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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF ONDANSETRON HYDROCHLORIDE

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ABSTRACT

The Buccal region offers an attractive route of administration for systemic drug delivery. Ondansetron is a serotonin 5HT 3 receptor antagonist is a potent antiemetic drug, which is used in control of nausea, vomiting associated with cancer chemotherapy. It exhibits only 60-70% of oral bioavailability because of first pass metabolism and has a relative short half-life of 3-5 h. Studies have shown that Ondansetron hydrochloride is well absorbed through the Buccal or sublingual mucosa. Buccal films were prepared using polymers like Chitosan, sodium alginate, HPMC, PVP, PVA. The evaluation parameters like surface pH study, Swelling index, Folding endurance, mucoadhesive strength, Content uniformity, in vitro residence time, in vitro release were observed. The release data were fitted according to release plots, first order, Higuchi's and Korsemeyer's equation and the mechanism of drug release was calculated according to Peppas equation and The calculated "n" values suggest that the mechanism of drug release followed class II diffusion transport mechanism. FTIR studies revealed no drug and polymer interaction and uniform amorphous distribution of drug into films. The short term stability studies were done for the formulation MBF6. The drug content and physical appearance was tested but no drastic variationwas observed.

KEYWORDS: Buccal films, Ondansetron hydrochloride, Chitosan, sodium alginate, HPMC, PVP, sodium CMC, PVA. In-Vitro release, FTIR.

INTRODUCTION

Since the early 1980s mucoadhesion has gained considerable interest in pharmaceutical technology. Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of many disorders. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. Buccal cavity). Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of drug.

The mucoadhesive drug delivery system includes the following:

1. Buccal drug delivery system
2. Sublingual drug delivery system
3. Vaginal drug delivery system
4. Rectal drug delivery system
5. Nasal drug delivery system
6. Ocular drug delivery system

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action.[1,2,3]

Oral Transmucosal Drug Delivery

Controlled drug delivery systems specifically designed for buccal cavity, where the drug releases in a controlled manner. The drug can be administered for local or systemic action. These systems are generally based on the polymers including bioadhesive polymers. The

various dosage forms including Buccal bioadhesive tablets, laminated film, hydro gels, Buccal patches, chewing gums and hollow fibers have been designed to extend the time of drug release from Buccal cavity. The absorption of drug through buccal mucosa can be increased using some absorption enhancers. Different peptides including insulin can be delivered to or through buccal cavity using control drug delivery systems. Particulate systems such as microspheres and nanoparticles have also been tried for the buccal control drug delivery.

Drug delivery via the membranes of the oral cavity can be subdivided as follows:

1. Sublingual delivery: involves administration of drug via the sublingual mucosa to the systemic circulation.

2. Buccal delivery: involves administration of drug via the buccal mucosa to the systemic circulation.

3. Local delivery: involves administration of bioadhesive system either to the palate, the gingiva or the cheek.[4,5]

Oral cavity

Components or structural features of oral cavity

Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth.

The oral cavity consists of two regions

Outer oral vestibule: which is bounded by cheeks, lips, teeth and gingival (gums)

Oral cavity proper: which extends from teeth and gums back to the fauces (which lead to pharynx) with the roof comprising the hard and soft palate? The tongue projects from the floor of the cavity.[3]

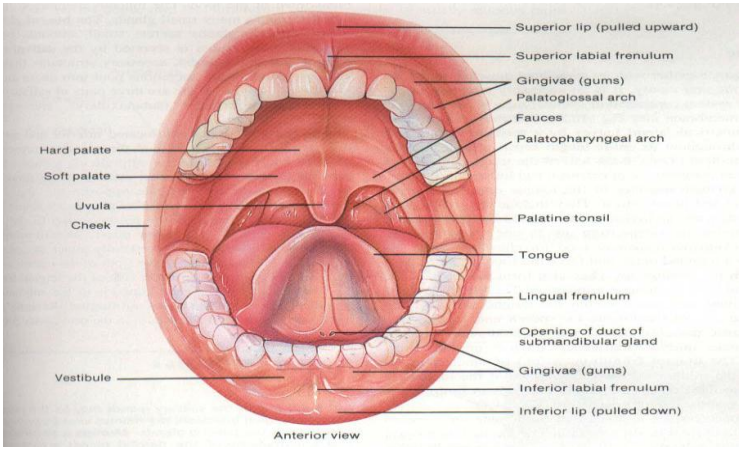

Fig.1: Structure of Oral Cavity

MATERIAL AND METHODS

Ondansetron hydrochlorideMegh Pharm. Pvt. Ltd. Modasa, Gujarat, India. Chitosan, Sodium dihydrogen orthophosphate, Xanthan Gum gifted by Loba Chemie laboratories, mumbai. Hydroxypropyl methylcellulose, Polyvinyl Alcohol gifted by Himedia Lab. Pvt. Ltd, Mumbai. Sodium Alginate gifted by S.D. fine chemicals, Mumbai. Polyvinyl pyrollidone K-30 gifted by WLPL, Tumkur, India. Glycerol, New India chemical enterprises, Cochin. Disodium hydrogen orthophosphate gifted by Finar chemicals limited, Ahmadabad, India. Methanol gifted by Qualegens chemicals, Mumbai. Glacial Acetic Acid gifted by Merck Specialties Pvt. Ltd. Water used was semi-quartz distilled (Qualigens). All other chemicals and reagents used were of A.R. grade, procured commercially and used as received.

Calibration curve of Ondansetron hydrochloride

Preparation of Phosphate Buffer pH 6.8

11.45 g of sodium dihydrogen orthophosphate and 22.8g of disodium hydrogen orthophosphate dissolved completely in 1000ml of water.

Preparation of calibration curve of Ondansetron hydrochloride

A spectrophotometer method based on the measurement of absorbance at 248nm in pH 6.8 buffer (phosphate) was used in the present study for the estimation of Ondansetron hydrochloride.

Procedure

100 mg of Ondansetron Hydrochloride was dissolved in 100 ml calibrated volumetric flask and completing to volume with phosphate buffer pH= 6.8. From this 10ml was pipette out in 100 ml calibrated volumetric flask and dilution was made with phosphate buffer pH= 6.8. From this stock solution 10ml was pipette out in 100ml calibrated volumetric flask and dilution was made with phosphate buffer pH= 6.8. From this solution 2ml, 4ml, 6ml, 8m & 10ml was pipette out in different volumetric flask and the final volume was making up with phosphate buffer pH= 6.8.

