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Design, Development and Evaluation of Oral Disintegrating Film of Ondansetron HCl

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ABSTRACT

Recently, Oral disintegrating drug delivery system has started gaining attractiveness and acceptance as new drug delivery systems, the reason behind that they are easy to administer and have enhanced compliant Recently popularity of Oral disintegrating Film was increased. The aim of the work is to design Oral disintegrating Film of Ondansetron HCl by using 3^2 factorial designs. Oral disintegrating Film (ODF Ondansetron HCl hydrochloride by using HPMC E15 was prepared by a solvent casting method. The formulated film was evaluated for thickness, folding endurance, disintegration time and *in vitro* dissolution of the films. Prepared films were found to be thin and fast disintegrating having desirable folding endurance as well as follow zero order kinetic model. As the polymer concentration increases the thickness of the formulated film also increases and thickness of formulated films obtained between 0.14±0.54 to 0.036±0.22 mm. The disintegration time of all the films was in the range of 87±1 sec to 123±2 sec. Because of less disintegration time, dissolution will be good that is good for absorption of the drug in the mucous membrane. The folding endurance of all the formulations was in the range of batches 222± 1 times to 250±1.73. The percentage drug content of all formulations was found to be between 94.55% to 99.88% which complies with limits established in the official compendia. The percent elongation of the formulated film was found to be in between the ranges for trial batches 19% to 85 % and for final batches 20% to 80%..D6 batch was selected as an optimized batch because of less disintegration time acceptable *in-vitro* drug release. Prepared films were found to be thin and fast disintegrating having desirable folding endurance as well as follow zero order kinetic model.

INTRODUCTION

Oral disintegrating Film (ODF) is the recent advance form of solid dosage form because of its flexibility. It increases the effectiveness of drug dissolving rapidly in the oral cavity after the contact with less volume of saliva as compared to dissolving tablet. The film is an ultimate intraoral Oral disintegrating drug delivery system, which fulfills requirements of the market, it is easy to handle and administer, maintains a simple and suitable packing, improves unpleasant taste, and is frank to manufacture[1,2,3].

Oral disintegrating Film (ODF) is classified into three categories they are as follows, Mucoadhesive melt-away wafer, Flash release, Mucoadhesive sustained-release wafers. In general, the Oral disintegrating film systems have an area of 2 – 8 cm^2, can be formed in each possible way and are between 20 and 500 µm thick. The attainable drug-load differs with the physicochemical properties of the drug and is up to 15 mg. Due to the naturally given absorption, the place of application is limited to the tongue, the gingiva the buccal region and the upper palate. Depending on the type of the ODF various properties can be used[4,5,6].

Ondansetron hydrochloride has a short biological half-life (3.5 ± 1.2 hours) and 62 % absolute bioavailability. Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8 mg tablet, is approximately 56%. Oral bioavailability of Ondansetron hydrochloride is almost 59%, and peak plasma about 0.03–0.04µg/ml is obtained after 1.5 to 2 h of administration[1,7].

MATERIALS AND METHODS

MATERIALS:

Ondansetron Hydrochloride was supplied as a gift sample by JB Chemicals and Pharmaceuticals. HPMC E15, Crospovidone, PEG-400 and Aspartame procured from Research-Lab Fine Chemicals Industries, Mumbai.

Method of Orodispersible film preparation:

The Oral disintegrating Film (ODF) ondansetron hydrochloride using HPMC E15 was prepared by the solvent casting method. An aqueous solution of the polymer was prepared in distilled water. Ondansetron hydrochloride was added to the aqueous polymeric solution.

This was followed by addition of distilled water and plasticizers like PEG 400. Sweeteners like sucralose added to the above solution. Disintegrant and flavor were also mixed with it. The solution was cast on a pet radish (diameter 9 cm) and dried in a hot air oven. The film was carefully removed from the petri dish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2 x 2 cm) per strip. The samples were stored in a desiccator.

Table 1: Batches formulation of orodispersible film

Ingredients	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**
Ondansetron Hydrochloride(mg)	32	32	32	32	32	32	32	32	32
HPMC E15 (mg)	100	100	100	200	200	200	300	300	300
Crospovidone (%)	2	4	6	2	4	6	2	4	6
PEG-400 (ml)	1	1	1	1	1	1	1	1	1
Aspartame (mg)	10	10	10	10	10	10	10	10	10
Water (ml)	10	10	10	10	10	10	10	10	10

EVALUATION PARAMETERS:

1) **Visual inspection of film**[4,5]

The film was checked visually for its transparency, Homogeneity, integrity and color of the prepared film.

2) Thickness[6]

The Thickness of the film was measured by Vernier caliper micrometer at different locations (five locations; Centre & four corners) and mean thickness was calculated.

3) Weight variation[7]

The prepared films of ondansetron HCl were 3 films randomly selected from each formulated batch and the average weight variations were determined.

4) Folding endurance[8]

The folding endurance is related to the flexibility of a film and it was measured manually by firmly folding a film repeatedly through the middle. The number of folds on the same crease, required to produce crack in the film was noted as the value of folding endurance.

5) Percentage moisture absorption[9,10]

In the study, the moisture absorption capacity of the films were determined by keeping the preweighed films in desiccator at room temperature for 72 hours. Then they were taken out and exposed to 84% relative humidity (saturated solution of potassium chloride). Values for the percentage of moisture uptake, calculated as per the following formula.

$$\textbf{Percentage moisture absorption} = W_2 - W_1 / W_1 \times 100 \ldots\ldots (1)$$

6) Drug content uniformity[11]

To determine the Ondansetron HCl content percent in the films, in 100 ml phosphate buffer (pH 6.8), the film that contains 4 mg of the drug, was dissolved in a volumetric flask with the aids of ultrasonicator for 30 min, then it was left undisturbed at room temperature for 24 hours, then after the solution was filtered via filter paper and examined by UV spectrophotometer at wavelength of 310 nm and drug content was calculated.

