medium was kept at 37º C ± 0.5º C and rotated at 500 rpm. The samples (5 ml) were withdrawn after every 30 sec and replaced with fresh buffer (pH 6.4) solution. One ml sample was then taken and diluted up to 10 ml in volumetric flask. The samples were analyzed for the drug content using U V spectrophotometer at 210 nm. Dissolution was performed 3 times for each formulation to calculate drug release profile[22].

Stability study

Short term accelerated stability studies was performed for optimized films were placed in plastic containers and exposed to 40˚C / 75 % RH (ICH guidelines) for a period of 4 months. Different film properties like physical appearance of the film, mechanical properties and drug content was evaluated at interval of one week[21,38].

RESULTS AND DISCUSSION

Preformulation Studies

FT-IR spectroscopy

Ondansetron HCl has shown a characteristic band at 758 cm^{-1} due to 0- disubstiuted benzene, the band at 1459 and 1480 cm^{-1} are due to methyl group. The C-N- stretching vibrations are observed at 1280 cm^{-1}. The band at 1531 cm^{-1} due to aromatic C=C and the band at 1638 was due to C=N, C=O in six member ring. The bands at 3487 and 3410 cm^{-1} are due to hydroxyl groups. The FT-IR spectra of pullulan gum exhibited characteristic peaks at 2928, 1638, 1460, 1419, 1080, 849 and 596 cm^{-1}. The FT-IR spectra of the mixture of drug and pullulan showed the characteristic peak of drug at 756, 1259, 1458, 1479, 1531, 1638, 3410 and 3487 cm^{-1} and pullulan at 2928, 1638, 1460, 1419, 1080, 849 and 596 cm^{-1} which indicates purity of drug; hence there is no interaction of drug with film former pullulan (Figure 1).

Differential Scanning Calorimetry (DSC)

DSC thermogram showed endothermic peak of ODS and pulluln at 185.68 and 80 °C which corresponded to their melting point.

Thermograms of mixture of drug and pullulan showed peak at 185.68 and 79 °C itself. There was no change in the melting point of drug when combined with film former. The evaluation of the thermogram obtained from DSC revealed that there is no interaction between the drug and film formr (Figure 2).