The absorbance was noted at 248 nm.[6,7]

Table No.1: Formulation Chart:

INGREDIENTS	MBF1 Mg	MBF2 mg	MBF3 Mg	MBF4 mg	MBF5 mg	MBF6 mg
Drug	50	50	50	50	50	50
Chitosan	300	150	150	150	150	150
HPMC	-	150	-	-	-	-
Xanthan Gum	-	-	150	-	-	-
PVP	-	-	-	150	-	-
Sodium Alginate	-	-	-	-	150	-
PVA	-	-	-	-	-	150
Glycerol	10%v/v	10%v/v	10%v/v	10%v/v	10%v/v	10%v/v
2% Acetic Acid Solution	10ML	10ML	10ML	10ML		

Preparation of buccal film

The films were prepared by the method of solvent casting Technique. Accurately weighed Chitosan alone or in combination Chitosan and HPMC, Chitosan and Xanthan Gum, Chitosan and PVP, Chitosan and Sodium Alginate, Chitosan and PVA was added to magnetically stirred solvent system (ethanol) containing Glycerol (which served the purpose of plasticizer as well as penetration enhancer) continuous Department of Pharmaceutics, B.L.D.E.A's COP, Bijapur. Page 76 stirring is necessary to prevent lump formation. Then drug was added to the above solution and stirred. The solution was then transferred quantitatively to glass ring kept on the surface of mercury in Petri-plates. The Petri-plates were covered with inverted funnels to allow controlled evaporation of solvent. These were left undisturbed at room temperature (20-35oC) for 1-2 days. The dried films were separated. Then the formulations were stored in desiccators until further use.

The process consist of six steps

1) Preparation of casting solution
2) Deareation of solution
3) Transfer of appropriate volume of solution into the mold
4) Drying the casting solution
5) Cutting the final dosage form to contain desired amount of drug
6) Packaging

Polymeric Films MBF1 to MBF6 were prepared by following method. Measured amount of distilled water (10ml) was taken in a beaker and accurately weighed polymers were added to it and stirred on a magnetic stirrer so that lump should not be formed and until clear solution

is obtained, then required amount of drug was incorporated in it and the Glycerol (plasticizer) was added. Kept it aside for sometime till it gets bubble free and then the solution is poured on to the molds on the glass surface and kept undisturbed till it dry. After drying Films were removed and packed in foils and kept in desiccators to maintain the integrity of the film.[8,9]

Fig.2: Picture of Buccal films from MBF6 Picture of film on glass substrate

RESULTS

CALIBRATION CURVE OF ONDANSETRON HYDROCHLORIDE

Table.no.2: Standard Calibration Curve for Ondansetron hydrochloride in phosphate buffer pH 6.8

concentration(µg/ml)	Absorbance			Average
	i	ii	iii	iv
0	0	0	0	0
1	0.038	0.035	0.041	0.038
2	0.076	0.077	0.078	0.077
3	0.113	0.117	0.116	0.115
4	0.148	0.149	0.150	0.149
5	0.185	0.182	0.188	0.185

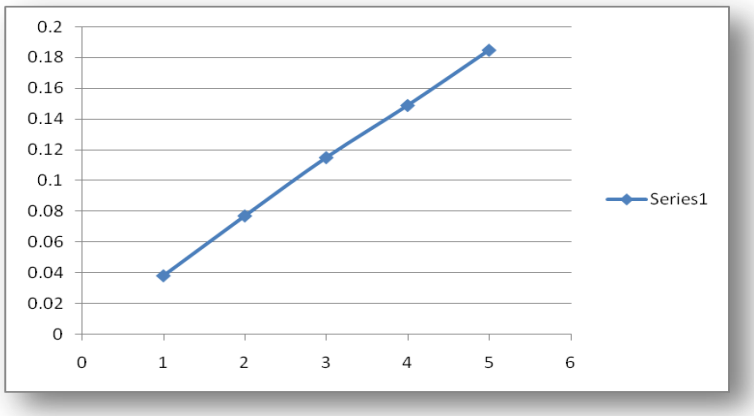

Fig.3: Calibration curve of Ondansetron hydrochloride in phosphate buffer pH 6.8

Evaluation of buccal films Physical Appearance.

Table.no.3. Physical Appearance

Sl.No	Formulation code	Appearance
1	MBF1	++
2	MBF2	++
3	MBF3	__
4	MBF4	++
5	MBF5	++
6	MBF6	++
7	MBF7	++

++ indicates Satisfactory

__ indicates not Satisfactory

Thickness, Film weight, Folding endurance, Surface pH of Buccal Films MBF1 to MBF7

Table.no.4

Sl.no	Formulation code	Thickness(mm) ±SD	Film weight(mg) ±SD	Folding Endurance	Surface pH ±SD
1	MBF1	0.19±0.02	301.81±0.02	>300	5.93±0.110
2	MBF2	0.15±0.01	362.04±0.03	>300	6.3±0.2
3	MBF3	___	___	___	___
4	MBF4	0.22±0.01	402.16±0.01	>300	6.53±0.112
5	MBF5	0.15±0.01	331.87±0.01	>300	6.36±0.155
6	MBF6	0.31±0.02	382.15±0.01	>300	6.46±0.103
7	MBF7	0.15±0.01	341.92±0.01	>300	6.63±0.155

% swelling index: Increase in weight of MBF1, MBF2, MBF4, MBF5, MBF6, MBF7

Table.no.5

Formulation Code	MBF1	MBF2	MBF4	MBF5	MBF6	MBF7
Initial Weight(mg)	22	23	43	26	23	46
%Swelling Index 30 min	13.63	17.39	20.93	11.53	21.73	21.73
%Swelling Index 60 min	22.72	39.13	37.20	30.76	34.78	47.82
%Swelling Index 90 min	45.45	43.47	44.18	53.84	65.21	63.04
%Swelling Index 120 min	54.54	68.18	48.83	76.92	82.60	78.26
%Swelling Index 150 min	77.27	77.27	55.81	84.61	91.30	106.52
%Swelling Index 180 min	81.81	95.45	65.11	92.30	100	126.08
%Swelling Index 210 min	90.61	113.63	74.41	100	113.04	136.95
%Swelling Index	104.5	118.18	86.04	103.84	121.73	141.82

240 min						
%Swelling Index 270 min	109.09	127.27	93.02	111.53	130.43	147.82
%Swelling Index 300 min	113.63	131.81	97.67	115.38	139.13	150