7) Disintegration test

Disintegration test was performed in the USP disintegration apparatus. Simulated salivary fluid (PH 6.8) was used as the medium. The films were placed in the tubes of the container and the disks were placed over it. The average disintegration time of three films from each formulation batch was noted.

8) Percent elongation

When stress is applied, a film sample stretches and this is referred to as strain. Strain is basically the deformation of film divided by original dimension of the sample. Generally, elongation of film increases as the plasticizer content increases.

% Elongation = increase in length/original length X 100…..(2)

9) Surface pH study

The pH meter was employed to measure the surface pH of the film by bringing the electrode in contact with a swollen yet intact film after exposure to 1 mL of distilled water for 1 min at the room temperature. The pH was recorded after direct contact between the electrodes with the surface to equilibrate for 1 minute.

10) *In-vitro* drug release

The drug release of the film was established with the aids of Franz diffusion cell, the lower compartment filled with 200 ml of phosphate buffer pH 6.8 at 37 ± 0.5°C, and 50 rpm stirring speed and at constant and defined interval, with constant volumes of both of sample withdrawal and media replacement (1 mL of each), finally the absorbance was taken for each sample by UV spectrophotometer at wavelength equals to 310 nm.

RESULTS AND DISCUSSION

RESULTS:

Drug-Polymer Compatibility Study by FTIR

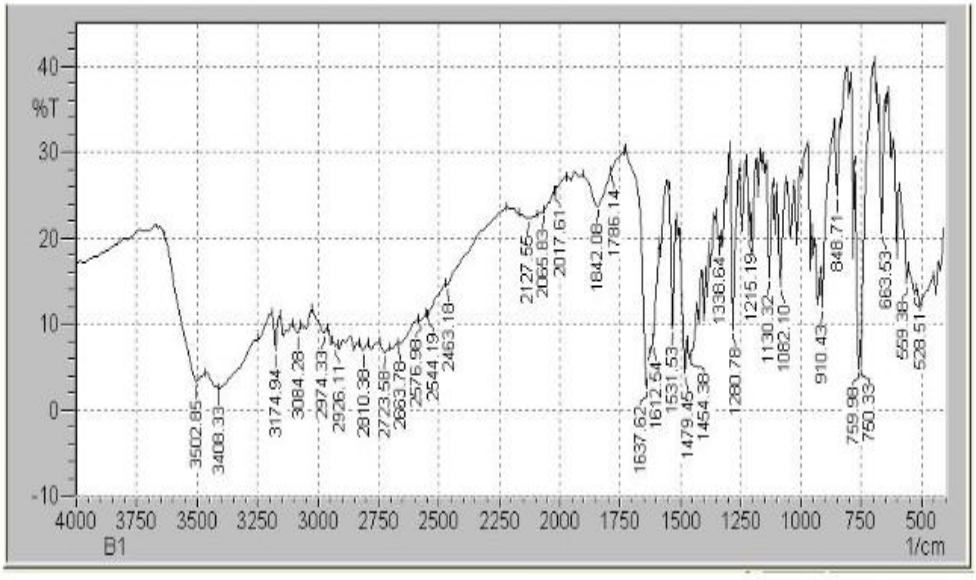

Figure 1: FT _IR spectra of a drug of Ondansetron HCL

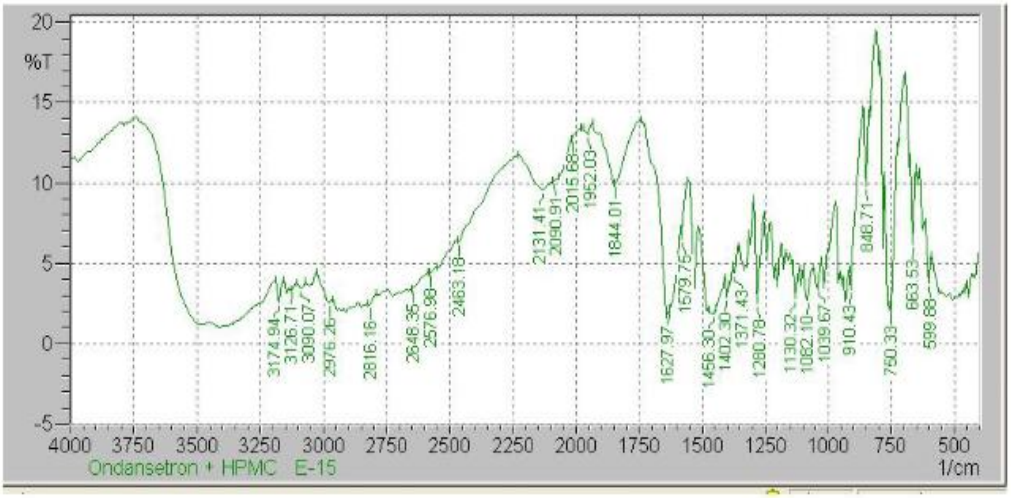

Figure 2: Ondansetron +HPMC E15+Excipients

FTIR studies conducted on pure drug and mixture of drug and excipients showed that there is no marked interaction between drug and excipients selected. It means that the drug compatible with the excipients used.