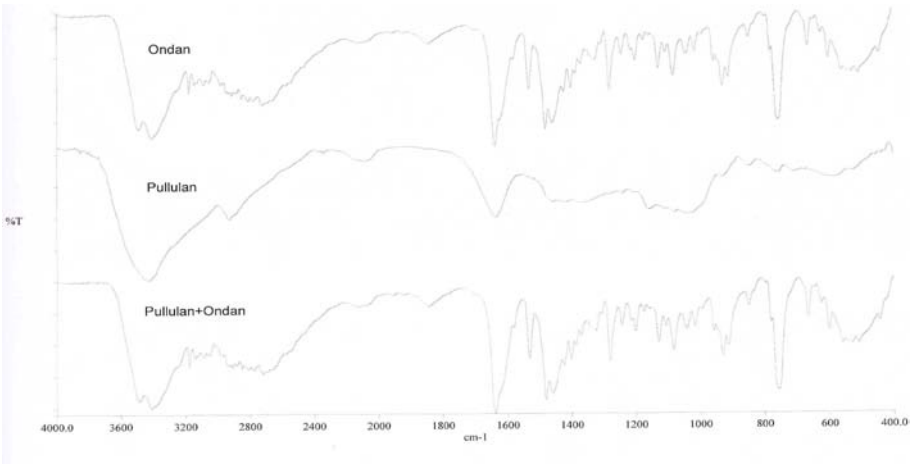

Fig. 1: **FT-IR of ondansetron, pullulan and mixture of both**

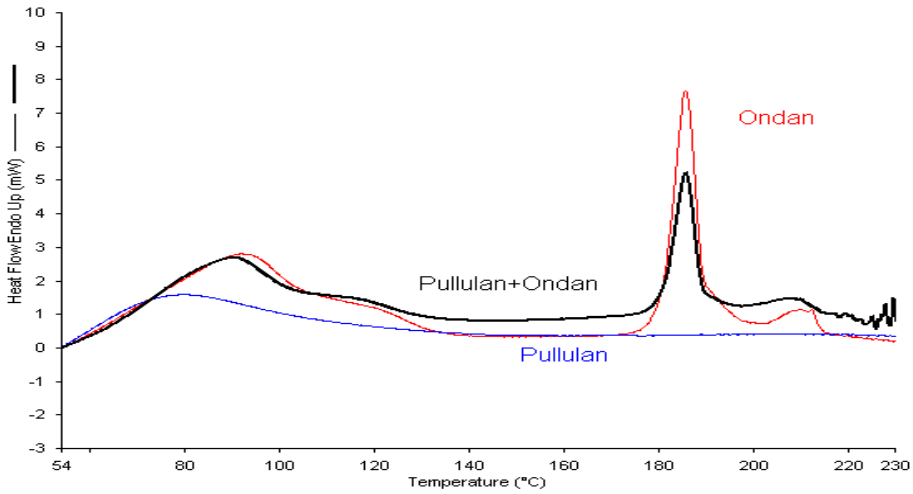

Fig. 2: Comparison of DSC thermograms of ondansetron, pullulan and mixture of both

Complexation of ODS with HPβ-CD

Literature survey showed that taste of ondansetron was successfully masked by using ion exchange resin polacriline potassium[26], Indion 204[5] and by making complex with aminoalkyl methacrylate co-polymer (Eudragit EPO)[6]. In this study an attempt was made to mask the bitter taste of ondansetron by making complex with HPβ-CD.

The complex forming ability of CDs have been widely exploited in the pharmaceutical field for various applications, taste masking of bitter drugs is one such application[39-41]. Bitterness of famotidine was successfully masked by making the complexation of drug with β-cyclodextrin[42].

FT-IR Spectroscopy

Ondansetron HCl has shown a characteristic band at 758, 1280, 1459, 1480, 1531, 1638, 3410 and 3487 cm^{-1}. However, the FT-IR spectrum of ODS – HPβ-CD inclusion complex was did not exhibit any significant difference in the characteristic peaks of ODS hydrochloride except 3410 and 3487. The identification peaks (3410 & 3487) of ondansetron did not appear in FTIR spectra of ODS – HPβ-CD inclusion complex, where as the frequency and intensity of others characteristic peaks of ondansetron have been defused. This revealed that there are modifications in the drug properties. This suggests that there is formation of new substances (Figure 3).

Differential Scanning Calorimetry (DSC)

DSC thermogram showed endothermic peak of ODS at 185.68 °C (Figure 4) and HPβ-CD at 92.34 °C, which corresponded to melting point ODS and HPβ-CD respectively. The thermogram of ODS- HPβ-CD complex showed a peak of ODS at 185.68°C with low intensity as compare to pure drug, which indicates that there is a change in the properties of ODS. The thermo gram peak of HPβ-CD in complex was observed at 82.72 °C.

X-Ray Diffraction (XRD)

The X-Ray diffractogram of ODS confirms its crystalline nature, as evidenced from the number of sharp and intense peak situated between 10^0 and 30^0 (2θ). The diffractogram of HPβ-CD showed diffused peak, indicating the amorphous nature. However the diffraction pattern of ODS- HPβ-CD complex represents less intense crystalline peaks of drug especially those situated between 10^0 and 30^0 (2θ). This diffraction pattern suggests that, there is a new solid phase formation with a lower degree of crystallinity due to complexation(Figure 5).

