RESEARCH ARTICLE

Development of Mouth Dissolving Films of Ondansetron Hydrochloride By Using Factorial Experimental Design

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ABSTRACT

The objective of this study was to develop a mouth dissolving film of ondansetron hydrochloride, an antiemetic drug that can not only serve in an active form but also provide rapid relief from motion sickness. Mouth dissolving oral film of ondansetron hydrochloride is a novel dosage form and was prepared by using HPMC E5, HPMC E15 and PVP K30 as a film-forming polymer in different concentrations. To study the effect of independent variables, i.e., concentration of HPMC E5, HPMC E15, and PVP K30 on various dependent variables like disintegration time and percentage drug content, 3^3 factorial designs was employed by using Design expert .11 After the application of 3^3 factorial experimental design, the process was optimized for the response variables R1-R2. The formulation showing disintegration time in the range (10-30 second), desired percentage drug release more than 85% is selected as optimized formulation. Formulation mouth dissolving films-5 (MDF-5), MDF-8, MDF-14, MDF-20, MDF-24, and MDF-25 shows desirable characteristics; all these formulations were taken as optimized formulation and subjected to *in vitro* dissolution study. MDF-25 containing 1% HPMC E5, 1% HPMC E15, and 1% PVP K30 show the promising faster disintegration time (19.66 seconds) followed by rapid and highest drug release (95.80%) within 120 seconds.

Keywords: Design expert, Factorial design, In vitro drug release, MDFs, Ondansetron hydrochloride.

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INTRODUCTION

The oral route is the most preferred route for drug administration because of its low cost and ease of administration, thus increasing patient compliance, but it has some disadvantages like hepatic first-pass metabolism and enzyme degradation within the gastrointestinal tract. Many patients like pediatric, geriatric, and psychiatric patients have difficulty in swallowing tablets and hard gelatin capsules. These types of patients are always unwilling to take solid preparations.[1] In the 1970's, rapid disintegrating mouth dissolving films based drug delivery system was developed as an alternative to tablets, capsules, and syrups for pediatric, geriatric, and psychiatric patients. Mouth dissolving films is a new drug delivery system designed for oral delivery of drugs and developed based on the technology of transdermal patches. Various methods have been developed to deliver therapeutic agents through various transmucosal routes to release the therapeutic agent to a specific site for action.[2]

Mouth dissolving oral films can be defined as a dosage form that employs a water dissolving polymer which allows the dosage form to hydrate by saliva quickly, adhere to the oral mucosa and disintegrates within a few seconds, dissolves and release the drug directly into systemic circulation avoiding hepatic first-pass metabolism, thereby increasing the bioavailability of the drug.[3]

Vomiting is the uncontrollable reflex that expels all the contents of the stomach through the mouth; this is called motion sickness. Moreover, it is also observed that patients who are undergoing thorough cancer or radiation therapy suffer from nausea and vomiting. It has been shown that approximately 70% of the patients with advanced cancer complaint of pain, and about half of them have symptoms that require medication with strong opioid analgesics. This analgesic creates an adverse reaction that may cause nausea and vomiting.[4]

Ondansetron hydrochloride, a $5HT_3$ receptor antagonist that is approved by United States food and drug administration (USFDA), is a potent antiemetic drug used to control chemotherapy-induced nausea and vomiting. It has been reported that ondansetron hydrochloride delays the time of onset of nausea significantly in patients who are on a high dose of cisplatin.[5] Ondansetron hydrochloride is commercially available in the form of conventional tablets, suppositories, and injections. However, Ondansetron hydrochloride usefulness is limited due to its low bioavailability (60%) due to hepatic first-pass metabolism and short plasma half-life (3-5 hrs), it requires repeated dosing which leads to side effect such as headaches,

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constipation or diarrhea, which is the cause of patient's un-compliance.[6] To reduce repeated dosing and overcome the hepatic first-pass metabolism, a novel formulation such as mouth dissolving film formulation is desirable.