Compatibility study of Ondansetron HCL with polymer was carried out. All the characteristic peaks of Ondansetron HCL were present in spectra which are indicating that compatibility between drug and polymers. No change in the peaks Ondansetron HCL in the mixture of polymers. So there is no interaction between pure drug and polymers. It means that all the polymers are compatible with a drug.

Drug-Polymer Compatibility Study by DSC

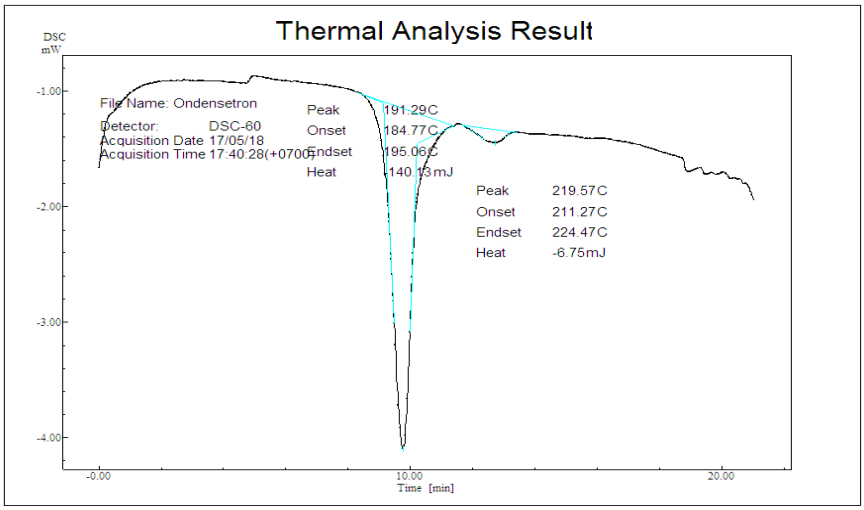

Figure 3: DSC spectra of drug

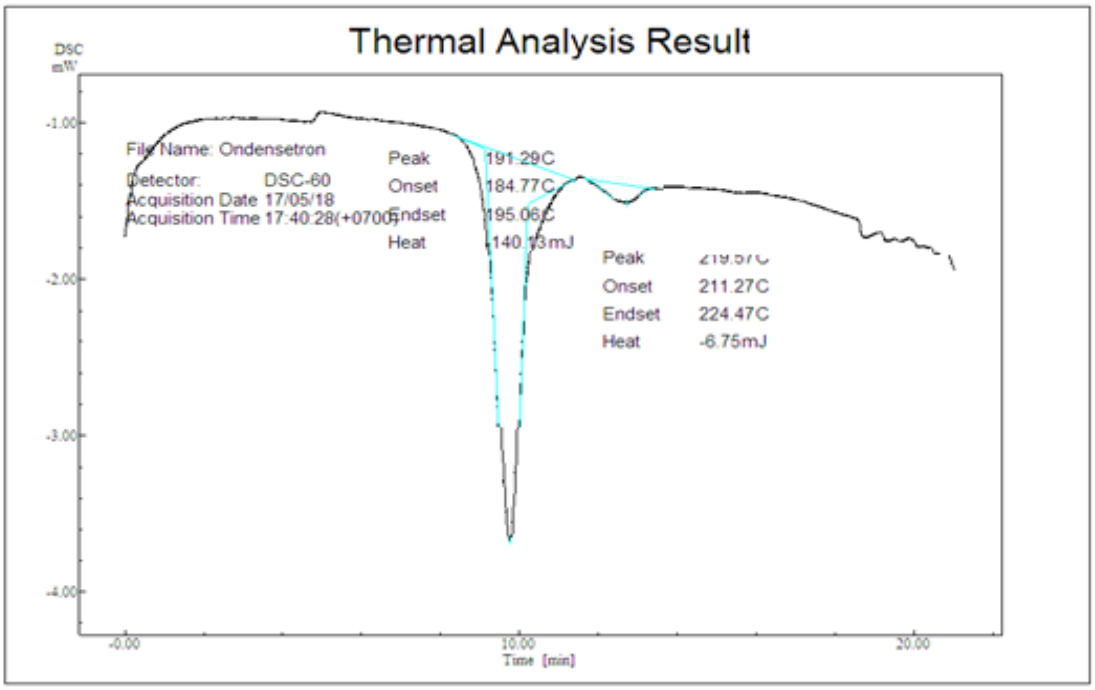

Figure 4: DSC spectra of a drug in its mixture

DSC studies conducted on pure drug and mixture of drug and excipients showed that there is no marked interaction between drug and excipients selected since no change in the endothermic peak of the drug in its mixture. It means that the drug compatible with the excipients used.

Table 2: thickness, %moisture content, disintegration time, weight variation, and folding endurance of formulated batches of ODFs

Formulation code	Thickness (mm)	% moisture Content	Disintegration Time (sec)	Weight variation	Folding Endurance
D1	0.14±0.54	1.56	97±1.04	19.2±0.51	250±1.73
D2	0.16±0.54	3.1	89±2.07	22.06±0.34	244±1.00
D3	0.18±0.44	2.0	88±1.55	19.40±0.31	240±1.00
D4	0.2±0.070	1.7	98±0.20	20.27±0.53	237±1.00
D5	0.24±0.14	0.9	97±2.02	19.66±0.23	231±1.00
D6	0.28±0.13	1.8	87±1.12	21.31±0.55	228±1.00
D7	0.32±0.83	0.94	123±2.02	20.75±0.31	225±1.00
D8	0.36±0.54	1.6	116±1.09	19±0.59	222±1.00
D9	0.38±0.22	0.94	100±2.02	21.23±0.44	233±2.00

1. Thickness

The thickness of the prepared batches was variable for a batch to batch ranging from 0.14±0.54 to 0.38±0.22 mm and indicated in table no.02**.** A very low standard deviation value is indicating that the method used for the formulation of films is reproducible and give films of uniform thickness and hence dosage accuracy in each film can be ensured.