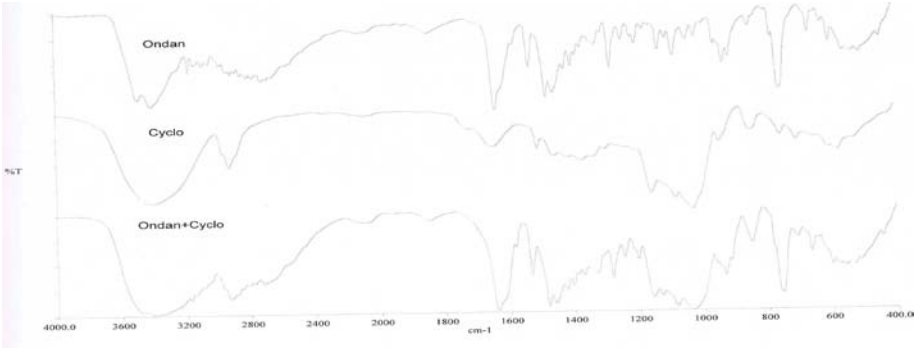

Fig. 3: FT-IR ODS- HPβ-CD Complex

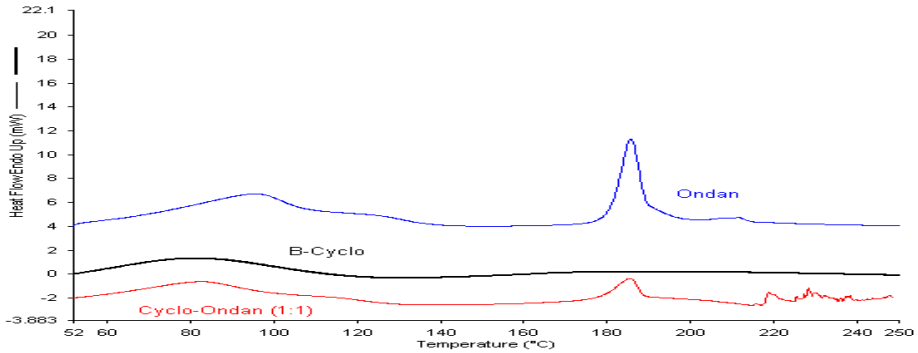

Fig. 4: Comparative DSC Spectra of Ondansetron, HPβ-CD and Drug – HPβ-CD Complex

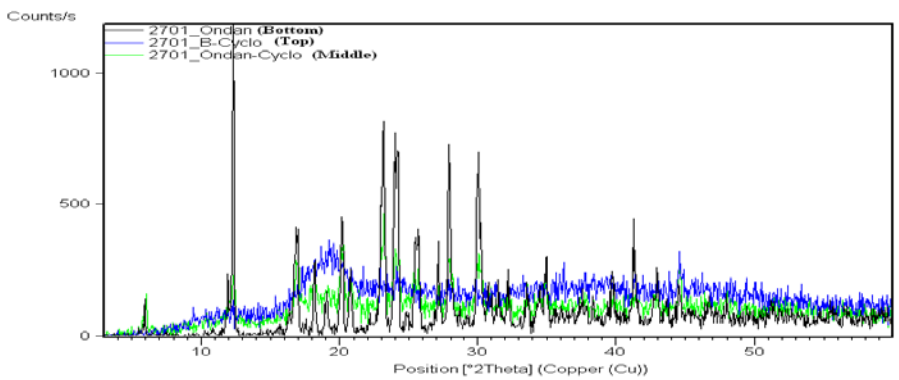

Fig. 5: Comparative XRD of ondansetron (Bottom), HP β -CD (Top), complex of pure drug and HPβ-CD (Middle)

Screening of base material for preparation of blank rapid dissolving films

Initially placebo films of pullulan gum were prepared by using different concentrations ranging from 1 % - 4 % w/v as shown in Table 4.7. Prepared films were evaluated for thickness and *in vitro* disintegrating time. All the prepared films were opaque. Films of P1 were very thin and breakable. Their thickness was 33 ± 3.2 µm. Films were found to disintegrate within 08 ± 0.9 sec. Formulation P2 showed good results. They have exhibited 44 ± 3.4 µm of thickness. They were disintegrated within 13 ± 1.2 sec. Films of P3 and P4 were thick, took more time to disintegrate. They were having thickness in the range 56 – 67 µm respectively. These films were disintegrated in range of 19 – 23 sec as shown in Table 1.

Table 1: Preliminary Screening of Pullulan gum

Ingredients	Formulations Code			
	P1	**P2**	**P3**	**P4**
Pullulan (% w/v)	1%	2%	3%	4%
Water (ml)	25	25	25	25
Thickness (µm)	33 ± 3.2	44 ± 3.4	56 ± 4.8	67 ± 5.5
Disintegrating time (sec)	08 ± 0.90	13 ± 1.2	19 ± 1.1	23 ± 2.2

Above prepared placebo films had tendency to chip from edges while peeling and cutting it was mainly because of inadequate plasticizing effect. In literature, it is reported that plasticizer helps in improving the flexibility and increase the elasticity of the films. Plasticizer significantly improves the film properties by reducing the glass transition temperature of the film former. The selection of plasticizer will depend upon its compatibility with the film former and also the type of solvent employed in the casting of film. The flow of film former will get better with the use of plasticizer and enhances the strength of the film former[37-38]. Three plasticizers namely PG, PEG 400, and tween 80 were used individually and in combination[45]. Initially all plasticizer were separately used. The concentrations of plasticizers were varied from 5 % -15 % w/w of film former concentration. Films prepared by using amount more than 10-15 % w/w of plasticizer were too soft to handle, they were greasy in nature and film distortion was observed. Films prepared with amount lesser than 10 % w/w were breakable while peeling.