The objective of this study was to develop the mouth dissolving films of ondansetron hydrochloride by factorial design using a software design expert,[11] which helps to directly enter the drug into systemic circulation by avoiding hepatic first-pass metabolism. Ondansetron hydrochloride administering via mouth dissolving films offers several advantages such as rapid absorption from highly vascularized oral mucosa and bypassing the first-pass metabolism, improve the efficacy of the drug, and increase patient compliance. The film we prepared by the solvent casting method and subjected for evaluation parameter such s: color, transparency, surface texture, surface pH, folding endurance, tensile strength, disintegration time, % drug content and *in vitro* drug release study.

MATERIAL AND METHODS

Materials

Ondansetron hydrochloride was obtained as a gift sample from Beaukev Pharmaceuticals Pvt. Ltd., Mumbai, India. Hydroxy Propyl Methyl Cellulose (HPMC) E5, HPMC E15, Poly Vinyl Pyrrolidone (PVP) K30 as film-forming polymers, Sodium saccharin as a sweetening agent and Polyethylene glycol (PEG) 400 as plasticizer were obtained from Central Drug House Pvt. Ltd., New Delhi, India. Citric acid used as saliva stimulating agent obtained from S.D Fine Chemicals Ltd., Mumbai. All other reagents used were of analytical grade.

Preparation of Mouth Dissolving Films (MDFs) of Ondansetron Hydrochloride

The solvent casting technique prepared mouth dissolving films of ondansetron hydrochloride. The polymeric solution was produced by dissolving a specified amount of polymers in 20 mL distilled water and stirred until a clear solution is prepared. To this polymeric solution, a weight quantity of citric acid, sodium saccharin, and the drug was added and stirred on a magnetic stirrer, and then PEG 400 was added. The final solution is then cast on a Petri dish and dried in a hot air oven at 60°C for 12 hours. The film was carefully removed from the Petri dish and check for any imperfection and cut according to the required size for testing (2x2 cm^2). The systematic representation of the solvent casting technique is shown in Figure 1.

Full Factorial Experimental Design

A 3^3 randomized factorial experimental design by using software design expert 11 was used for the optimization of ondansetron hydrochloride mouth dissolving films (MDFs). The design was also applied to study the effect of concentration of HPMC E5, HPMC E15 and PVP K30 on physicochemical evaluation parameters of prepared MDFs. The amount or concentration (%) of HPMC E5 (A), HPMC E15 (B), and PVP K30 (C) were selected as independent variables. These three factors were evaluated at each three levels. The variables units of higher, middle and lower level of A, B, and C were 1%w/v, 1.5%w/v and 2%w/v, respectively. By using 3^3 factorial design, 27 different formulation combinations were obtained are presented in Table 1. The disintegration time and percentage of drug content were considered as response variables.[7]

Dose Calculation of Drug for Each Film

The dose of ondansetron hydrochloride is 4 mg. Therefore, the amount of ondansetron hydrochloride in a film of diameter 2.0 cm is 4 mg. The amount of drug added in MDFs was calculated by using the following formula:

$$\text{Drug to be added in each film} = \frac{\text{Dose of drug per film x Area of Petri plate}}{\text{Area of one film}}$$

- Area of the Petri dish of 9 cm diameter is 63.64 cm^2
- Area of the film of 2cm diameter is 4 cm^2
- The amount of drug to be present in 4 cm^2 of a film is 4 mg.
- Amount of drug present to be added to the 63.64 cm^2 area of Petri dish is 63.64 mg ≈ 64 mg

Characterization of Mouth Dissolving Films (MDFS) of Ondansetron Hydrochloride

Morphological properties

The films were evaluated visually for its color, transparency and surface texture.[8]

Surface pH

The surface pH of prepared MDFs was determined by using digital pH meter. To check surface pH, one film was dissolved in 5 mL of phosphate buffer having pH 6.8 and pH is measured by bringing the electrode in contact with the solution and allows it to equilibrate for 1 minute.

