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FORMULATION AND EVALUATION OF ORAL DISSOLVING FILMS OF ONDANSETRON HCL

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ABSTRACT

The present research was done to formulate an oral dissolving film of ondansetron Hcl with the objective to attain maximum therapeutic efficacy, patient compliance by decreasing the dosing frequency and other problems associated with conventional or parenteral formulation. Ondansetron Hcl is an antiemetic drug developed to control cancer chemotherapy/radiotherapy induced vomiting and later found to be highly effective in Postoperative nausea and vomiting and disease/drug associated vomiting as well. The oral dissolving films were prepared by using solvent casting method with varying concentrations of HPMC and PVA. The formulated films were evaluated under standard procedures of various physicochemical parameters, drug release and disintegration. The formulated films were found uniform in thickness, with good folding endurance (>300) and having surface pH similar to that of buccal cavity. The drug release showed that the formulation F5 showed the highest drug release which was around 91.6% in 5 minutes. The drug release was found in the order F5>F1>F4>F2>F3. Formulation F5 was best not only in terms of drug release but also had highest drug content and minimum disintegration time. Hence the films containing more concentrations of PVA were found to be better than the films containing HPMC.

KEYWORDS: Ondansetron Hcl, solvent casting method, HPMC, PVA, drug release.

1. INTRODUCTION

Among the various routes of drug delivery, buccal drug delivery offer distinct advantages over other routes of administration for systemic effect. Among various transmucosal routes, buccal mucosa is the most suited for local, as well as systemic delivery of drugs. The unique physiological features make the buccal mucosa as an ideal route for mucoadhesive drug

delivery system. These advantages include bypass of hepatic first-pass effect and avoidance of pre systemic elimination within the gastrointestinal tract.[1]

Buccal drug delivery has a high patient acceptability compared to other non-oral transmucosal routes of drug administration. Direct access to the systemic circulation through the internal jugular vein avoids acid hydrolysis in the gastrointestinal (GI) tract and bypasses drugs from the hepatic first pass metabolism leading to high bioavailability.[2] Buccal delivery systems offer numerable advantages in terms of accessibility, administration and withdrawal, retentivity, economy and high patient compliance.

Buccal films have gained importance as efficacious novel drug delivery systems and are cost effective with a good patient compliance. As buccal films are implied for attachment to the buccal mucosa, they can be formulated to exhibit local as well as systemic action. Buccal film may be preferred over buccal tablet, in terms of flexibility and comfort. Buccal films have direct access to the systemic circulation through the internal jugular vein, which bypasses the drug from the hepatic first pass metabolism leading to high bioavailability. Further, these dosage forms are self-administrable, pharmacoeconomic and have superior patient compliance.[3] Buccal drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time and the ability to maintain a delivery system at a particular location for an extended period of time has great appeal for both local as well as systemic drug bioavailability.[4]

ODFs are useful for the patients such as pediatric, geriatrics, emetic patients, sudden episode of allergic attacks, diarrhea, coughing, or for those having an active life style. It is also useful were local action is desired such as local anesthetic for toothaches, old sores, oral ulcers or teething. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfills the needs of patients.[5]

2. MATERIALS AND METHODS

2.1 MATERIALS

Ondansetron Hcl was obtained as a gift sample from Alkem Laboratories Ltd. Polymers and other excipients such as HPMC, PVA, Sorbitol were obtained from SDFCL, Fine chemical Ltd. Mumbai, Fructose, Citric acid were obtained from Merk Specialities Private Ltd. Mumbai, Polyethylene glycol-400 was obtained from Otto Kemly Pvt. Ltd. Mumbai,

Glycerine was obtained from La Pharma Chemical Ltd. Mumbai. All the reagents used were of Analytical grade.

2.2 METHODS

2.2.1 Preformulation Studies

Studies on various physico-chemical properties of procured drug were done along with chemical authentication by physical appearance, melting point determination, Solubility analysis and FTIR spectra.

- **Physical Appearance:** The physical appearance of the drug sample was characterized on the basis of colour, odour, taste and appearance. All these parameters were recorded and compared with standard.
- **Melting point determination:** Melting point of the drug sample was determined by using capillary tube method using melting point apparatus (Macro Scientific Works) by filling small amount of drug sample in the capillary. The samples were heated slowly and observed continuously for most accurate results. The melting range was recorded which begins when the sample first start to melt and ends when the sample is completely melted. This process was repeated for three times and the average of three readings were taken.[6]
- **Solubility Analysis:** Solubility of Ondansetron Hcl was studied in various solvents such as water, Hcl, buffer (Ph-6.4). Drug was added to 10 ml of each solvent separately at room temperature and shaken at various interval of time for 42 hrs. After that the solubility was observed visually.[7]
- **FTIR study of drug and other excipients:** FTIR spectra of drug Ondansetron Hcl and other excipients used in the formulation were recorded by using FTIR Spectrophotometer (Shimadzu IR Affinity 1, Tokyo, Japan) in the region 4000-500 cm^{-1}. The samples were crushed and mixed with potassium bromide (1:10 ratio by weight) and pressed at 15000 psig to make a disc. These compressed discs were scanned using FTIR Spectrophotometer. After running the spectra, significant peaks relating to major functional groups were identified. Spectra of subsequent sample and the other compounds were compared with original.[8]

2.2.2 Analytical method adoption by UV spectrophotometer

For the analysis of Ondansetron Hcl concentration in formulation, the UV spectrophotometer was used and for method adopting following steps were performed.

- **Preparation of stock solution**: For the preparation of stock solution 100 mg of the pure drug was accurately weighed and dissolved in 10 ml water and then volume was made up to 100 ml with water to give solution of 1000 µg/ml. From this solution 1 ml was withdrawn and dissolved in 100 ml of water to give standard stock solution of 10 µg/ml. This solution works as the stock solution.