Flexible and peelable films were developed but tendency of chipping from edges still was a concern, when all plasticizers were used individually. Shiji Shen et al has reported that the use of tween 80 in combination with PG or PEG 400 can reduce the chipping form edges and produce film with good peelability, integrity and flexibility[46]. Hence 10 % w/w of PG, PEG 400 and 5 % w/w of tween 80 was selected for further research. Films of P5 containing PG:Tween 80 (2:1) (15% w/w) has produced satisfactory results than films of P6 containing PEG 400:Tween 80 (2:1) (15% w/w). Films containing PEG 400 in combination with tween 80 has taken more time (16 sec) to disintegrate when compared to PG with tween 80 (12 sec). The combination of PG and tween 80 has produced films of good peelability, flexibility, integrity and uniformity as shown in table 2.

Table 2: Preliminary Screening of Plasticizers for RDFs

Ingredients	Formulation Code	
	P5	**P6**
Pullulan Gum (% w/v)	2	2
PG:Tween 80 (2:1) (15% w/w)	√	-
PEG 400:Tween 80 (2:1) (15% w/w)	-	√
Peelability	A	A
Integrity	A	A
Flexibility	A	A
Uniformity	A	B
Stickiness	A	B
Thickness (µm)	56 ± 3.5	58 ± 3.5
DT (sec)	12 ± 0.7	16 ± 1.1

Various film modifiers like Xanthan gum, carragenan gum and locust bean gum was used to provide proper texture to film and reduce recrystallization of drug[47-48]. They were employed in different concentrations ranging from 0.2 % to 0.6 % w/w of polymer concentration. High disintegrating time and low mechanical properties were observed when films prepared by using κ-carrageenan. It might be attributed due to their gel forming property before converting into solution, low water solubility and offer certain barrier for drug release[49-50]. Films prepared by using 0.4% w/w xanthan gum and locust bean gum have exhibited excellent texture and mechanical property and satisfactory disintegrating time[17-19]. Films with low concentration (0.2 % w/w) of xanthan and locust bean gum have low mechanical property and poor texture. High concentration (0.6 % w/w) of xanthan and locust bean gum resulted very viscous solution which was too viscous to cost in to petrisish. Hence 0.4% w/w of xanthan and locust bean gum was selected for further studies (Table 3).

Table 3: Screening of Film Modifiers

Ingredients	Formulation code								
	P7	**P8**	**P9**	**P10**	**P11**	**P12**	**P13**	**P14**	**P15**
Pullulan gum % w/v	2	2	2	2	2	2	2	2	2
Carrageenan gum % w/v	0.2	0.4	0.6	-	-	-	-	-	
Xanthan gum % w/v	-	-	-	0.2	0.4	0.6	-	-	-
Locust bean gum % w/v	-	-	-	-	-	-	0.2	0.4	0.6
PG:Tween 80 (2:1) % w/w	15	15	15	15	15	15	15	15	15
Thickness (µm)	57 ± 4.60	59 ± 3.9	62 ± 4.1	58 ± 4.5	60 ± 3.9	-	58 ± 3.8	63 ± 4.2	-
DT (sec)	21 ± 2.3	25 ± 2.6	32 ± 2.9	16 ± 1.6	18 ± 1.7	-	17 ± 1.1	20 ± 1.0	-

Sweetening agent Neotam and saliva stimulating agent citric acid were also varied. Neotam was varied from 0.020 % w/w to 0.035 % w/w. 0.03 % w/w has given satisfactory results. Citric acid was varied from 0.2 % w/v to 0.35 %% w/v. The concentration of citric acid was found suitable with film was 0.3% w/v. Film distortion was observed when more 0.3% w/v of citric acid was used.

Mechanical Proprieties

Fast dissolving films should be tough, flat and should not curl on the edges. It should be easy to cut into as per size (6 cm^2) and efficiency filled into the unit-dose packing (e.g. plastic container). It should be robust enough to be removed from unit-dose packing without breaking[51]. The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. Suitable FDFs must have moderate tensile strength, good percentage elongation and low elastic modulus.