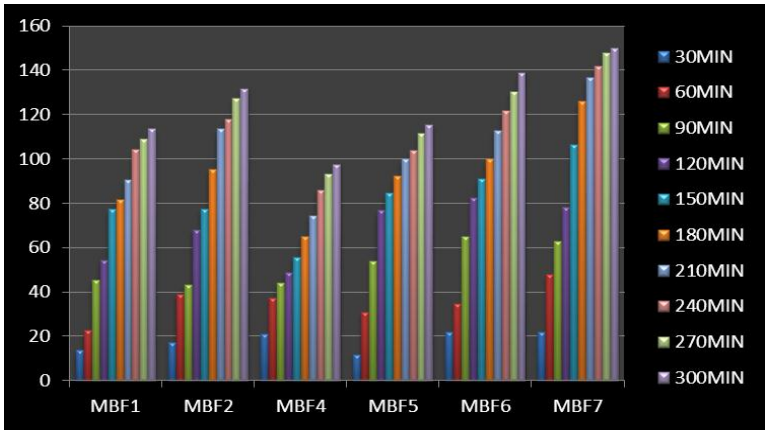

Fig.4: % Swelling index of increase in weight

Percentage Drug content of Buccal Films MBF1 to MBF7:

Table.no.6

Sl.no	Formulation code	% of drug present AM±SD*
1	MBF1	81.13575
2	MBF2	86.4693
3	MBF3	___
4	MBF4	89.54025
5	MBF5	91.803
6	MBF6	92.2878
7	MBF7	93.580

Mucoadhesive strength and in vitro residence time of buccal Films MBF1 to MBF7:

Table.no.7

Sl.no	Formulation code	Mucoadhesive strength (g)	In vitro residence time (hrs)
1	MBF1	8	2.7
2	MBF2	9.33	3.3
4	MBF4	8.66	3.1
5	MBF5	10	2.7
6	MBF6	6	4.2
7	MBF7	11.66	4.36

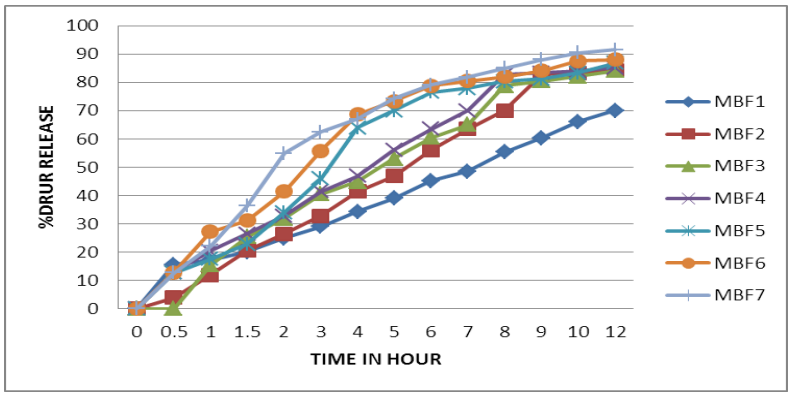

Fig.5: Zero order Release plots for formulations MBF1, MBF2, MBF4, MBF5, MBF6, MBF7