2. Weight variation

The weight of the prepared films was determined by using digital balance. All the films were tested for uniformity of weight and the results are given in table no.02**.** The weight of films ranges from 19.2±0.51 to 22.06±0.34 mg. Because of less weight variation, it was assured that the stability of films was good.

3. Folding endurance

The folding endurance was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of the folding endurance. The folding endurance of all the formulations was in the range of 222±1.00 times to 250±1.73.

4. Disintegration Time

The disintegration time of all the films was in the range of 87±1 sec to 123±2 sec which is indicated in table no.02. .Because of Crosspovidone less disintegration time dissolution will be good that is good for absorption of the drug in the mucous membrane.

5.% Moisture Content

The % Moisture Content of all the films was in the range of 0.94% to 3.1% given in table no.02.

Table 3: Drug content, %elongation and surface pH of Formulated Batches

Formulation code	% Dug content	% elongation	Surface Ph
D1	98.14%	80%	6.62±0.13
D2	99.88%	75%	6.68±0.13
D3	94.55%	65%	6.60±0.14
D4	97.45%	50%	6.66±0.13
D5	99.65%	40%	6.64±0.14
D6	99.88%	25%	6.70±0.15
D7	98.74%	20%	6.72±0.14
D8	95.68%	20%	6.76±0.10
D9	97.68	19%	6.72±0.10

5. Drug content

The percentage drug content of all formulations was found to be between 94.55% to 99.88%which complies with limits established in the official compendia. % which indicated in table no.03. All the films were found to contain an almost uniform quantity of the drug. As per the USP requirements, the films found to meet the criteria for content uniformity (85-115) % of the label claim. No significant difference in the drug content among the films indicated that the drug was dispersed uniformly throughout the film.

6. Surface pH study

The surface pH was found in between the ranges from 6.60±0.14 to 6.76±0.10 which is given in table no.03. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable.

7. % Elongation

The percent elongation of the formulated film was found to be in between the ranges for trial batches 19% to 85 % which tabulated in table no. 03.

8. *In-vitro* Drug Release Study

The drug release of the film was Determined with the help of Franz diffusion cell and the percent drug release of optimized batches was obtained in the range between 88.21% to 98.23% within 9 which is tabulated in table no. 04.

Table 4: Drug release from formulated batches of film

Time in min	D1	D2	D3	D4	D5	D6	D7	D8	D9
0	0	0	0	0	0	0	0	0	0
1	4.27	4.92	2.32	1.02	8.82	2.97	10.12	10.00	11.20
2	10.07	11.37	21.72	10.07	28.83	24.31	23.01	17.84	20.85
3	19.68	22.25	35.13	20.96	41.56	42.85	39.63	40.92	37.30
4	29.19	28.54	44.56	34.31	50.32	55.45	65.05	53.52	55.20
5	49.43	41.14	51.98	44.97	61.54	64.09	76.19	58.35	70.20
6	66.93	68.83	65.03	54.88	68.20	73.90	89.75	69.46	78.44
7	76.05	81.09	82.98	68.48	77.94	83.62	92.12	82.98	85.20
8	81.30	86.95	90.71	73.77	86.32	84.44	93.22	88.83	91.10
9	88.21	93.16	96.32	84.30	95.44	98.23	93.97	94.61	97.20