- **Preparation of calibration sample:** Calibration samples were prepared from the stock solution (10 µg/ml). From the stock solution 1, 2, 3, 4, 5, 6 ml of the solution was withdrawn and volume was made upto 10 ml with water to get serial dilutions (1, 2, 3, 4, 5 and 6 µg/ml).

- **Determination of λmax of Ondansetron Hcl:** The Stock solution of Ondansetron Hcl (10 µg/ml) was prepared in distilled water. This sample was filtered and scanned in the range 200-400 nm using UV spectrophotometer to determine λmax.

- **Preparation of calibration curve for Ondansetron Hcl:** To prepare calibration curve the serial dilutions of Ondansetron Hcl in concentration range of 1µg/ml to 6µg/ml were prepared in water and the absorbance of these dilution were determined on UV spectrophotometer at λmax 248 nm using water as blank. The absorbance values corresponding to each concentration were than statistically evaluated and plotted as a standard graph between absorbance on Y-axis and concentration on X-axis.[9]

2.3 Formulation of Oral Dissolving Films

The oral dissolving films containing Ondansetron Hcl were prepared by solvent casting method. The required amount of polymer (Hydroxypropylmethyl cellulose, Polyvinyl alcohol) were weighed and dispersed in 25 ml of casting solvent (25 ml of water) by continuous stirring. To this solution sorbitol, fructose and citric acid was added. This solution was stirred until all the materials get completely dissolved. Later PEG 400 was added to the polymer solution while stirring. Drug (Ondansetron Hcl) was added to this polymeric solution. 2 drops of vanilla essence was added to the solution and then stirred until homogeneous. The solution was then left at room temperature to remove air bubbles. After the disappearing of air bubbles, the solution was poured into the petridish. The mixture was then air dried at room temperature. After drying, the film was removed from the petridish carefully and cut according to the size of 2cm x 2cm. The components of the formulation are shown in the table below.

Table 1: Components of the formulation.

Ingredients	Formula				
	F1	F2	F3	F4	F5
Ondansetron Hcl(mg)	32	32	32	32	32
HPMC (mg)	380	230	190	150	-
PVA (mg)	-	150	190	230	380
Sorbitol (mg)	298	298	298	298	298
Fructose (mg)	20	20	20	20	20
Citric acid (mg)	45	45	45	45	45
PEG 400 (mg)	336	336	336	336	336
Vanilla essence	qs	qs	qs	qs	qs
Water (ml)	25	25	25	25	25

2.4 Evaluation of oral dissolving films

2.4.1 Weight variation: For weight variation five films of every formulation were taken and weighed individually on digital balance then the average weight was calculated.[10]

2.4.2 Thickness: The thickness of five randomly selected films from every batch was determined by using a standard digital Vernier Caliper. The thickness was measured at different strategic points of the film and average values were reported.[11]

2.4.3 Folding endurance: Folding endurance is determined by repeated folding of 3 films from each formulation at the same place till the strip breaks. The number of times the oral dissolving films are folded without breaking are computed as the folding endurance value.[12]

2.4.4 Surface pH: For the evaluation of the surface pH of the films, the films were dissolved in 10 ml of distilled water in the petridish and the surface pH was measured by using a pH meter.[13]

2.4.5 Disintegration time: The disintegration time was performed by placing the film in a beaker containing 20 ml of water. It was stirred at every 10s time interval. The time required for the film to disintegrate was recorded.[14]

2.4.6 Drug content: The amount of drug present in the oral dissolving film was determined by dissolving the strip in 100 ml of water with stirring for 4 hrs. The resulting solution was filtered through a whatman filter paper. The drug content was then determined by UV Spectrophotometer (Shimadzu Japan – 1601) at λmax 248 nm. The experiments were carried out in triplicate.[15]

2.4.7 In-vitro drug release: The USP rotating paddle method was used to study the drug release from the films. The dissolution medium used was distilled water. The release rate was determined at 37±5ºC with a rotation speed of 50 rpm. The oral dissolving film was then added to the dissolution medium. The samples (2 ml) were withdrawn at predetermined interval i.e., at every 30 seconds and were replaced with fresh medium. The samples were filtered and analysed for drug release.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Preformulation studies

- **Physical properties:** The physical properties of the drug powder when observed were that the drug powder was white to off white in colour, odourless, crystalline in nature. The appearance compiled with that described for standard as reported in I.P.
- **Melting point:** Melting point of the drug was found to be 178ºC and the normal range is 178.5-179.5ºC.[16]
- **Solubility analysis:** Solubility of Ondansetron Hcl was studied in different solvents at room temperature revealed that it was freely soluble in Hcl, soluble in water, and sparingly soluble in buffer pH-6.8. Drug was also soluble in methanol, ethanol, acetone and acetic acid.

3.1.2 Determination of λmax of Ondansetron Hcl

A stock solution of 100 µg/ml of Ondansetron Hcl was prepared in water and scanned in UV range 200-400 nm. The λmax of Ondansetron Hcl was found to be 248 nm, while the λmax reported was also 248 nm.[17]

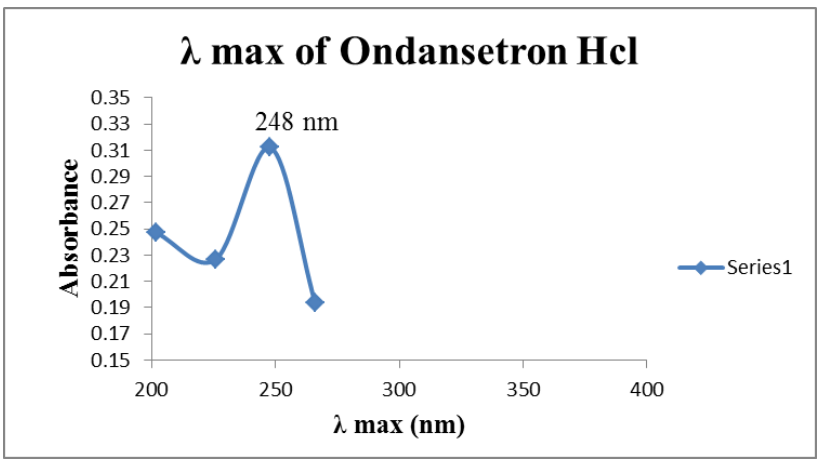

Fig. 1: λmax of Ondansetron Hcl.