IR SPECTRUMS

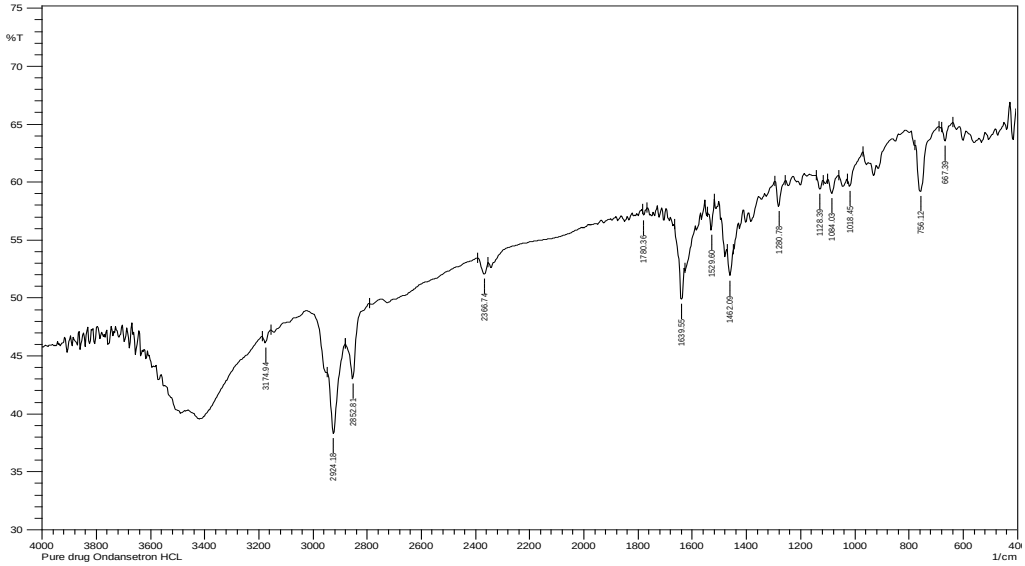

Fig.6(A): IR Spectrum of Ondansetron hydrochloride

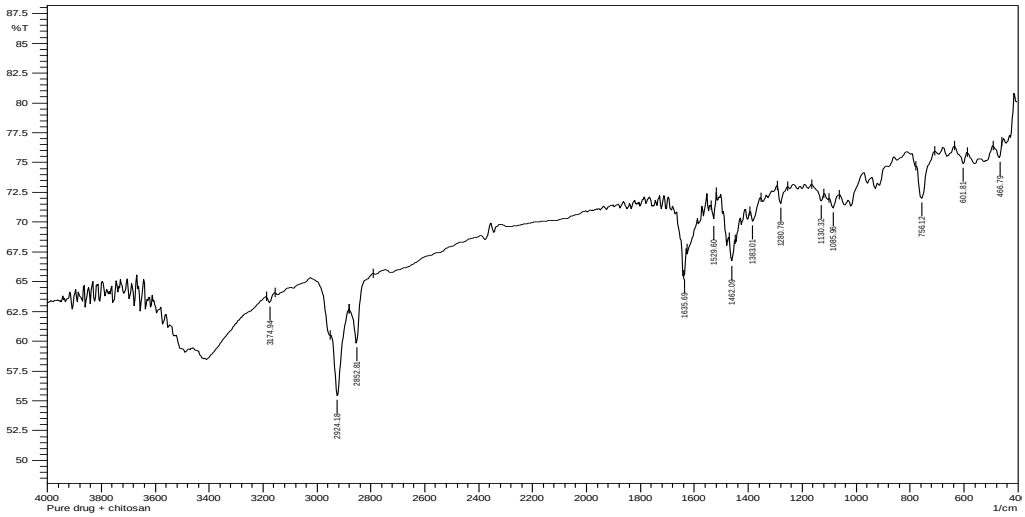

Fig.6(B): IR Spectrum of Pure drug+ Chitosan

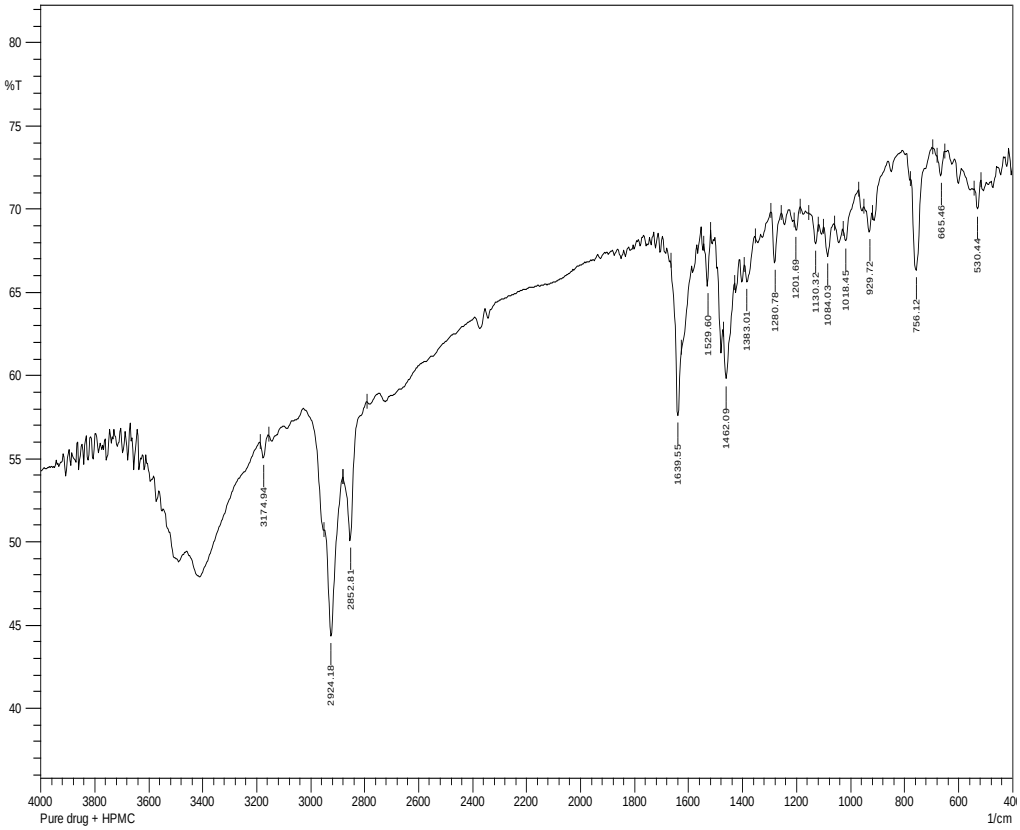

Fig.6(C): IR Spectrum of PURE DRUG+ HPMC

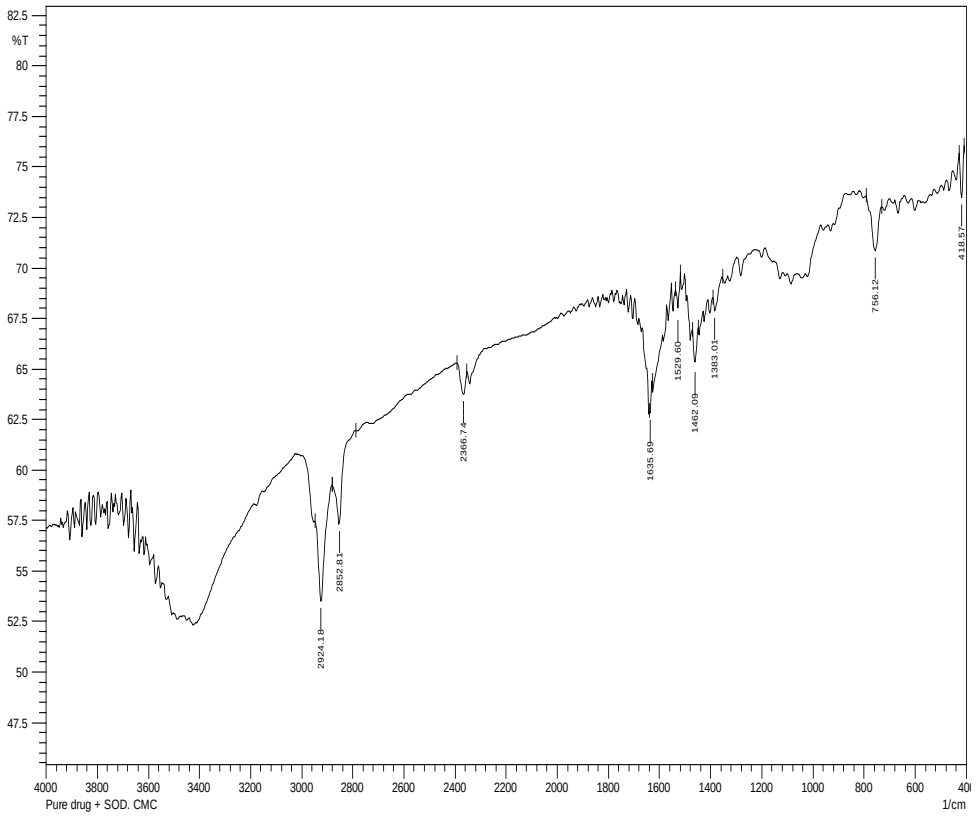

Fig.6(D): IR Spectrum of DRUG+SOD.CMC

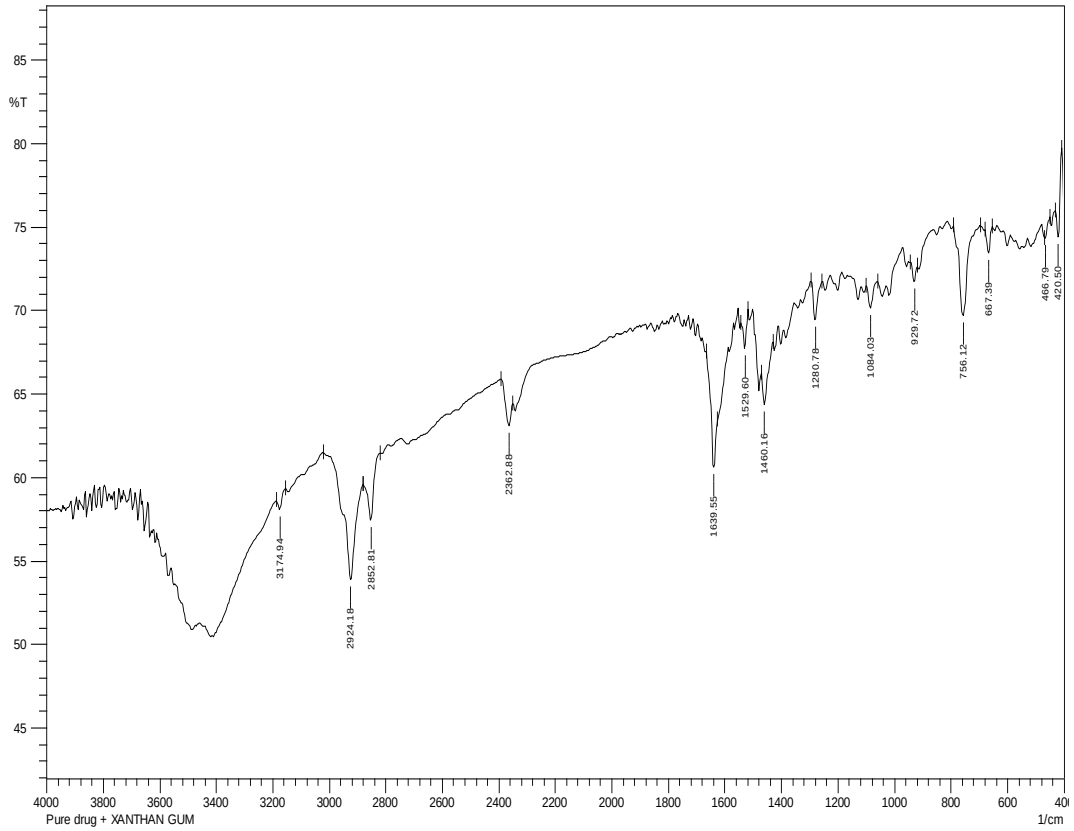