Figure 6, shows force-deformation curves for the placebo films containing only polymer (A, P2), placebo with plasticizer and modifiers (B, P11) and the drug loaded film (C, P16). The portion of the curve at lowest stress appeared linear and the deformation of the samples was elastic. The elastic modulus, is an index of stiffness, was higher for B where as less for A and C. Increasing the strain, the deformation becomes plastic and values of maximum load reached by the samples were not significantly different. The feature implies that the films had a comparable strength at deformation stress. After tensile strength the curves became significantly different. A and C were characterized by lower value of elongation break that expressed the ductility of film. For all the films with increasing strain the stress decreases; neck formation and neck growth were observed, but this behavior was more evident for B. Finally the toughness, expressed as the tensile energy to break the film, was reduced due to addition of drug, neotam and citric acid. Placebo formulation containing plasticizer and modifier (B), resulted good toughness.

The addition of the drug and other excipients decrease the deformation of film when subjected to a stress. These results matched with those previously describe research work for piroxicam[21] and diclofenac sodium[52] suggested that the addition of amount of drug determine an increase of the stiffening of the film.

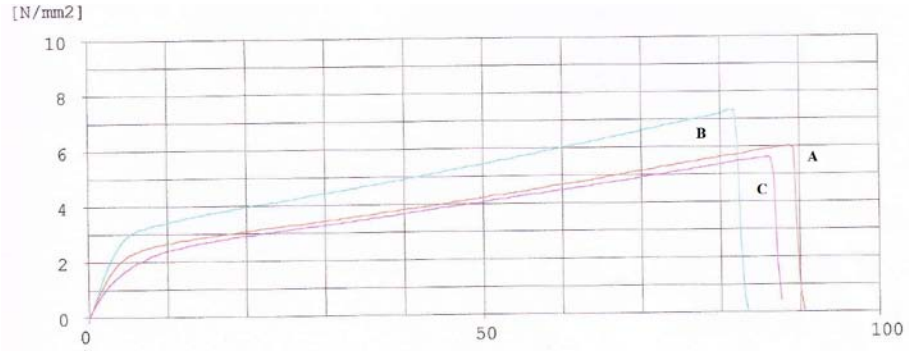

Fig. 6: Strain stress relationship of films of formulations of (A) Film containing only polymer (P2) (B) Film containing polymer, plasticizer and modifiers (P11) (C) Film containing polymer, drug and other excipients (P16).

Films of pullulan containing xanthan gum (P16) had exhibited better mechanical properties as compare to locust bean gum films (P17). Films of P16 showed good tensile strength (5.74 N/mm^2), high % elongation (84.34), low young's modulus (9.12 N/mm^2) and better folding endurance (116) as compare to P17 films as shown in table 5.

Table 4: Optimized Formulations of Ondansetron RDFs

Ingredients	Quantities	Formulation Code	
		P16	P17
ODS:HPBCD Complex (1:1 molar ratio; % w/v)	0.68 %	√	√
Pullulan (%w/v)	2 %	√	√
Xanthan gum (% w/w)	0.4 %	√	-
Locust bean gum (% w/w)	0.4 %	-	√
PG:Tween 80 (2:1) % w/w	0.45 %	√	√
Neotam (%w/v)	0.030%	√	√
Citric acid (%w/v)	0.3%	√	√
Water ml	25	√	√

Table 5: Evaluation of Optimized Formulations

Parameters	Results	
	P16	P17
Appearance	Opaque	Opaque
Weight variation (mg)	85 ± 6.6	83 ± 3.7
Thickness (µm)	72 ± 6.6	75 ± 2.56
Tensile strength (N/mm^2)	5.74 ± 1.34	5.62 ± 2.02
% Elongation	84.34 ± 3.5	75.70 ± 5.2
Young's modulus (N/mm^2)	9.12 ± 1.5	15.48 ± 1.7
Folding endurance (No. of folding)	116 ± 10	98 ± 8
Surface pH	6.1 ± 0.07	6.1 ± 0.08
Content uniformity	96.6 ± 4.2	97.35 ± 5.8
In vitro disintegration time (sec)	14 ± 0.34	21 ± 0.47