3.1.3 Standard curve of Ondansetron Hcl

Concentrations from 0 µg/ml-6 µg/ml of the drug were prepared from the stock solution. The absorbance of the drug solution was taken at 248 nm against reference. The variable Absorbance was recorded against concentrations. The results are given in table 2. A plot between concentration and absorbance was found to be linear in concentration range 1µg/ml to 6µg/ml with R^2 value 0.997 and obeyed Lambert beer law also. The equation of the line was y = 0.0338x + 0.0059. The results are shown in fig. 1 and 2.

Table 2: Calibration reading.

Concentration (µg/ml)	Absorbance
0	0
1	0.043
2	0.075
3	0.108
4	0.145
5	0.176
6	0.203

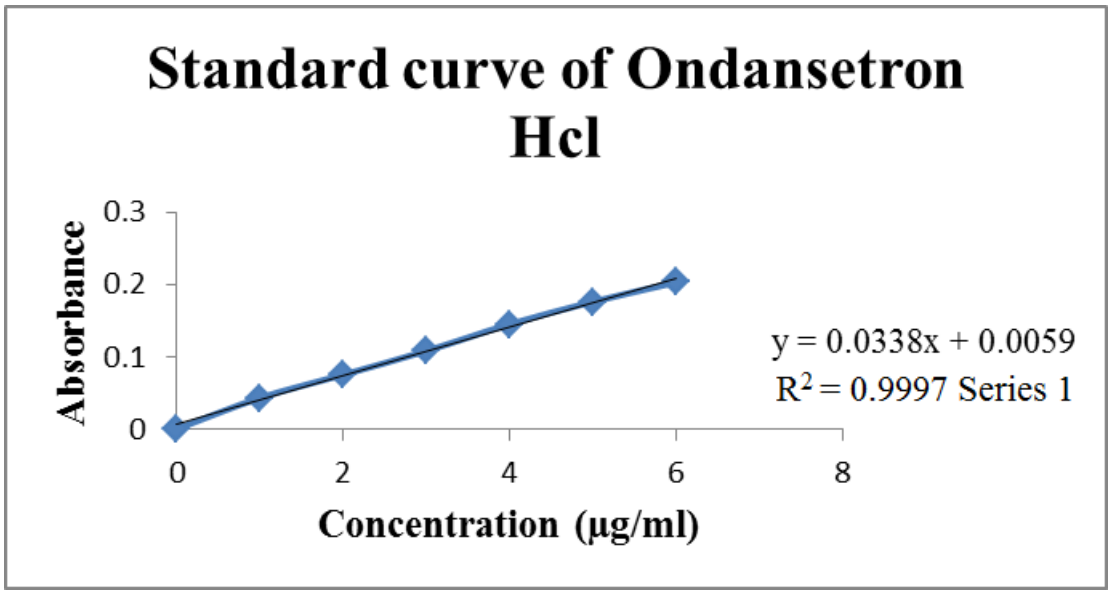

Fig. 2: Standard curve of Ondansetron Hcl.

3.1.4 Formulation table: Five different types of formulation of oral dissolving films of Ondansetron Hcl were prepared by solvent casting method. Quantities of Ondansetron Hcl, citric acid, fructose, sorbitol, PEG 400 were kept same in all the formulations. Two formulations contained 380 mg of HPMC and PVA in each of the two formulations. The other three formulations contained HMPC and PVA in ratios (i.e., 230:150, 190:190 and 150:230).

The composition of each type of formulation is shown in the following table.

Ingredients	Formula				
	F1	F2	F3	F4	F5
Ondansetron Hcl(mg)	32	32	32	32	32
HPMC (mg)	380	230	190	150	-
PVA (mg)	-	150	190	230	380
Sorbitol (mg)	298	298	298	298	298
Fructose (mg)	20	20	20	20	20
Citric acid (mg)	45	45	45	45	45
PEG 400 (mg)	336	336	336	336	336
Vanilla essence	qs	qs	qs	Qs	qs
Water (ml)	25	25	25	25	25

3.1.5 FTIR studies of drug, excipients

The FTIR studies were done to confirm the identity of pure drug and to detect the interaction of drug with excipients used in the preparation of oral dissolving films of Ondansetron Hcl. The IR spectra of drug was analysed which showed peak at 1834.76 cm^{-1} which was assigned to C=O stretching. Vibrational peak at 3408.36 cm^{-1} represented N-H, N-CH_3 stretching; whereas 1235.86 cm^{-1} peak was assigned to C=N stretching. Further the peak at 757 cm^{-1} showed the presence of aromatic groups.

Other peaks observed were 2928.07 cm^{-1}, 2717 cm^{-1}, 2136.1 cm^{-1}, 2131.43 cm^{-1}, 1467.89 cm^{1}, 1634.76 cm^{-1}, 1027.20 cm^{-1}, 994.9 cm^{-1} which represented the drug analysed was Ondansetron Hcl in the oral dissolving film. F1 formulation showed peaks at 4381.49 cm^{-1} and 2124.68 cm^{-1} which indicate the presence of HPMC and Ondansetron Hcl respectively in the film. F4 formulation showed peaks at 4381.49 cm^{-1} which represented presence of HPMC, peak at 3999.57 cm^{-1} represented presence of PVA, other peaks at 2126.61 cm^{-1}, 1736.01 cm^{-1} indicated the presence of drug in the film. F5 formulation showed peaks at 4001.50 cm^{-1}, 2136.26 cm^{-1} which indicated the presence of PVA and Ondansetron Hcl respectively in the film. The results are shown in the fig no. 3, 4, 5, 6.