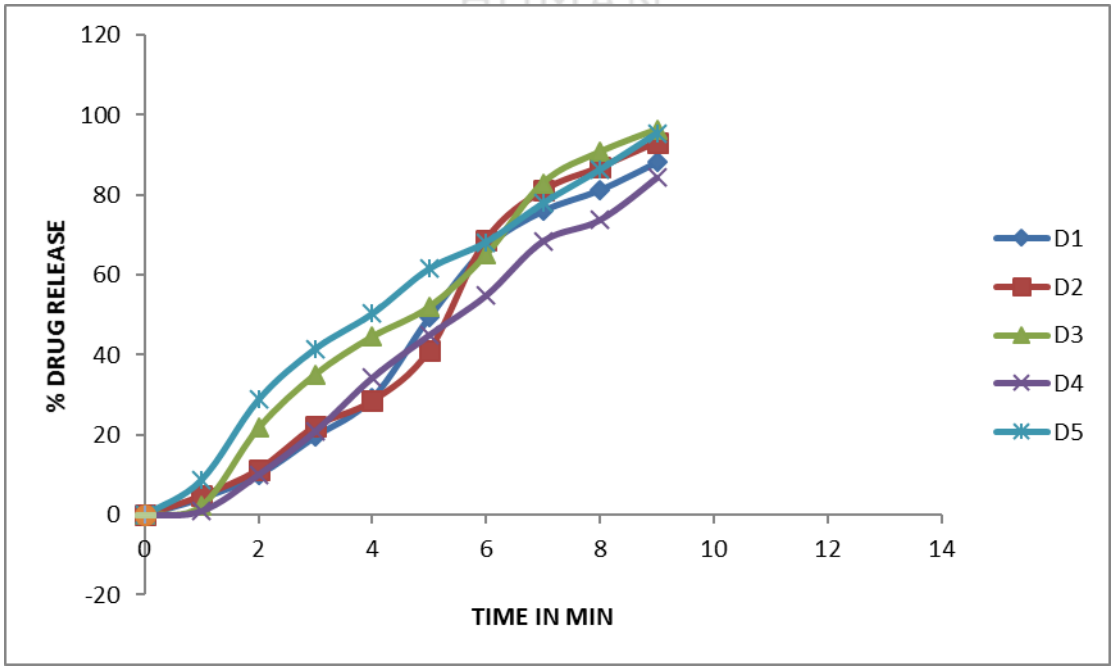

Figure 5: %Drug release of Batch D1 TO D5

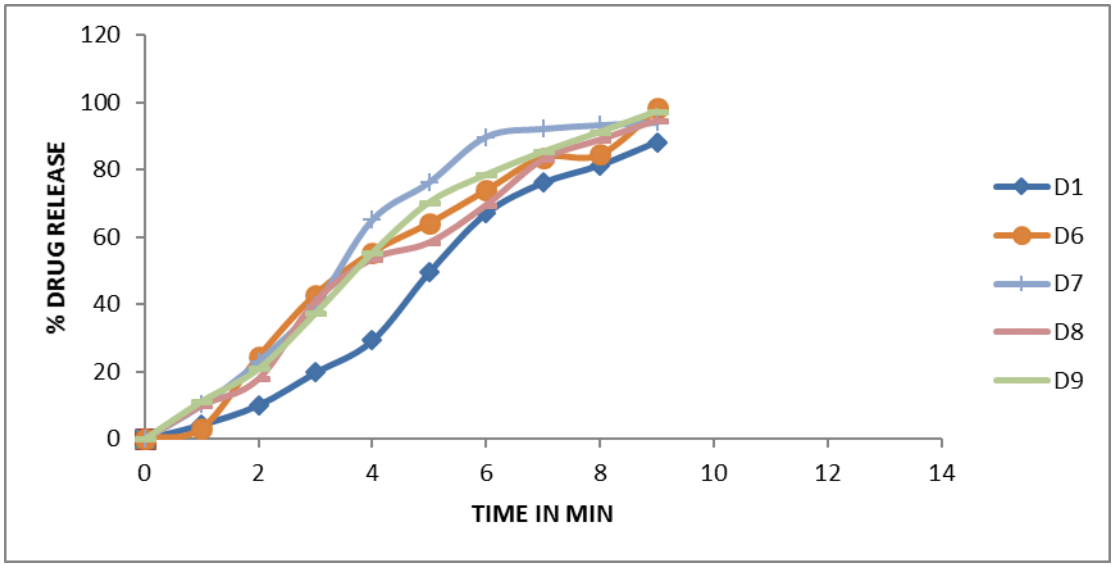

Figure 6: %Durg release of Batch D5 TO D9

9. Drug release kinetics

Table 5: Drug release kinetics

Formulation code	Higuchi	Zero Order	First Order	Hixoncro well	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	N
D7	0.93	O.97	0.91	0.85	0.99	1.9