Fig.6(E): IR Spectrum of DRUG+ XANTHAN GUM

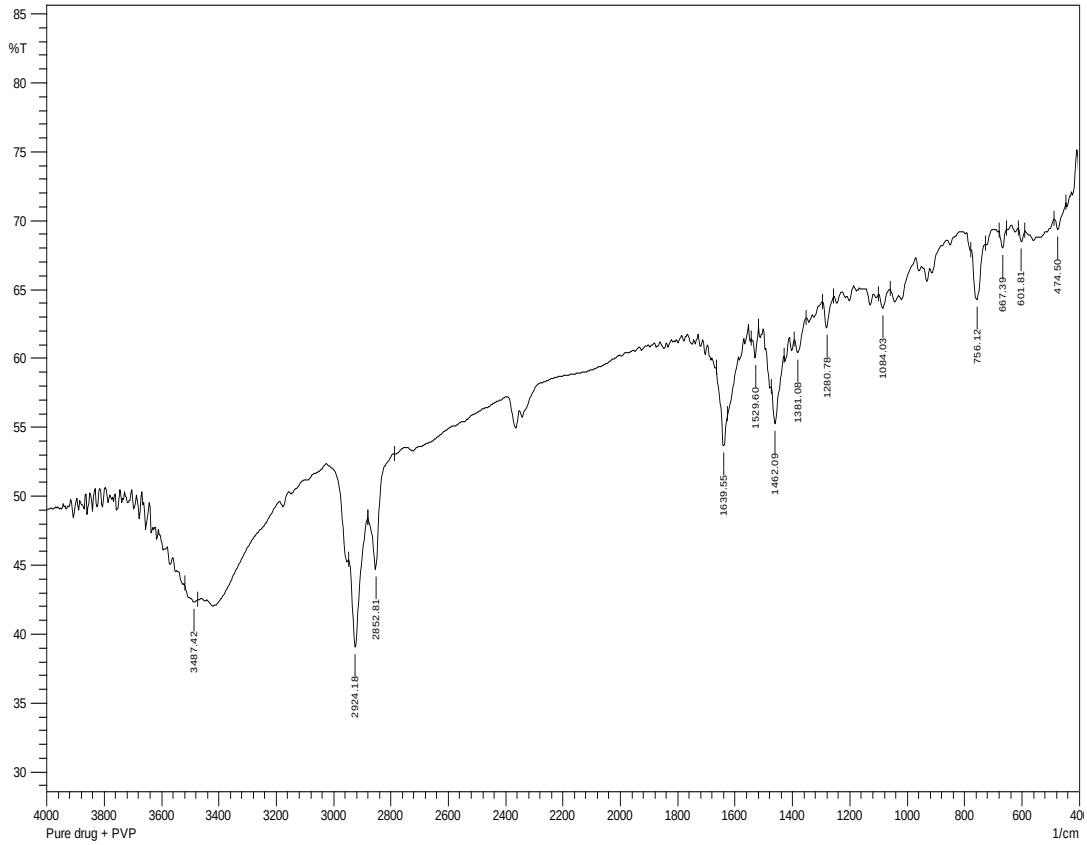

Fig.6(F): IR Spectrum of PVP K-30

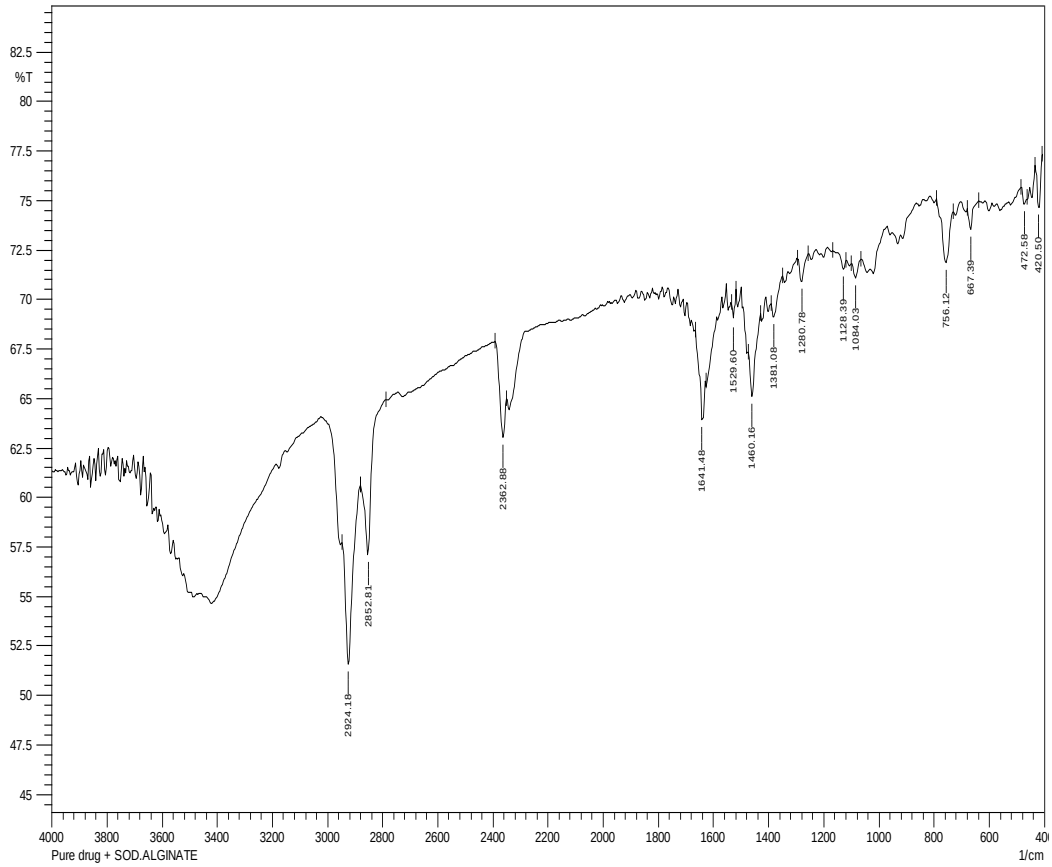

Fig.6(G): IR Spectrum of PURE DRUG+SOD.ALGINATE

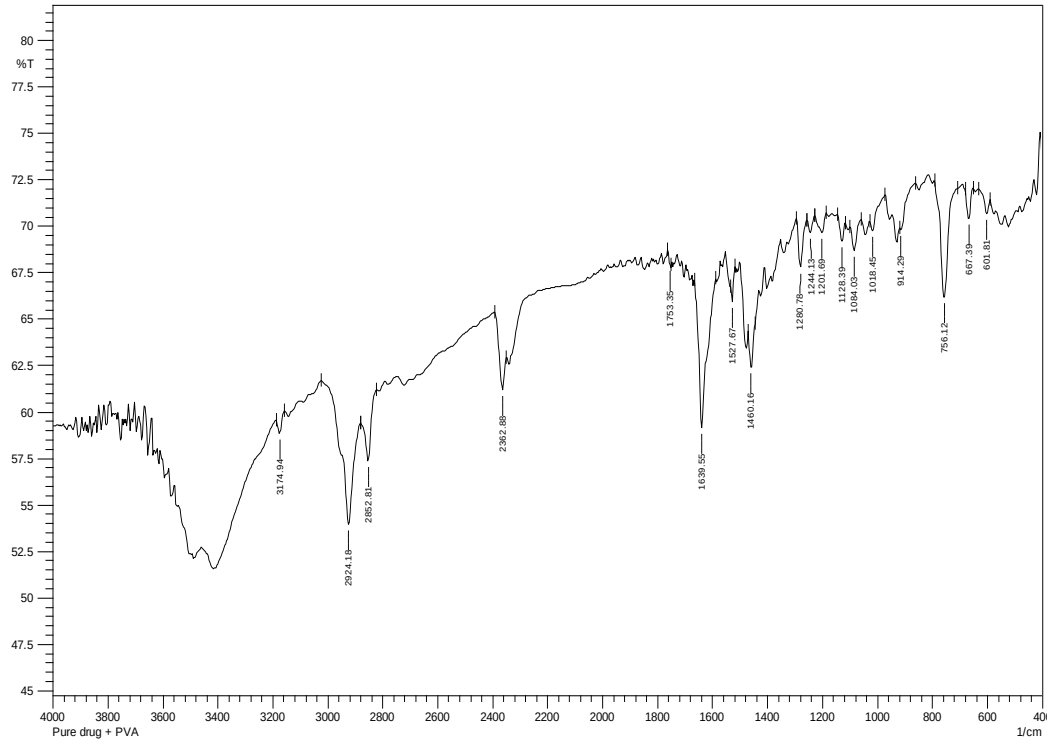

Fig.6(H): IR Spectrum of DRUG+PVA

Module: DSC
Data Name: ONDENSETRON
Measurement Date: 9/17/2013
Sample Name: ONDENSETRON
Sample Weight: 10.000 mg
Reference Name: ALUMINA
Reference Weight: 10.000 mg