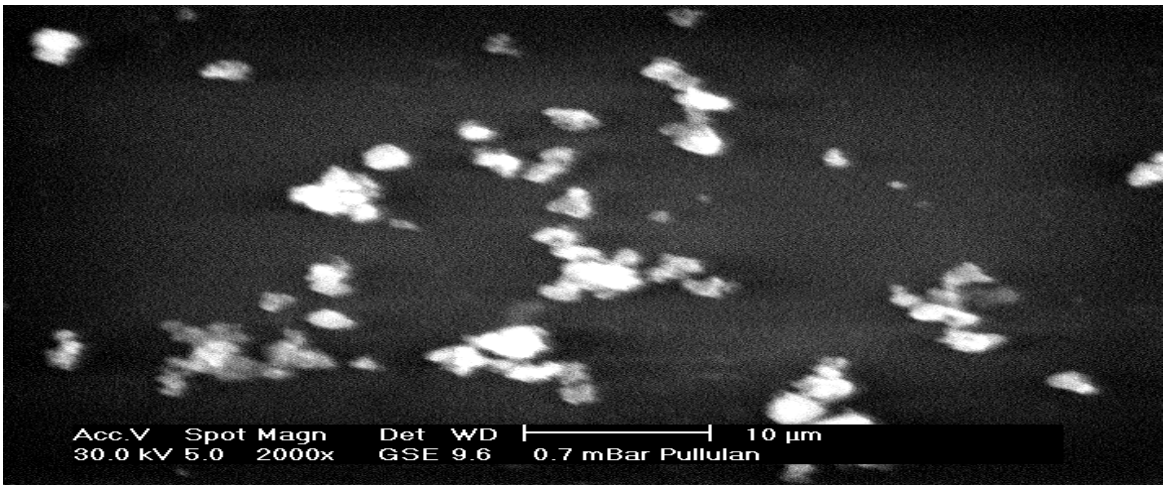

Fig. 7: SEM image of film of pullulan containing Ondansetron

Morphology of film

The scanning electron photomicrograph of pure drug (Figure 8) and the films of P16 (Figure 7) at 2000X magnification showed smooth surface without any scratches or transverse striations which indicates the even distribution of ondansetron and uniform film.

Surface pH

Since surface pH of films should to be around neutral pH to avoid any kind of irritation to the mucosal lining of the oral cavity. Surface pH of the film was ranging from 6.0 to 6.2.

Uniformity of Content

Theoretically ODS content in each film was 8 mg, this was considered as 100%. The ODS content in P16 and P17 was evaluated. The ODS content in P16 and P17 was found to be 96.6 ± 4.2 and 97.35 ± 5.8 respectively. As per USP requirement the drug content must be in the range of 85% to 115%. The above result for both the formulations passes the test of uniformity of drug content.

***In-vitro* disintegration time**

All the films of formulation P16 and P17 were found to disintegrate in 14 ± 0.34 and 21 ± 0.47 sec respectively.

***In-vitro* dissolution studies**

Drug released study revealed that films of P17 released 84 % of drug in 90 sec where as films of P16 released 91.5 % of drug in same time.

Stability Studies

When the oral films of P16 was stored in plastic container at room temperature and under accelerated condition 40 ° C / 75 % RH for 4 months. There was no change in the ODS content, appearance, but slight changes were observed in mechanical properties and in vitro disintegrating time. The tensile strength was reduced from 5.74 N/mm^2 to 5.53 N/mm^2 and disintegration was increased from 14 sec to 19 sec.

CONCLUSION

The Rapid-dissolving films of ODS was prepared using pullulan (PI 20) as film former by solvent-casting method. Plasticizers PG in combination with tween 80 and film modifier xanthan gum played a great role in maintaining the peelability and integrity of films. Films of pullulan P16 exhibited satisfactory mechanical properties, *in vitro* disintegrating time and drug release. ODS a water soluble and bitter drug could be incorporated in the FDFs by making the forming inclusion complex with HPBCD, which is confirmed by evaluating complex using FT-IR, DSC and XRD. Films of P16 were found stable for 4 months.