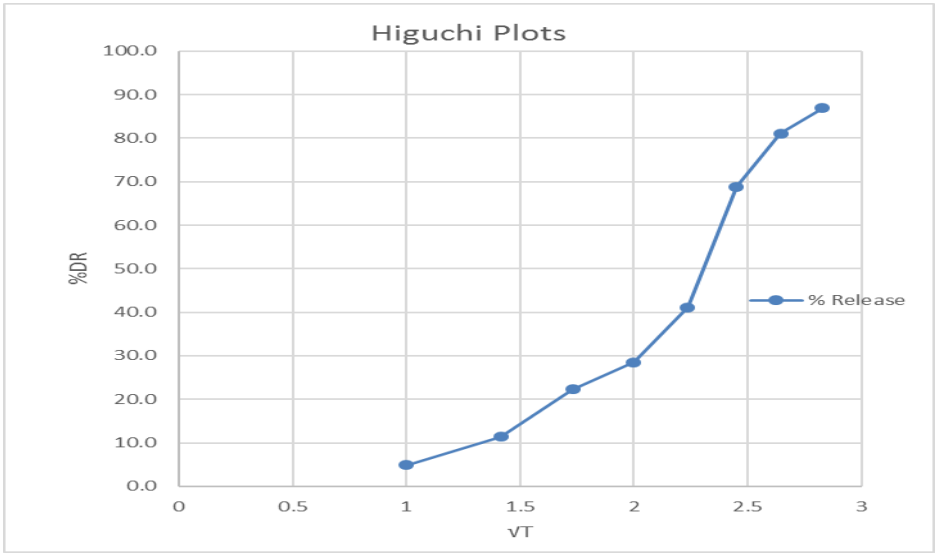

Figure 7: Higuchi Plots

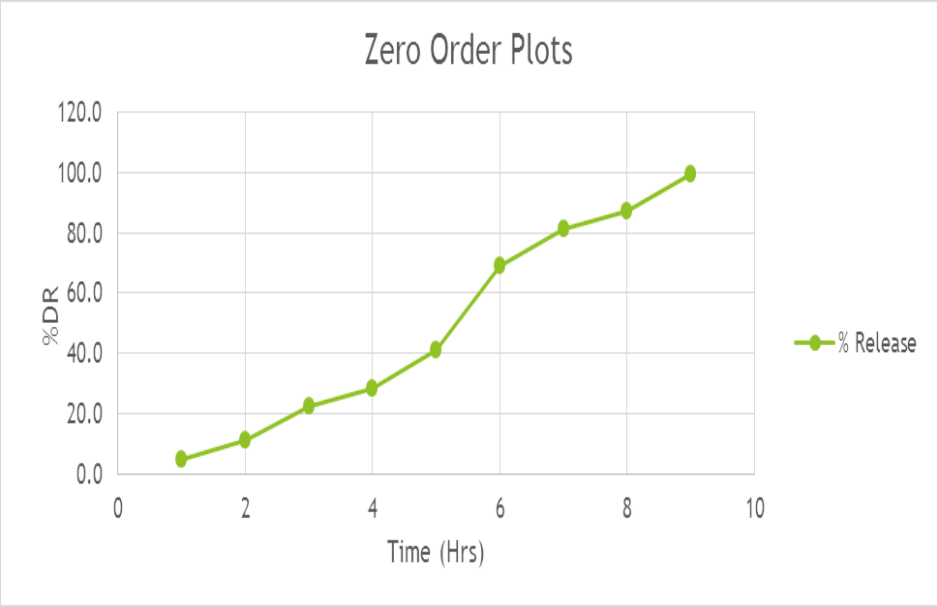

Figure 8: Zero Order Plots

Figure 9: First Order Plots

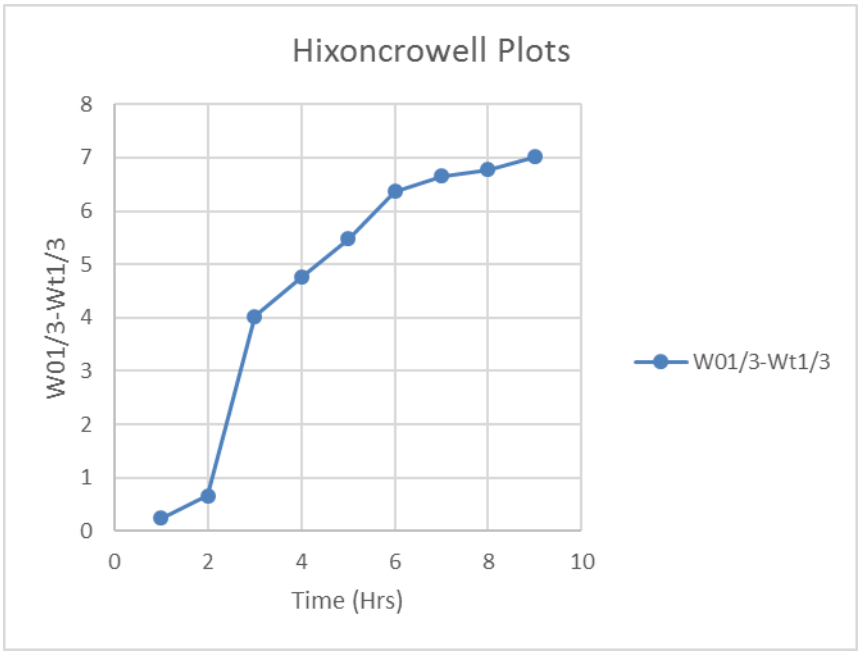

Figure 10: Hixoncrowell Plot

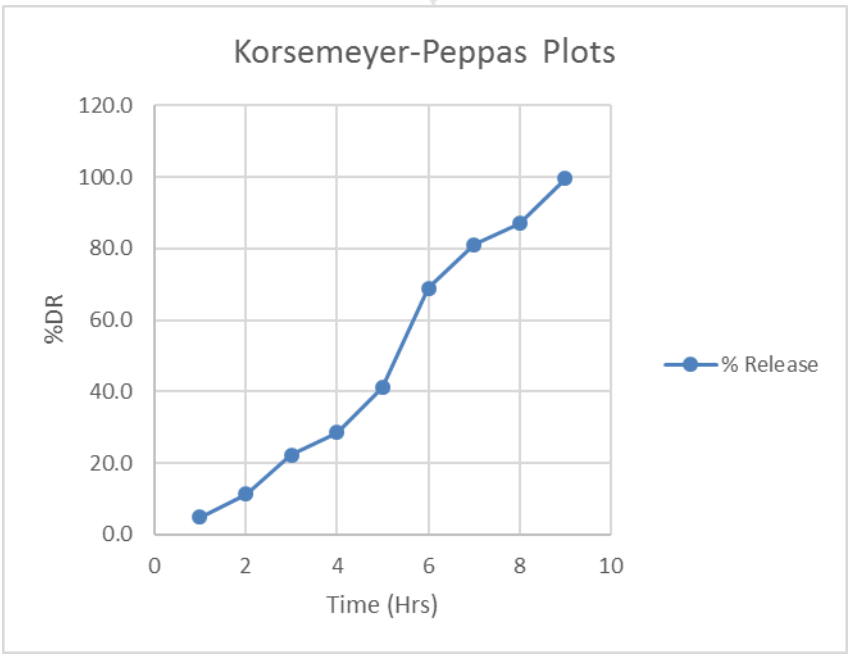

Figure 11: Korsemeyer-Peppas Plots

Table 6: Result of ANOVA

A result of ANOVA suggests the feasibility of model for the development of the orodispersible film.