Weight uniformity

The weight uniformity of prepared MDFs was determined by weighing all the films individually, collectively, and calculating the average weight of the film. All the reading was carried out in triplicate.

Folding endurance

The folding endurance is expressed as the number of folds required for breaking the film or develops visible cracks; this

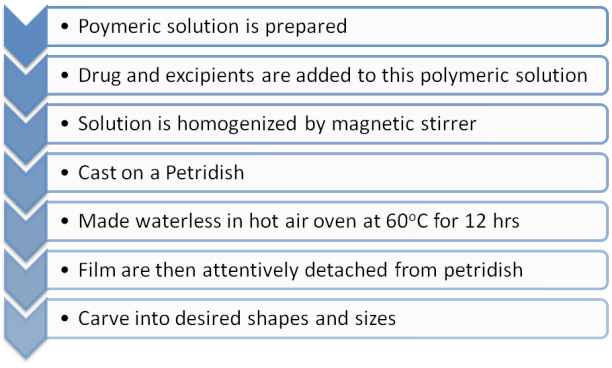

Figure 1: Systematic representation of solvent casting technique

Table 1: Formulation compositions of Ondansetron Hydrochloride MDFs by 3^3 full factorial design

Formulation Code	*HPMC E5 (% w/v)*	*HPMC E15 (% w/v)*	*PVP K-30 (% w/v)*	*Citric Acid (mg)*	*Sodium Saccharin (mg)*	*PEG 400 (ml)*	*Drug (mg)*
MDF-1	1	2	1.5	10	10	3	64
MDF-2	1.5	2	2	10	10	3	64
MDF-3	2	2	2	10	10	3	64
MDF-4	2	1	1	10	10	3	64
MDF-5	1	1	1.5	10	10	3	64
MDF-6	1.5	1.5	2	10	10	3	64
MDF-7	1.5	2	1.5	10	10	3	64
MDF-8	1	1.5	1	10	10	3	64
MDF-9	1	1.5	1.5	10	10	3	64
MDF-10	2	1	2	10	10	3	64
MDF-11	2	1.5	2	10	10	3	64
MDF-12	1.5	1.5	1	10	10	3	64
MDF-13	2	2	1	10	10	3	64
MDF-14	1.5	1	1	10	10	3	64
MDF-15	1	1.5	2	10	10	3	64
MDF-16	1.5	1.5	1.5	10	10	3	64
MDF-17	2	1	1.5	10	10	3	64
MDF-18	1.5	2	1	10	10	3	64
MDF-19	1.5	1	2	10	10	3	64
MDF-20	1	2	1	10	10	3	64
MDF-21	2	1.5	1.5	10	10	3	64
MDF-22	1	2	2	10	10	3	64
MDF-23	2	1.5	1	10	10	3	64
MDF-24	1	1	2	10	10	3	64
MDF-25	1	1	1	10	10	3	64
MDF-26	1.5	1	1.5	10	10	3	64
MDF-27	2	2	1.5	10	10	3	64

gives an indication of the brittleness of the film. Number of times the film is folded at the same plane without breaking gives the value of folding endurance.[9]

Thickness of the film

The thickness of prepared MDFs is determined by calibrated digital Vernier caliper. For this purpose thickness of the films was individually measured. All the readings were carried out in triplicate.[10]

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip breaks. The MDFs were placed between the two paper clips; one clip is stick to the burette stand while the other clip holds the weighing pan. The film is pulled by putting the weight in the weighing pan until the film breaks. All the readings were carried out in triplicate. Tensile strength is calculated by applying load at rupture divided by the cross-sectional area of the film.

$$\text{Tensile strength} = \frac{\text{Load at failure (weight in grams + pan weight)}}{\text{Strip thickness x strip width}} \text{ x } 100$$

In vitro disintegration study

In vitro disintegration test of the prepared MDFs was performed by petridish method. The MDFs were placed in 25 ml of phosphate buffer having pH 6.8 and the time at which film starts to break is recorded. All the experiments were carried out in triplicate