Temperature Program:
Cel Cel Cel/min min s
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Comment:
Operator: BVCOP
Gas1: N2
Pan: Al

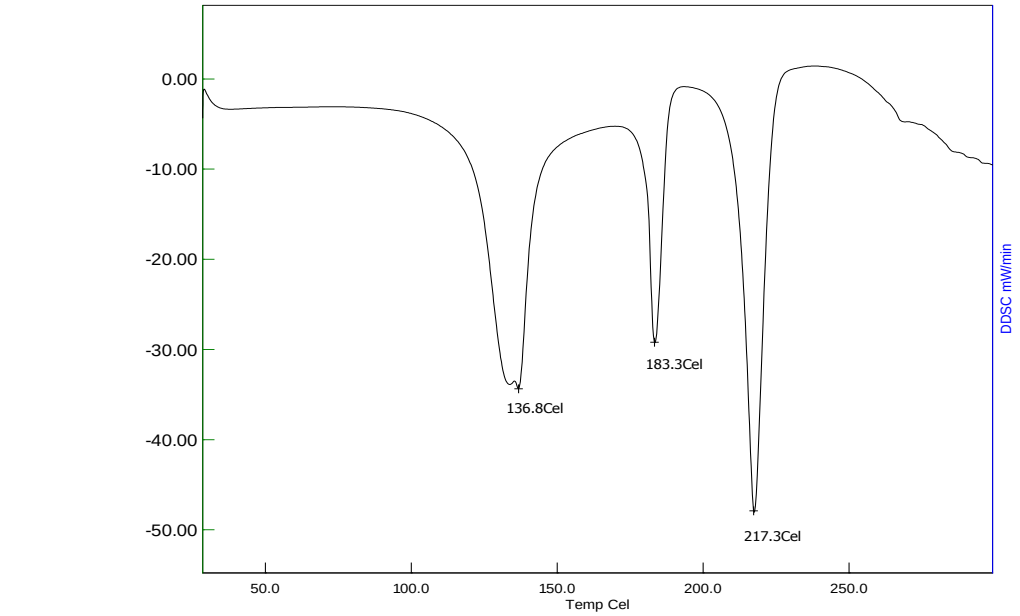

Fig.7(A): DSC Chromatogram of Ondansetron HCl

Module: DSC
Data Name: DRUG LOADED FILM F4
Measurement Date: 9/16/2013
Sample Name: DRUG LOADED FILM F4
Sample Weight: 10.000 mg
Reference Name: ALUMINA
Reference Weight: 10.000 mg