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant Not/ Significant
% drug re ease	4712.00	12	1294.08	6.09	0.0186	0.9076.	**Significant**
Disintegration time	170.77	12	60.42	12.10	0.0021	0.9493…	**Significant**

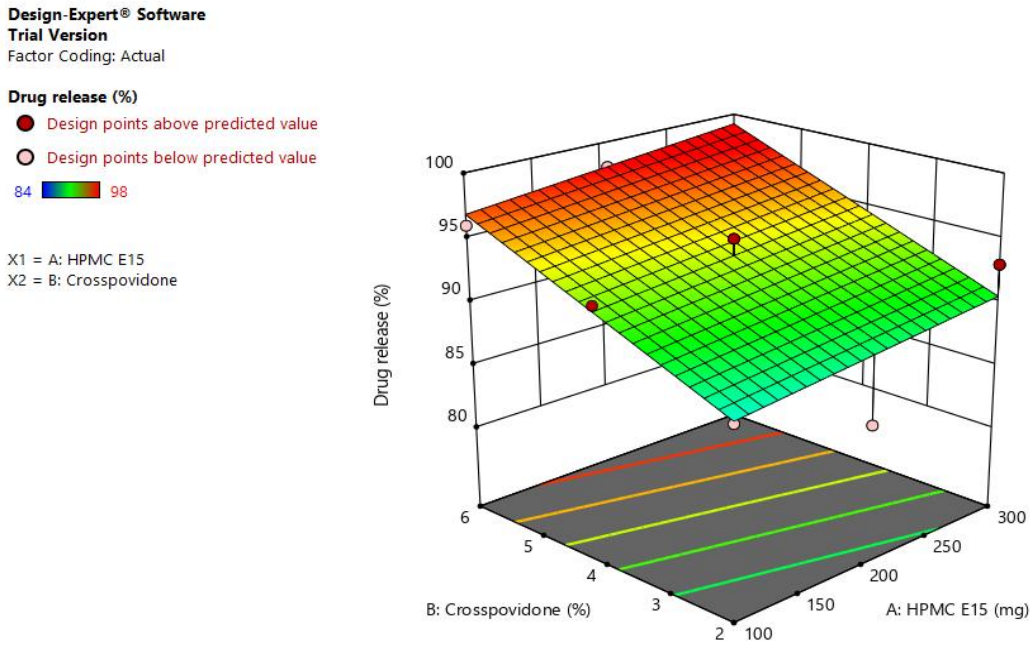

Figure 12: A response surface plot showing the effect of concentration of independent variables on the % drug release

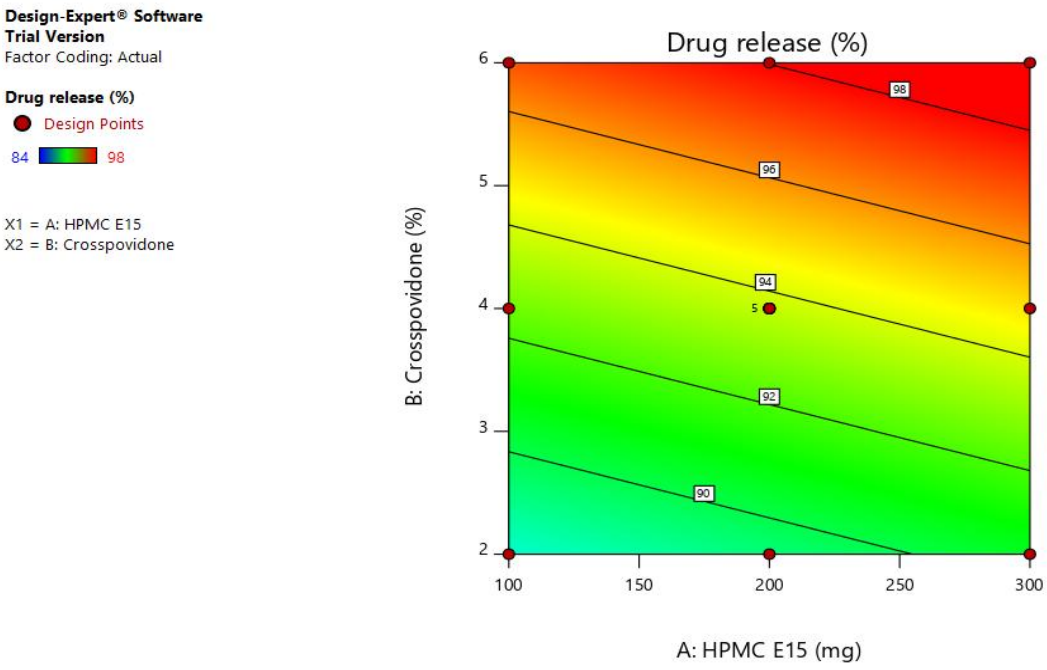

Figure 13: A counterplot of showing the relationship between various levels of independent variables to gain fixed value of % drug release.