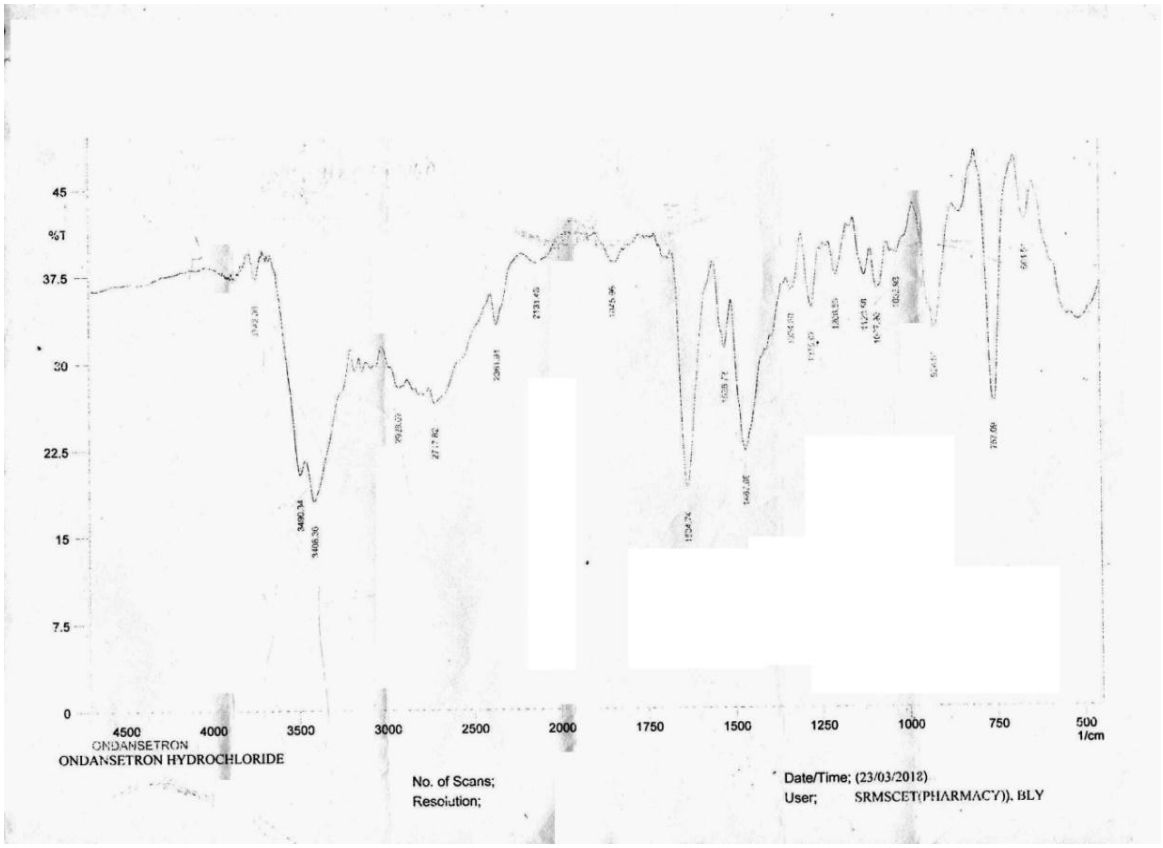

Fig. 3: FTIR spectra of Ondansetron Hcl.