Temperature Program:
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Comment:
Operator: BVCOP
Gas1: N2
Pan: Al

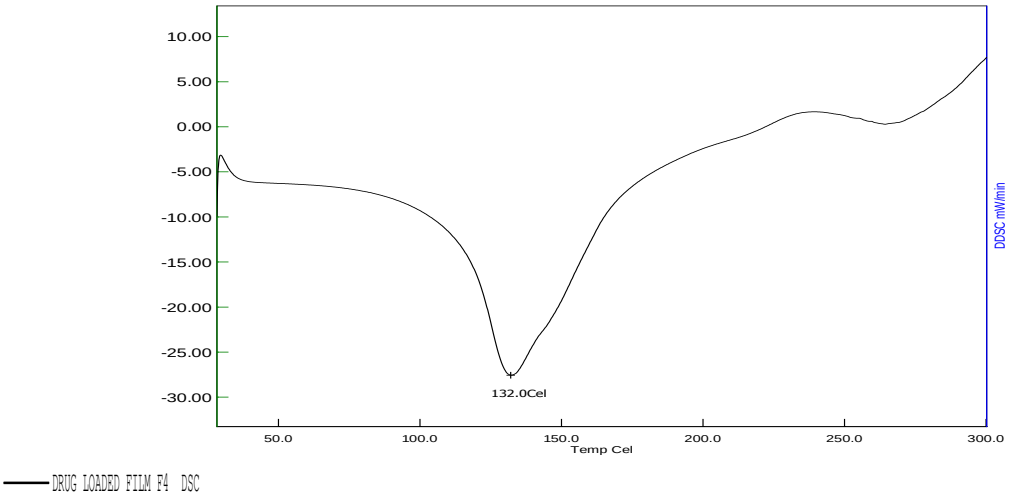

Fig.7(B): DSC Chromatogram of DRUG LOADED FILM F4

Module: DSC
Data Name: DRUG LOADED FILM F6
Measurement Date: 9/14/2013
Sample Name: DRUG LOADED FILM F6
Sample Weight: 10.000 mg
Reference Name: ALUMINA
Reference Weight: 10.000 mg

Temperature Program:
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Comment:
Operator: BVCOP
Gas1: N2
Pan: Al

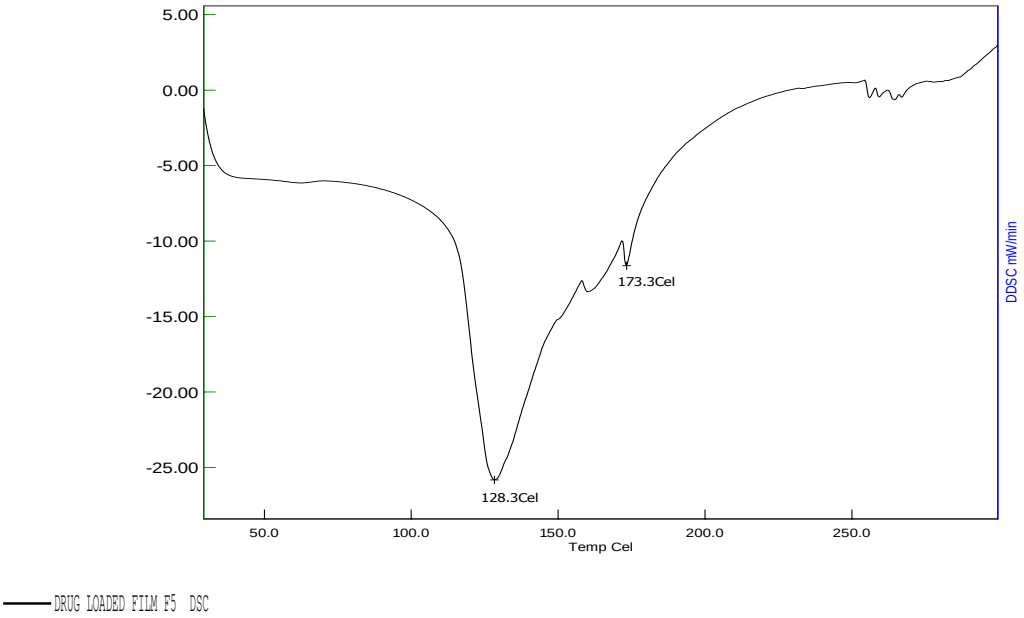

Fig.7(C): DSC Chromatogram of Drug Loaded Film F5

Module: DSC
Data Name: DRUG LOADED FILM F6
Measurement Date: 9/14/2013
Sample Name: DRUG LOADED FILM F6
Sample Weight: 10.000 mg
Reference Name: ALUMINA
Reference Weight: 10.000 mg

Temperature Program:
Cel Cel Cel/min min s
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Comment:
Operator: BVCOP
Gas1: N2
Pan: Al

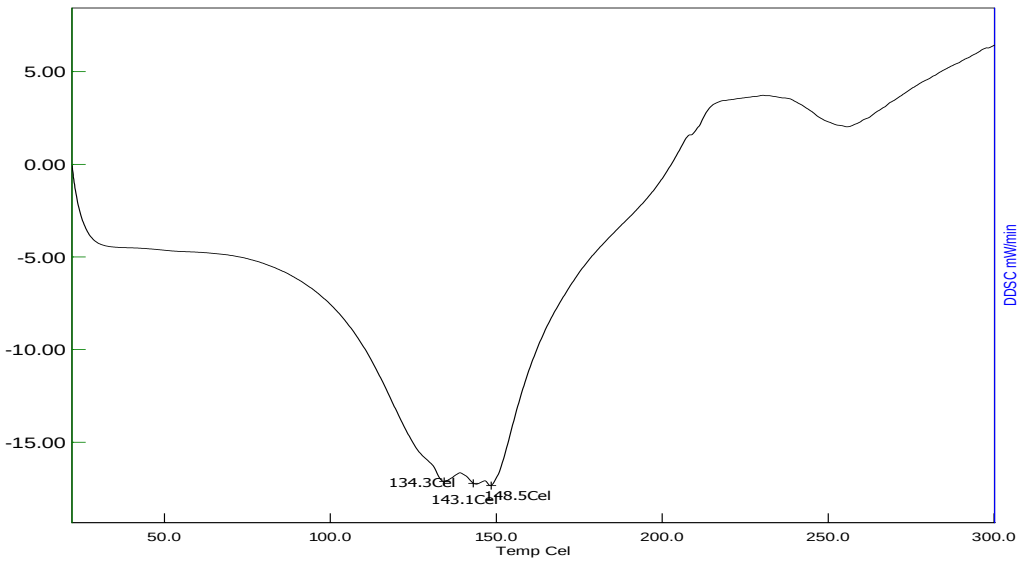

Fig.7(D): DSC Chromatogram of Drug Loaded Film F6

Module: DSC
Data Name: DRUG LOADED FILM F7
Measurement Date: 9/13/2013
Sample Name: DRUG LOADED FILM F7
Sample Weight: 10.000 mg
Reference Name: ALUMINA
Reference Weight: 10.000 mg