Determination of % drug content

For the determination of drug content, individual film containing 4 mg equivalent weight of ondansetron hydrochloride was suspended into 100 ml of distilled water with shaking for about 10 min and filtered using 0.45 µm membrane filter. Then 1 ml of the sample was diluted with 10 ml distilled water and analyzed at 310 nm using UV spectrophotometer (Shimadzu 1800). All the tests were carried out in triplicate.[11] The % drug content was determined by using following formulae:

$$\text{Drug content (\%)} = \frac{\text{Practical drug content in film}}{\text{Theoretical amount of the drug}} \text{x } 100$$

In vitro drug release studies

The *in vitro* dissolution test of prepared MDF was carried out in phosphate buffer (pH 6.8) using USP paddle (Type-II) apparatus at 37±0.5ºc. Samples were withdrawn at regular intervals 0, 10, 20, 30, 40 up to 120 seconds with the replacement of the same amount with fresh dissolution media. Absorbance was determined by using a UV-Visible spectrophotometer at 310 nm.[12]

RESULTS AND DISCUSSION

The goal of the study was to develop MDFs of ondansetron hydrochloride, and 3^3 full factorial design was successfully applied by using the software design expert 11 for formulation compositions optimization of MDFs. MDFs of ondansetron hydrochloride were successfully prepared by using solvent casting technique and prepared MDFs were subjected for the following characterization

Morphological Properties

The color, transparency, and surface texture of all prepared MDFs were evaluated visually and represented in Table 2. The result shows that all MDFs were found to be smooth, transparent, and free from air bubbles.

Surface pH

The result of surface pH of MDFs is shown in Table 2. It was found the surface pH of MDFs was found to be in the rage 6.70 ± 0.015 to 6.82 ± 0.01. This indicates that the found value of surface pH is close to the neutral pH, which show that MDFs have less potential to irritate the mucosal lining of the oral cavity and was acceptable by the patients. Hence no mucosal irritation was expected from these prepared MDFs.

Weight Uniformity

The average weight variation values of the ondansetron hydrochloride MDFs are reported in Table 2. The value was found between 93.00 ± 1.00 mg to 236.00 ± 1.00 mg. The result indicates that a proportional gain in the weight of MDFs was observed with the increase in thickness of films.

Folding Endurance

Folding endurance was determined by repeated folding the films at the same plane, and the result was found greater than 300 folds for all MDFs, which were satisfactory to reveal good film-forming property for all the formulations, as shown in Table 2.

Thickness of the Film

Thickness of the MDFs was determined by digital Vernier caliper and was found in the range of 0.064 ± 0.02 to 0.366 ± 0.11 mm (Table 2). The results indicate that a proportional increase in the thickness of the film was observed when the concentration of the polymers increases. This might be due to formation of a strong hydrogen bond between polymer and plasticizer, thereby imparting flexibility to withstand breakage.

Tensile Strength

The tensile strength of all films was determined and reported in Table 2. It was found that the tensile strength of the MDFs decreases with the increase in the concentration of polymer's tensile strength of all the MDFs. The values show that the mechanical stress of the MDFs of ondansetron hydrochloride was enough to bear the stress during transport.