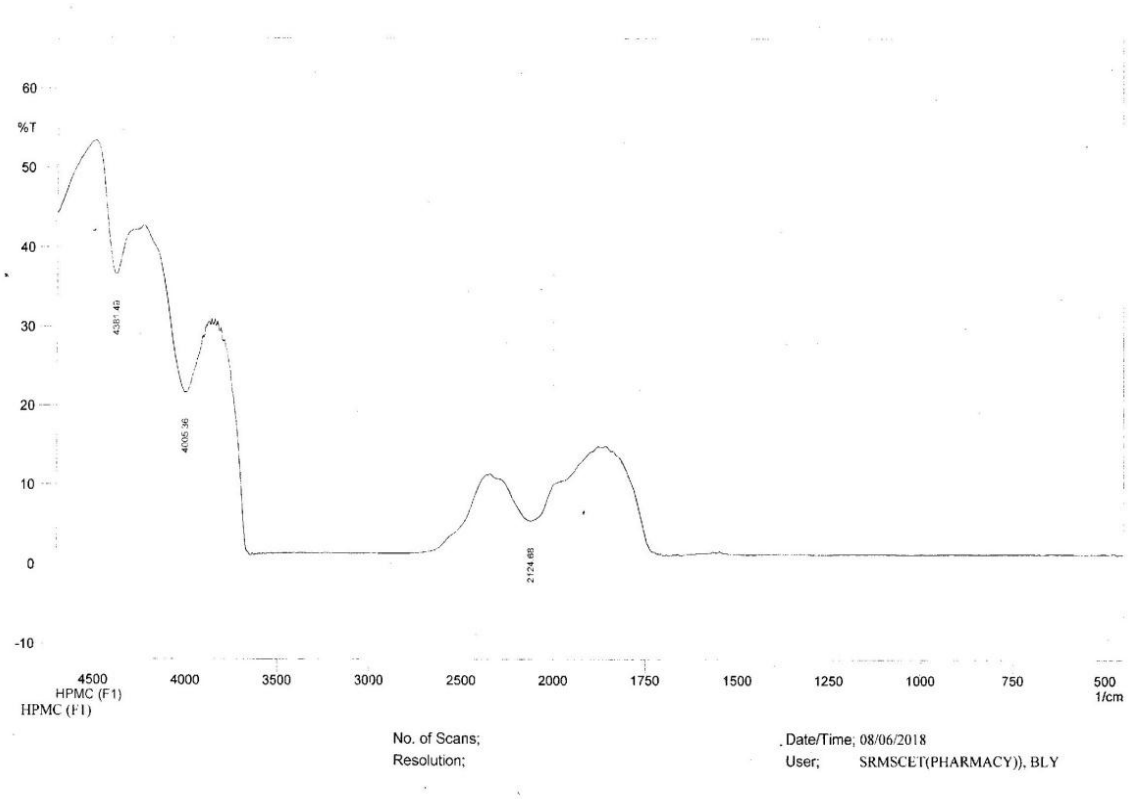

Fig. 4: FTIR spectra of formulation F1.

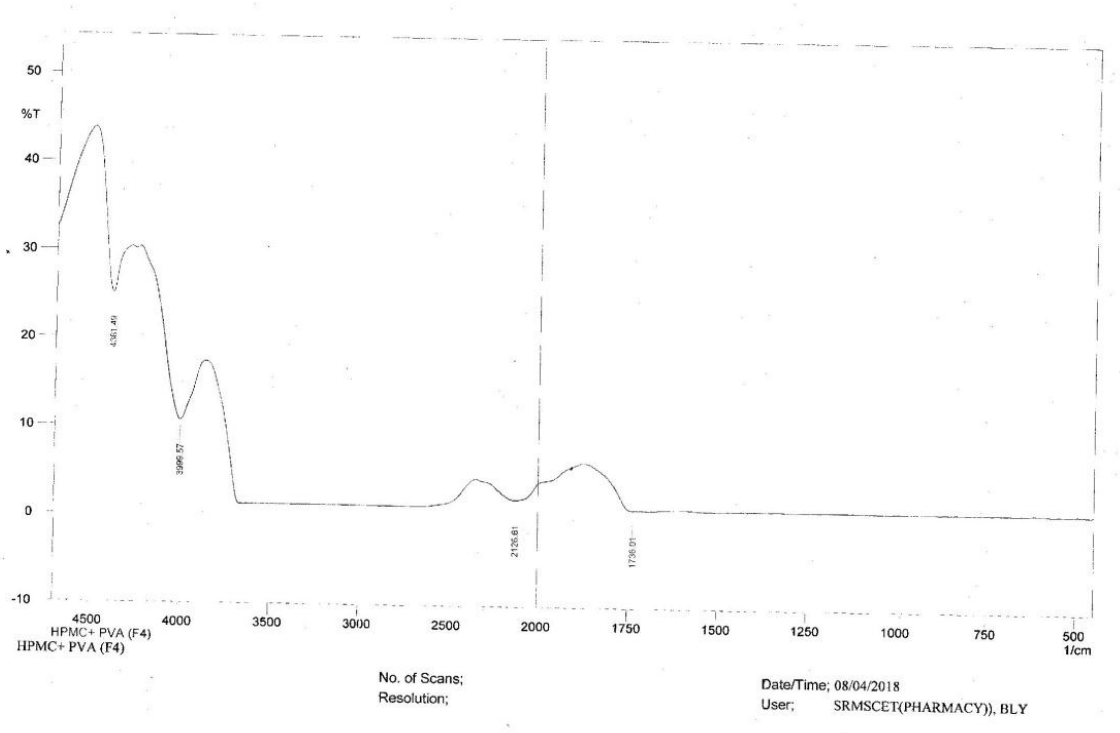

Fig. 5: FTIR spectra of formulation F4.

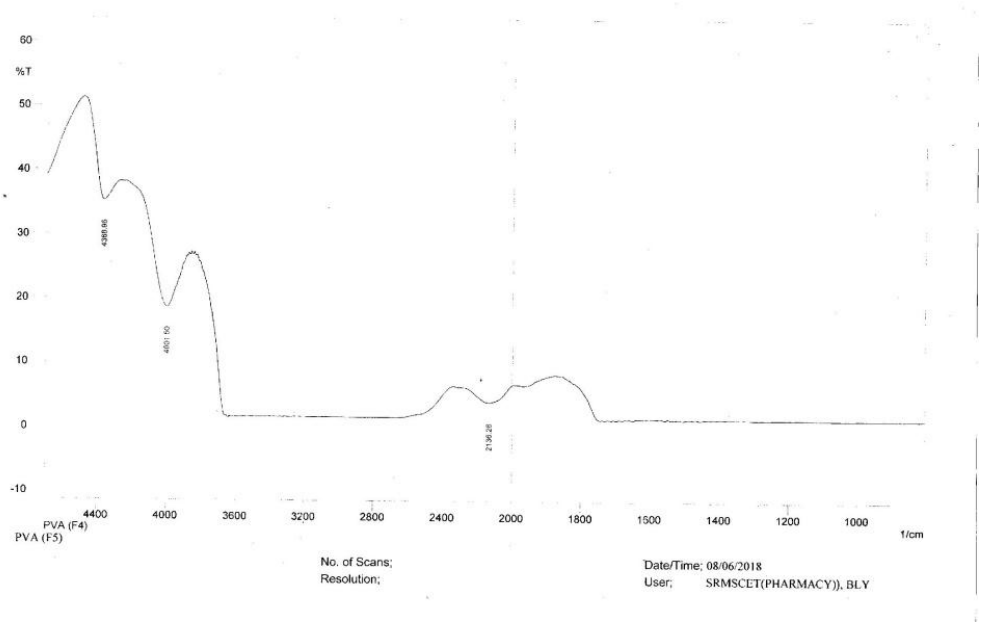

Fig. 6: FTIR spectra of formulation F5.