Temperature Program:
Cel Cel Cel/min min s
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Comment:
Operator: BVCOP
Gas1: N2
Pan: Al

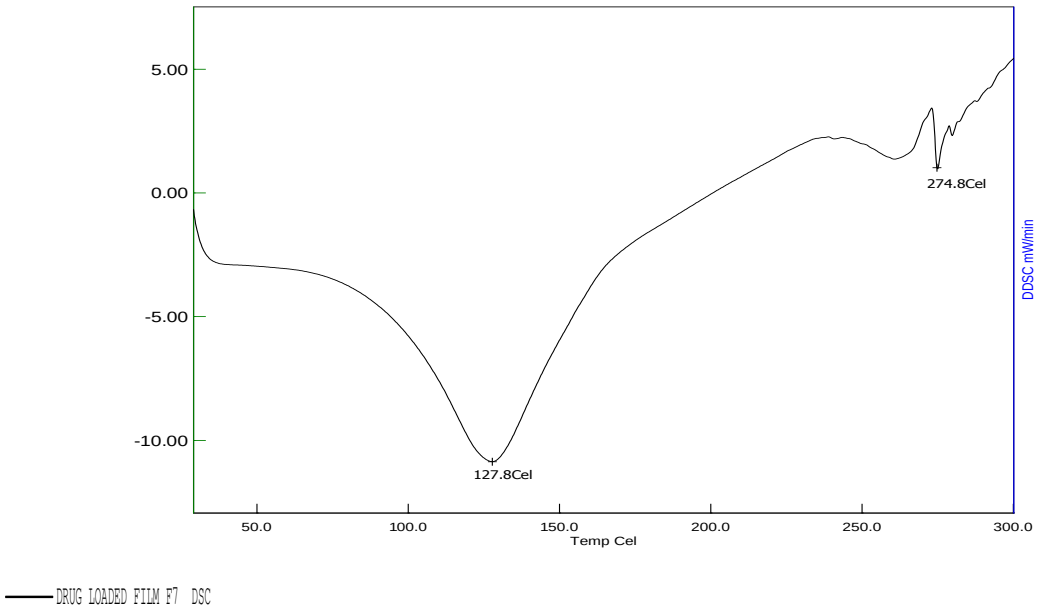

Fig.7(E): DSC Chromatogram of Drug Loaded Film F7

Short term stability studies

Table.no.8

Sl.no	Parameters	Observation
1	Physical appearance	Satisfactory
2	% drug release	90%
3	Bioadhesion strength	10.66gm

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DISCUSSION

In the present study, Chitosan along with hydroxy propyl methyl cellulose, polyvinyl pyrollidone (PVP K-30), sodium alginate and polyvinyl alcohol were used for the development of buccal films for delivery of Ondansetron hydrochloride. Ondansetron hydrochloride standardized as per IP complied with the IP limit. Hydroxy propyl methyl cellulose, Xanthan Gum, polyvinyl pyrollidone (PVP K-30), sodium alginate, polyvinyl alcohol were standardized as per IP complied with the IP limit. Glycerol was used as plasticizer in formulations. Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5),

Chitosan and PVA (MBF6) showed thickness in the range of 0.15 to 0.31mm. Suggesting that films were of uniform thickness.

Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) showed average weight between the ranges of 301 to 402mg. Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) showed folding endurance of buccal films were below 300.

Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) showed surface pH values in the range of 5.9 to 6.6 the results suggests that surface pH values of films prepared were nearer to the buccal pH which suggests that the films prepared will not cause any irritation to the buccal mucosa. The swelling index was carried out for 5 hr and swelling in weight was observed. Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) showed weight increase in the range of 97.67% to 150%. Among all the formulations prepared MBF6 Showed highest percent of swelling in weight. This may be due to the water absorption capacity of polymers used.

Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) were observed for the drug content. The drug content was in the range from 81.13 to 93.58 % Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) showed Mucoadhesion strength in the range of 6 to 11.66gm. among all the formulations MBF6 showed highest Mucoadhesion, this may be due to mucoadhesion of

the polymers used. Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) were observed for in vitro residence time and the values were in the range of 2.7 to 4.36 hrs. MBF6 showed highest residence time and this may be due to strong mucoadhesive nature of the polymers.

Ondansetron Hydrochloride buccal films prepared using polymers are alone Chitosan (MBF1), and in combination Chitosan and HPMC (MBF2), Chitosan and Xanthan Gum (MBF3), Chitosan and PVP (MBF4), Chitosan and Sodium Alginate (MBF5), Chitosan and PVA (MBF6) were studied for in vitro release and the values were in the range of 70.03% to 91.47 %. The data of all the formulations were plotted for graphs like release plots, first order. The drug was released by first order kinetics. The data of all the formulation showed fairly linear curve in both the cases. Linearity was well supported by the values calculated and this suggests that drug was released by diffusion mechanism. To know the diffusion mechanism the slope values of Peppas equation was calculated and was in the range of 0.601 to 0.685. The calculated slope values are in all the cases suggesting that the drug was released by class II transport mechanism.

Drug-polymers interaction was studied by FTIR analysis and is presented in figure. The pure drug has shown Characteristic peaks at 3489 , 3410, 2924, 1520, 1280, 756 cm-1 due to functional groups -0H, -NH, -CH, & -C=O etc. the similar peaks were also noticed in the spectra of mixture of drug & polymers. This indicates chemical stability of drug in the formulations.

DSC Chromatogram of pure drug has shown an endothermic peak in at 183 0C due to its melting point. While the Spectra of drug loaded Film F4, F5, F6 did not show an endothermic peak at 1830C indicating the amorphous dispersion of drug in the Films.

The short term stability studies were done for the formulation MBF6 Presented. The drug content, bioadhesion strength and physical appearance was tested but no drastic variation was observed.

CONCLUSION

Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability

and buccal Film offer greater flexibility and comfort .In the present study, Chitosan along with hydroxy propyl methyl cellulose, polyvinyl pyrollidone (PVP K-30), sodium alginate, polyvinyl alcohol and Glycerol was used as plasticizer for the development of buccal Films for delivery of Ondansetron hydrochloride.

The evaluation parameters like surface pH study, Swelling index, Folding endurance, mucoadhesive strength, Content uniformity, in vitro residence time, in vitro release were observed.

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