REFERENCE

1. Dixit R, Puthli P. Oral strip technology: Overview and future potential. Journal of Controlled Release 2009; 139: 94-107
2. Gavaskar B, Kumar SV, Sharan G, Rao YM. Overview on Fast Dissolving Films. IJPPS 2010; 2(3): 29-33
3. The 'Dis-solution' of Classic Personal Care, Cosmetics & Toiletries, August 2005
4. Ghosh T, Pfister W. Drug Delivery to the Oral Cavity: Molecules to Market. Florida: CRC Press, Taylor &Francis 2005. 337-340
5. Margret R et al. Formulation and evaluation of taste masked fast dissolving tablets of ondansetron Hydrochloride. Journal of Pharmacy Research 2008; 1: 200-207
6. Khan S, Kataria P, Nakhat P, Yeole P. Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating tablets. AAPS Pharm Sci Tech 2007; 8(2): 1-7
7. Vollmer U, Galfetti P. RapidFilm: Oral Thin Films (OTF) as an innovative drug delivery system and dosage form, Technology overviews. Drug Delivery Report Spring/Summer 2006; 4: 18-21
8. Frey P. film strip and pharmaceuticals. Pharma. Mfg. and packing. Sourcer , winter 2006; 92-93
9. Watcha F, White P. Postoperative nausea and vomiting: its etiology, treatment, and prevention. Anesthesiology 1992; 77:162–184
10. Foubert J, Vaessen G. Nausea: the neglected symptom? European journal of oncology nursing 2005; 9: 21-32
11. Jantunen IT, Kataja VV, Muhonen T T. An overview of randomised studies comparing 5-HT_3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy induced vomiting. Eur J Cancer 1997; 33: 66–74
12. Tortorice PV, O'Connell MB. Management of chemotherapy-induced nausea and vomiting. Pharmacotherapy 1990; 10: 129–145
13. Koland M, Sandeep VP, Charyulu NR. Fast dissolving sublingual films of ondansetron hydrochloride: Effect of additives on in vitro drug release and mucosal permeation . Journal of Young Pharmacist 2010 ; 3: 216-222
14. Farsiya F et al. Formulation and Evaluation of Matrix-Type Transdermal Delivery Systemof Ondansetron Hydrochloride Using Solvent Casting Technique. Research J. Pharm. and Tech. 2011; 4(5): 806-814
15. Eunsook C, Hyesun G, Inkoo C. Formulation and evaluation of ondansetron nasal delivery systems. International Journal of Pharmaceutics 2008; 349: 101-107
16. Bhise SB, Rajkumar M. Controlled Nasal Delivery of Ondansetron HCl. Indian J.Pharm. Educ. Res. 2007; 41(3): 229-235
17. Choudhary DR, Patel VA, Patel HV, Kundawala AJ. Exploration of Film Forming Properties of Film Formers Used in the