3.1.6 Evaluation of Oral Dissolving Films

The oral dissolving films of Ondansetron Hcl were evaluated. The oral dissolving films of Ondansetron Hcl were successfully prepared by solvent casting method as described in the formulation table. By this method five films were prepared containing different ratio of polymer.

All the films were evaluated for weight variation, thickness, folding endurance, surface pH, disintegration time, % drug content and % drug release. The results of all the five oral dissolving films are given in the following table.

Table 3: Evaluation of oral dissolving films.

Parameters	F1	F2	F3	F4	F5
Weight variation (gm)	0.82±0.075	0.068±0.007	0.08±0.01	0.106±0.01	0.066±0.008
Thickness (mm)	0.21±0.02	0.18±0.01	0.17±0.02	0.24±0.01	0.12±0.02
Folding endurance	317±2.3	327±2.6	346±1	311±3	2354±1.1
Surface pH	6.5±0.264	6±0.152	7±0.208	7±0.251	7.5±0.167
Disintegration time (sec.)	84±4.35	69±2	58±1	49±2	43±1.52
Drug content (%)	88.84±1.25	91.17±1.04	91.48±2.28	92.63±0.90	90.2±2.83

**All values are expressed as mean ± S.D.*

3.1.7 Percentage drug release of formulation

The prepared 5 films of Ondansetron Hcl were evaluated for the percentage drug release at various time intervals in distilled water, the results are shown in the following table no. 4 and fig no. 7, 8, 9, 10, 11, 12.

Table 4: Combined % Drug release from all the formulations.

Time(min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0.30	19.43±3.37	11.56±1.6	12.88±4.57	14.43±3.48	20.43±6.88
1	43.13±3.76	22.23±3.72	17.6±3.61	20.22±6.17	46.7±3.25
1.30	51.06±1.72	30.27±4.72	21.9±6.43	27.13±5.71	55.3±3.04
2	58.06±3	38.3±5.46	30.9±2.70	32±7.53	61.63±3.44
2.30	64.87±5.14	47.2±5.25	39.03±5.07	39.3±6.59	68.83±3.44
3	70.8±5.24	56.1±3.79	47.03±3.98	44.5±6.22	72.93±3.17
3.30	75±3.21	61.1±5.1	53.73±3.97	50.67±4.27	80.7±2.50
4	78.3±1.27	65.77±5	56.87±4.72	62.76±3.42	86.26±4.15
4.30	80.2±1.70	70.1±2.25	65.5±6.05	72.7±2.56	90.5±7.53
5	82.43±2.40	73.37±3.17	68.43±4.24	77.93±3.26	91.6±9.01

**Values represent mean ± S.D.*

These oral dissolving films contained different ratio of materials such as drug HPMC, PVA, sorbitol, fructose, citric acid, PEG 400. The drug releases from these films are given below.

- **% Drug release from F1 formulation:** F1 formulation contained polymer HPMC (380 mg) and drug Ondansetron Hcl (32 mg). The drug release from this formulation is given in fig. 7.

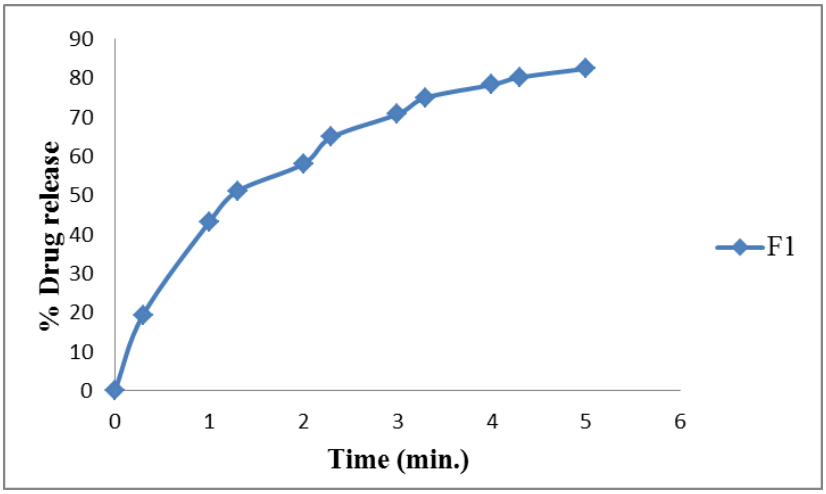

Fig. 7: Drug release from F1 formulation.

- **% Drug release from F2 formulation:** F2 formulation contained ratio of polymer's HPMC (230 mg) and PVA (150 mg) and drug Ondansetron Hcl (32 mg). The drug release from this formulation is given in fig. 8.

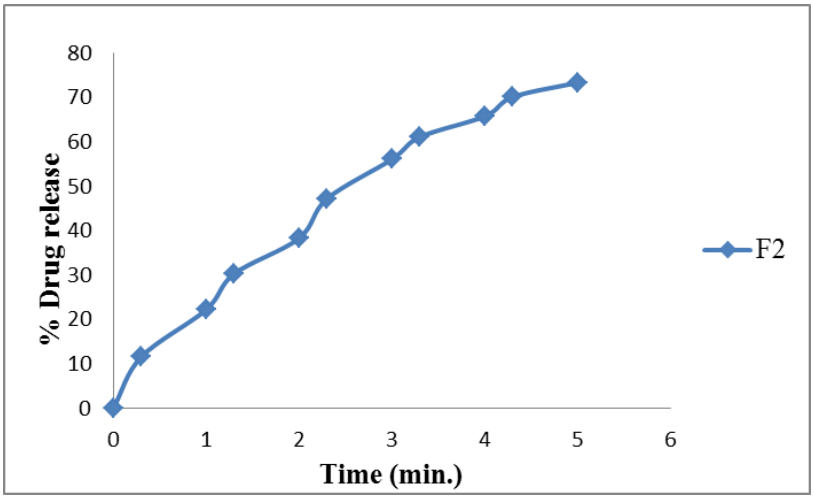

Fig. 8: Drug release from F2 formulation.