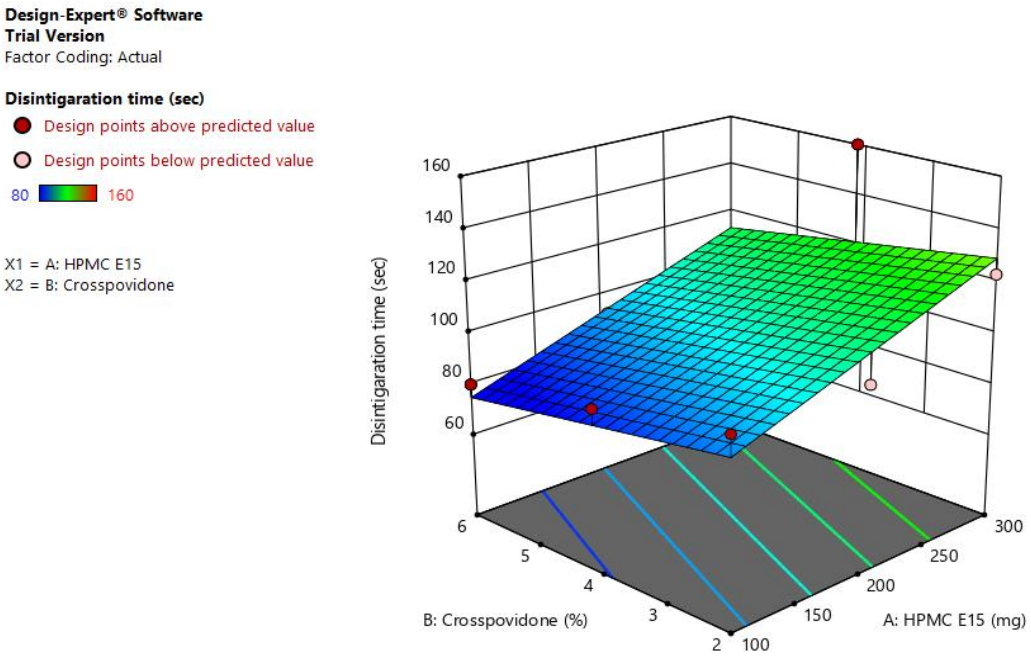

Figure 14: A response surface plot showing an effect of concentration of independent variables on the Disintegration time.

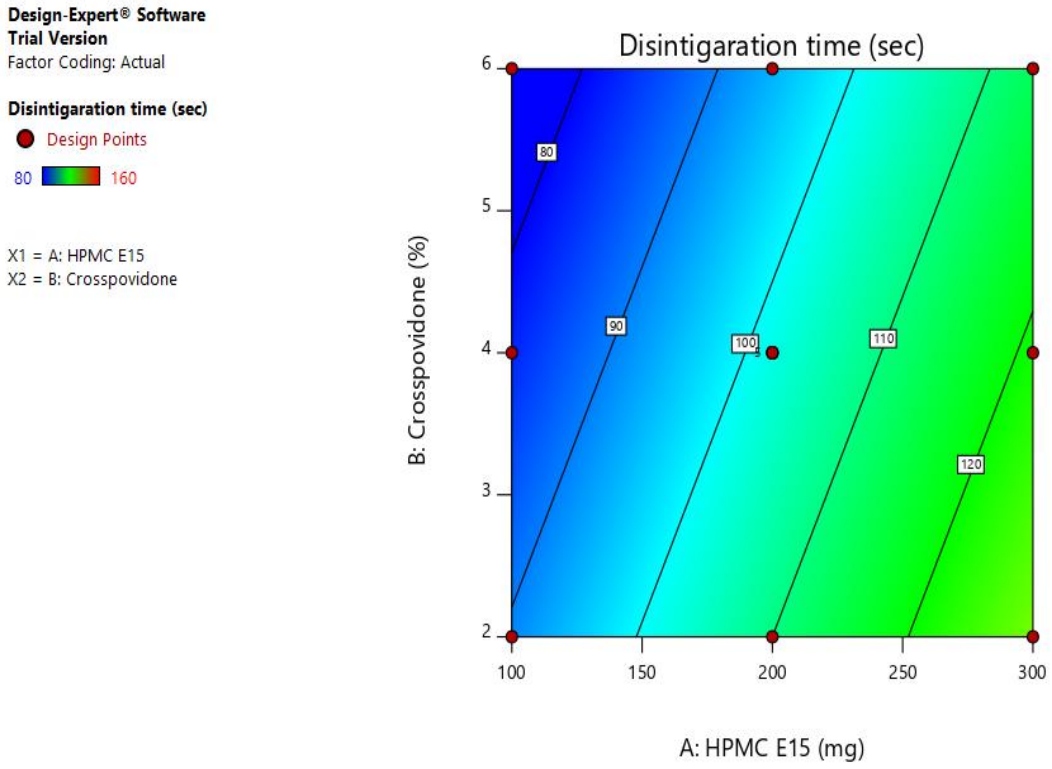

Figure 15: A counter plot showing the relationship between various levels of independent variables to gain fixed value of Disintegration time.

CONCLUSION

Oral disintegrating thin films of Ondansetron hydrochloride, formulated by using HPMC E 15 as a film forming material, Aspartame as a sweetener and PEG 400 as a plasticizer. HPMC E 15, were found to influence thickness, folding endurance, disintegration time and *in-vitro* dissolution of the films by using solvent casting method. FTIR, DSC studies conducted on pure drug and mixture of drug and excipients showed that there is no marked interaction between drug and excipients selected. As the polymer concentration increases the thickness of the formulated film also increases and thickness of formulated films obtained between 0.14±0.54 to 0.036±0.22 mm. The disintegration time of all the films was in the range of 87±1 sec to 123±2 sec. Because of less disintegration time, dissolution will be good that is good for absorption of the drug in the mucous membrane. The folding endurance of all the formulations was in the range of batches 222± 1 times to 250±1.73. The percentage drug content of all formulations was found to be between 94.55% to 99.88%which complies with limits established in the official compendia.D6 batch was selected as an optimized batch. Prepared films were found to be thin and fast disintegrating having desirable folding

endurance as well as follow zero order kinetic model. The result of ANOVA suggests the feasibility of model for the development of the orodispersible film.

Therefore, Ondansetron Hydrochloride can be conveniently administered orally in the form of films with the lesser occurrence of its side effects and with improved bioavailability.

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