Table 2: Physical Characterization of Ondansetron Hydrochloride MDFs

Form. Code	*Color*	*Transparency*	*Surface*	*Surface pH*	*Folding Endurance*	*Weight (mg)*	*Thickness (mm)*	*Tensile Strength (Kg/mm²)*
MDF-1	Colorless	Transparent	Smooth	6.81 ± 0.01	>300	167.00 ± 1.00	0.160 ± 0.04	0.634 ± 0.018
MDF-2	Colorless	Transparent	Smooth	6.80 ± 0.01	>300	192.00 ± 1.00	0.211 ± 0.05	0.701 ± 0.008
MDF-3	Colorless	Transparent	Smooth	6.79 ± 0.02	>300	162.00 ± 1.00	0.211 ± 0.05	0.860 ± 0.047
MDF-4	Colorless	Transparent	Smooth	6.83 ± 0.01	>300	181.00 ± 1.00	0.194 ± 0.04	0.845 ± 0.015
MDF-5	Colorless	Transparent	Smooth	6.57 ± 0.01	>300	134.00 ± 1.00	0.064 ± 0.02	1.168 ± 0.014
MDF-6	Colorless	Transparent	Smooth	6.80 ± 0.01	>300	187.00 ± 1.00	0.211 ± 0.05	0.585 ± 0.007
MDF-7	Colorless	Transparent	Smooth	6.76 ± 0.01	>300	152.00 ± 1.00	0.194 ± 0.07	0.663 ± 0.014
MDF-8	Colorless	Transparent	Smooth	6.81 ± 0.01	>300	156.00 ± 1.00	0.160 ± 0.04	0.854 ± 0.008
MDF-9	Colorless	Transparent	Smooth	6.80 ± 0.0	>300	155.00 ± 1.00	0.160 ± 0.04	0.767 ± 0.003
MDF-10	Colorless	Transparent	Smooth	6.82 ± 0.01	>300	198.00 ± 1.15	0.211 ± 0.05	0.576 ± 0.013
MDF-11	Colorless	Transparent	Smooth	6.83 ± 0.01	>300	186.00 ± 3.00	0.262 ± 0.07	0.891 ± 0.013
MDF-12	Colorless	Transparent	Smooth	6.82 ± 0.01	>300	152.00 ± 1.00	0.245 ± 0.05	0.714 ± 0.017
MDF-13	Colorless	Transparent	Smooth	6.78 ± 0.02	>300	190.00 ± 1.00	0.296 ± 0.03	0.720 ± 0.013
MDF-14	Colorless	Transparent	Smooth	6.77 ± 0.01	>300	137.00 ± 1.00	0.160 ± 0.04	0.645 ± 0.008
MDF-15	Colorless	Transparent	Smooth	6.76 ± 0.02	>300	183.66 ± 0.57	0.211 ± 0.05	0.589 ± 0.008
MDF-16	Colorless	Transparent	Smooth	6.79 ± 0.01	>300	151.66 ± 0.57	0.194 ± 0.04	0.830 ± 0.012
MDF-17	Colorless	Transparent	Smooth	6.77 ± 0.01	>300	205.00 ± 2.00	0.228 ± 0.05	0.967 ± 0.010
MDF-18	Colorless	Transparent	Smooth	6.78 ± 0.01	>300	176.33 ± 1.15	0.228 ± 0.05	0.872 ± 0.005
MDF-19	Colorless	Transparent	Smooth	6.77 ± 0.01	>300	164.00 ± 1.00	0.177 ± 0.06	0.709 ± 0.011
MDF-20	Colorless	Transparent	Smooth	6.75 ± 0.01	>300	129.33 ± 0.57	0.160 ± 0.07	1.304 ± 0.023
MDF-21	Colorless	Transparent	Smooth	6.75 ± 0.01	>300	145.33 ± 0.57	0.228 ± 0.08	0.652 ± 0.011
MDF-22	Colorless	Transparent	Smooth	6.76 ± 0.02	>300	227.00 ± 1.00	0.346 ± 0.10	0.552 ± 0.026
MDF-23	Colorless	Transparent	Smooth	6.73 ± 0.01	>300	189.00 ± 1.00	0.279 ± 0.06	0.772 ± 0.012
MDF-24	Colorless	Transparent	Smooth	6.72 ± 0.01	>300	113.00 ± 1.00	0.092 ± 0.04	0.952 ± 0.009
MDF-25	Colorless	Transparent	Smooth	6.74 ± 0.01	>300	93.00 ± 1.00	0.092 ± 0.04	1.037 ± 0.009
MDF-26	Colorless	Transparent	Smooth	6.72 ± 0.02	>300	145.00 ± 1.00	0.143 ± 0.05	0.925 ± 0.009
MDF-27	Colorless	Transparent	Smooth	6.73 ± 0.01	>300	236.00 ± 1.00	0.366 ± 0.11	0.426 ± 0.008