Formulation of Rapid Dissolving Films. International Journal of Chem Tech Research 2011; 3: 531-533
18. Kulkarni AS, Deokule HA, Mane MS, Ghadge DM. Exploration of different polymers for use in the formulation of oral fast dissolving strips. JCPR 2010; 2(1): 33-5
19. Ming JC et al. Film-forming polymer in fast dissolving oral films 2006; 2: 1-5
20. Kunte S, Tandale P. Fast dissolving strips: A novel approach for the delivery of verapamil. Journal of Bioallied Science 2010; 2: 325-28
21. Francesco C, et al. Fast dissolving films made of maltodextrins. European J. Phar. and Bio 2008; 70: 895-900
22. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of Triclosan to the oral cavity. AAPS Phram. Tech 2008; 9: 349-56
23. Mishra R, Amin A. Formulation Development of Taste-Masked Rapidly Dissolving Films of Cetirizine Hydrochloride. Pharmaceutical Technology 2009; 2: 48-56
24. Doaa AE, Nevine SA. Formulation of a Novel Tianeptine sodium orodispersible film. AAPS 2010;11:1018-24
25. Patel R, Naik S, Patel J, Baria A. Formulation Development and Evaluation of Mouth Melting Film of Ondansetron. Arch Pharm Sci & Res 2009; 1(2): 212 - 17
26. Sumitha C, et al, Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapid-disintegrating films. International Journal of Chemical Research 2009; 1(2): 24-27
27. Murata Y, Isobe T, Kofuji K, Nishida N, Kamaguchi R. Preparation of Fast Dissolving Films for Oral Dosage from Natural Polysaccharides. Materials 2010; 3: 4291-99
28. Kennedy SW, Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients. Pharmaceutical press, London 2006: 792–93.
29. Kennedy SW, Rowe RC, Sheskey PJ, Owen SC. Handbook of Pharmaceutical Excipients. Pharmaceutical press, London 2006: 796–97.
30. Rekha MR, Chandra PS. Pullulan as a Promising Biomaterial for Biomedical Applications: A Perspective; Trends. Biomater. Artif. Organs 2007; 20: 1-6
31. Mishra R, Amin A. Formulation and Characterization of Rapidly Dissolving Films of Cetirizine hydrochloride using Pullulan as a Film Forming Agent. Indian Journal of Pharmaceutical Education and Research 2011; 45: 71-7
32. Mahesh A, Shastri N, Sadanadam M. Development of Taste Masked Fast Desintegrating Films Of Lecocetirizine Dihydrochloride For Oral Use. Current drug delivery 2010; 7: 21-27
33. Sakellariou P, Rowe RC. Interactions in cellulose derivative films for oral drug delivery. Prog. Polym. Sci 1995; 20: 889-942.
34. Banker GS. Film coating theory and practice. J. Pharm. Sci, 1966; 55: 81–9
35. Brindle LP, Krochta JM. Physical properties of whey protein-hydroxyl propyl methyl cellulose blend edible films. Journal of Food Science 2008; 73: 446-54.
36. Felton L, O'Donnell P, McGinity J. Mechanical Properties of Polymeric Films Prepared from Aqueous Dispersions, In: Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms. New York, USA: Informa health 2008; 176-78.
37. Mashru RC, et al. Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Development and Industrial Pharmacy 2005; 1: 25-34.
38. ICH Steering Committee. Stability testing of new drug substances and products Q1A (R2) 2003.
39. Noriaki F, Ikumi U, Takashi O, Shun H, Saburo N. Masking mechanisms of bitter taste of drugs studied with ion selective electrodes. Chem. Pharm. Bull 2006; 54:1155-61.
40. Giancarlo C, Arianna B, Enzo B, Paolo C, Trotta F. Cyclodextrins as food additives and in food processing. Curr. Nutri. Food Sci 2006; 2: 343-50.
41. Sohi H, Sultana Y, Khar R. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. Drug Dev. Ind. Pharm 2004; 30: 429–48.
42. Ashok RP, Pradeep RV. Preparation and Evaluation of Taste Masked Famotidine Formulation Using Drug/β-cyclodextrin/Polymer Ternary Complexation Approach. AAPS PharmSciTech, 2009; 10: 544-50
43. Dobetti L. Fast melting tablets; development and technologies. Pharm. Technol. Eur, 2000; 12: 32-42
44. Siewert M, Dressman J, Brown CK, Shah VP. FIP/AAPS guidelines to dissolution / invitro release of novel/special dosage forms. AAPS Pharm. Sci. Tech 2003; 4: 1-10
45. Roy A, et al. Effects of plasticizers and surfactants on the film forming properties of hydroxypropyl methylcellulose for the coating of diclofenac sodium tablets, Saudi Pharmaceutical Journal 2009; 17(3): 238-46
46. Shiji S, et al. Penelope Pullulan Films and Their Use in Edible Packaging. Patton Publication, Patent application number: 20100068350, 2010
47. Goff HD. Gums and Stabilisers for the Food Industry 13.Williams P A, Phillips G O, eds. Cambridge: Royal Society of Chemistry 2006; 403–12
48. Towle GA. Gums and Stabilisers for the Food Industry 8. Phillips G O, Williams P A, Wedlock D J, eds. New York: Oxford University Press, Inc.1996; 79–87
49. Thommes M, Blaschek W, Kleinebudde P. Effect of drying on extruded pellets based on κ-carrageenan. European Journal of Pharmaceutical Sciences 2007; 31(2): 112-18
50. Tuleu C, et al. A scintigraphic investigation of the disintegration behaviour of capsules in fasting subjects: a comparison of hypromellose capsules containing carrageenan as a gelling agent and standard gelatin capsules. European Journal of Pharmaceutical Sciences 2007; 30: 251-55
51. Siewert M, Dressman J, Brown CK, Shah VP. FIP/AAPS guidelines to dissolution / invitro release of novel/special dosage forms. AAPS Pharm. Sci. Tech. 2003; 4: 1-10
52. Cilurzo Fet al. Diclofenac fast-dissolving film: Suppression of bitterness by taste a sensing system. DDIP 2010;1-8