- **% Drug release from F3 formulation:** F3 formulation contained ratio of polymer's in ratio 1:1 i.e. HPMC (190 mg) and PVA (190 mg) and drug Ondansetron Hcl (32 mg). The drug release from this formulation is given in fig. 9.

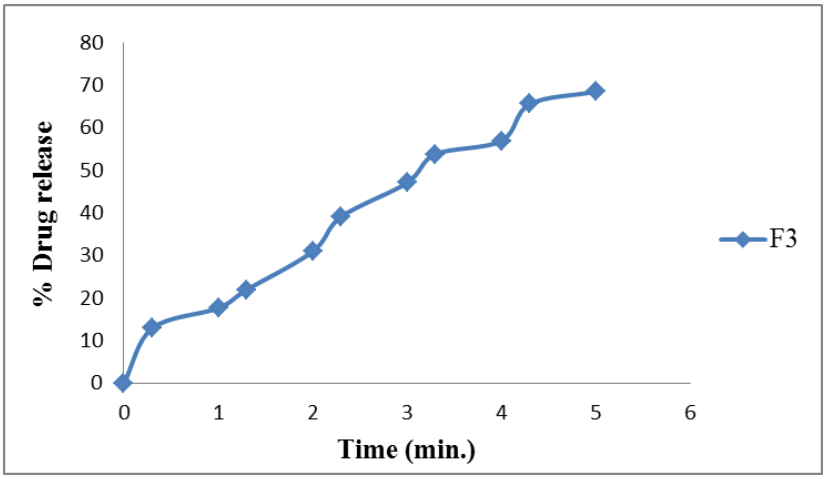

Fig. 9: Drug release from F3 formulation.

- **% Drug release from F4 formulation:** F4 formulation contained ratio of polymer's HPMC (150 mg) and PVA (230 mg) and drug Ondansetron Hcl (32 mg).

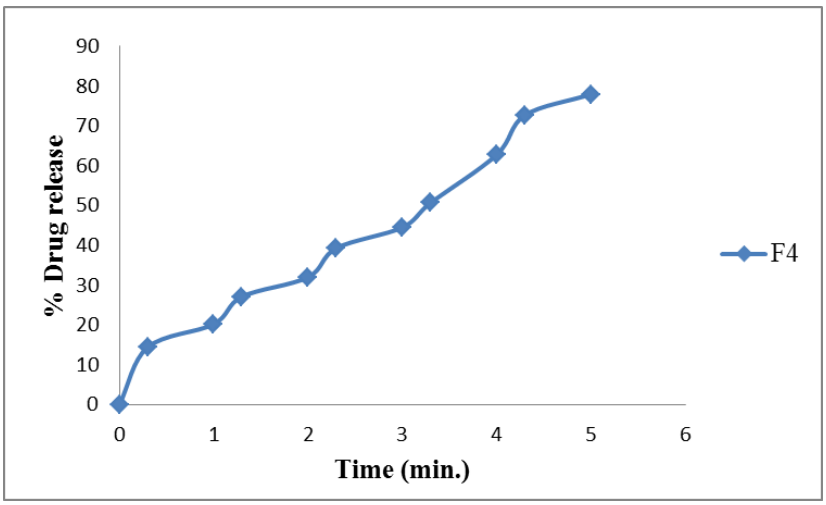

Fig. 10: Drug release from F4 formulation.

- **% Drug release from F5 formulation:** F5 formulation contained polymer PVA (380 mg) and drug Ondansetron Hcl (32 mg).

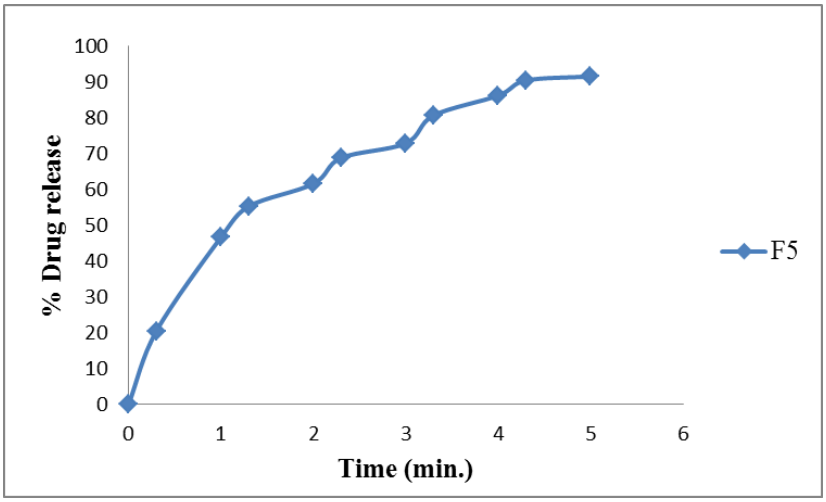

Fig. 11: Drug release from F5 formulation.

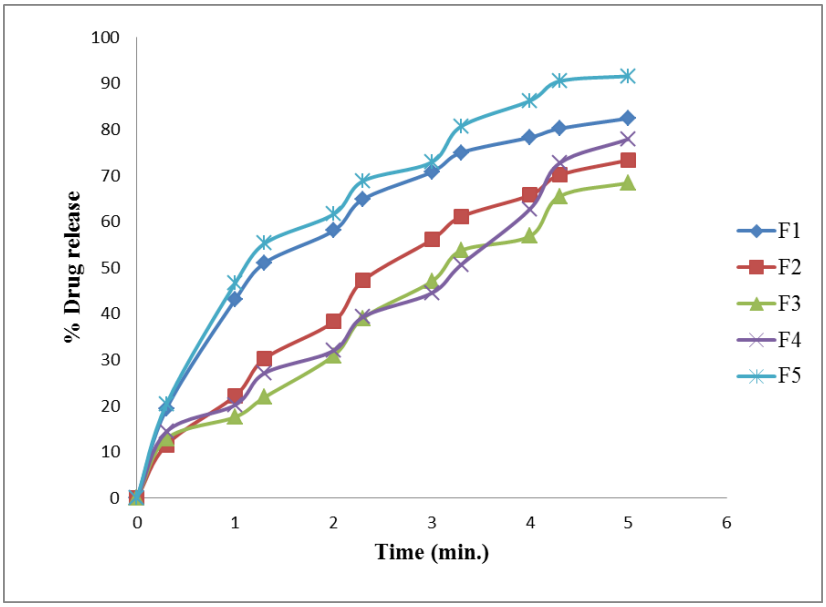

Fig. 12: Combined release graph of all formulations.

3.2 DISCUSSION

Preformulation studies were done to verify drug and to access suitability of the drug powder to be formulated into buccal film. The physical properties when accessed were found that the drug powder was white to off white in colour, odourless, crystalline in nature. Same characteristics have been described in I.P. Melting point was found to be 178ºC and the reported range is 178.5-179.5ºC. Hence the drug is authentic as per physiochemical properties.

The solubility of Ondansetron Hcl was studied in different solvents at room temperature. Drug was added to 10ml of each solvent separately viz. Hcl, water, buffer pH-6.8, methanol, ethanol, acetone and acetic acid.

Solvent of solubility study	Solubility assessment
Hcl	Freely soluble
Methanol	Soluble
Ethanol	Soluble
Water	Soluble
Acetone	Soluble
Acetic acid	Soluble
Buffer pH-6.8	Sparingly soluble

Drug when assessed for determination of λmax so as to authenticate the drug sample. The λmax was found to be 248 nm in water whereas the reported value of λmax of the drug was 248 nm. This was compiled with the reported value.

The results of the Preformulation studies indicate that the drug was authentic and suitable for being formulated into the oral dissolving film. Standard curve of the drug was prepared so as to setup a standard analytical method of the drug by U.V. spectrophotometry. The absorbance versus concentration graph was plotted. The curve was linear showing R^2 0.9997 and obeyed Lambert's law from 0 µg/ml-6 µg/ml concentration range.

The weight variation of all the formulations varied from 0.066 to 0.106 gm. All the formulations have low standard deviation which shows that all the formulations weighed similar. The variation in the weight of each formulation with other was due to the variation of polymer's quantity used.

The thickness of all the films varied from 0.12 to 0.24 mm which were thin thus having good patient compliance. Low standard deviation value of all the films showed that these films were uniform in thickness for the buccal cavity. The thicknesses of all the films were found to be in ascending order as given below.

F4 > F1 > F2 > F3 > F5.

The oral dissolving films of Ondansetron Hcl were also studied for folding endurance. The folding endurance of all the films was found to be more than 300 folds. All the films were 100% flat and uniform. The results indicate that the films had good folding endurance indicating that the preparations had good stability against breaking.

The surface pH of all the formulations was compiled with that of mouth that is 6 to 7. All the formulations had low standard deviations which indicate that all the films were generally similar. These were accordance to that described in literature.

Disintegration time is expected to provide an overview of Oral dissolving film time of disintegration. It was observed that the F5 formulation was the fastest to disintegrate i.e., in 43 seconds and the F1 formulation was the slowest to disintegrate i.e. in 84 seconds. The formulated films had low standard deviation which indicated that the prepared films were almost similar. The disintegration time of the films when expressed in ascending order was F5>F4>F3>F2>F1. This was instigated by the water's ability to hydrate PVA better than HPMC, causing oral film to disintegrate quickly.

The drug content evaluation of all the 5 films was performed to determine the percentage of drug present in the formulations. The results showed that there was enough amount of drug present in the films which varied from 88.84 to 92.63%. The quantity of the drug present in the formulation was close to the dose.

The percentage drug release at each interval was calculated and plotted against time. The drug release from the formulations F1 to F5 which had varying proportions of HPMC, PVA, citric acid, sorbitol, fructose, PEG 400. The drug release showed that the formulation F5 showed the highest drug release which was around 91.6% in 5 minutes. The drug release was found in the order F5>F1>F4>F2>F3.

Polymer PVA showed the higher release rate when compared to that of the film containing HPMC as polymer. The films prepared in combination of both the polymers showed less release rate when compared with the films containing both the polymers HPMC and PVA individually.

Formulation F5 had the highest release rate in comparison to other formulations due to the water's ability to hydrate PVA better than HPMC, causing oral film to have a better release rate than the other formulations. Formulation F4 showed better release rate than formulation F2 which had higher concentration of PVA as compared to F2 formulation. Hence, increase in PVA concentration, increased drug release.

4. CONCLUSION

Ondansetron Hcl oral dissolving film were formulated successfully and evaluated with the objective of providing maximum therapeutic efficacy, patient compliance by decreasing the dosing frequency and other problem associated with conventional, parenteral formulation. From the results of evaluation study it was found that all the formulated films exhibited certain satisfactory characteristic regarding integrity and dispersion of the drug.

All the films were uniform in thickness, had good folding endurance (>300) indicating good stability against wear and tear. The formulations had the surface pH similar to that of the buccal cavity and had fast disintegration ability which will provide good patient compliance by providing softness on getting wet by the saliva and releasing drug quickly after absorbing water. The formulation F5 showed maximum release (92.63%) in 5 minutes. Formulation F5 was best not only in terms of drug release but also had highest drug content and minimum disintegration time. Hence the films containing more concentrations of PVA are better than the films containing HPMC. Formulation F5 can be further taken for in depth studies.

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