Full Factorial Experimental Design

Design expert 11 software was used for studying effects of independent variables on responses. The experimental design layout developed for 27 possible combinations of ondansetron hydrochloride MDFs are shown in Table 3. Various models such as linear, 2FI, Quadratic, and Cubic were fitted to the data and the model which fit well was suggested by software and was tested for analysis of variance (ANOVA). Regression polynomials were calculated for the individual independent variables, and then contour plots and 3D surface graphs were obtained for each individual dependent variable on response (R) and expressed as Equations. 1 and 2. The main effects (A, B, and C) represent the average results of changing one factor at a time when moving from low to high concentration. The polynomial terms B^2 was included to investigate nonlinearity.

Effect of Formulation Variables on In Vitro Disintegration Time

The disintegration time of MDFs was found to be in range of 19.66 ± 2.51 to 65.66 ± 6.02 sec (Reported in Table 3). Formulation MDF-27 containing highest concentration of HPMC E5 (2% w/v), HPMC E15 (2% w/v), and medium concentration of PVP K30 (1.5% w/v) show the highest disintegration time and Formulation MDF-25 containing lowest concentration of HPMC E5 (1% w/v), HPMC E15 (1% w/v) and PVP K30 (1% w/v) show the lowest disintegration time. On applying factorial design, quadratic model was suggested by Design expert 11 and found to be significant with model F value of 10.22, p-value < 0.0002 and R^2 value of 0.5714, which implies that the model was significant. P-value < 0.05 indicates that every model terms are significant. The model response R1 (Disintegration time) is as follows:

$$R1 = +37.92 + 7.39A + 7.13B + 3.35C \quad \text{Eq.-1}$$

The above Eq.-1 indicates that the A (concentration of HPMC E5), B (concentration of HPMC E15), and C (concentration of PVP K30) has a positive effect on disintegration time. That is an increase in A (HPMC E5), B (HPMC E15), and C (PVP K30) concentration led to an increase in the disintegration time of film. The disintegration time of ondansetron hydrochloride MDFs was found to be dependent on the concentration of polymers. The coded equation was used for identifying the relative impact factor by comparing the factor coefficients. The combined effects of factor A, B and C was further interrupted with the help of contour plot (Figure 2) and 3D response surface plots (Figure 3) which show the effect

Table 3: Experimental design layout of Ondansetron Hydrochloride MDFs

Run	*Formulation code*	*Factor 1 A:HPMC E5 (% w/v)*	*Factor 2 B:HPMC E15 (% w/v)*	*Factor 3 C:PVP K30 (% w/v)*	*Response 1 Disintegration Time (Second)*	*Response 2 Drug Content (%)*
1	MDF-1	1	2	1.5	37.33	68.67
2	MDF-2	1.5	2	2	48.66	65.33
3	MDF-3	2	2	2	35	80
4	MDF-4	2	1	1	40	67.17
5	MDF-5	1	1	1.5	27.67	93.5
6	MDF-6	1.5	1.5	2	48	63
7	MDF-7	1.5	2	1.5	34.66	77.5
8	MDF-8	1	1.5	1	21	89.17
9	MDF-9	1	1.5	1.5	35.66	69.67
10	MDF-10	2	1	2	40	67.67
11	MDF-11	2	1.5	2	64	65.33
12	MDF-12	1.5	1.5	1	38.33	65
13	MDF-13	2	2	1	55.33	55.5
14	MDF-14	1.5	1	1	28.33	88.83
15	MDF-15	1	1.5	2	36.66	67.5
16	MDF-16	1.5	1.5	1.5	38.33	71
17	MDF-17	2	1	1.5	37.33	73.83
18	MDF-18	1.5	2	1	38.33	76.33
19	MDF-19	1.5	1	2	28.66	83.33
20	MDF-20	1	2	1	29.66	86.5
21	MDF-21	2	1.5	1.5	33.33	82.33
22	MDF-22	1	2	2	47.33	69.17
23	MDF-23	2	1.5	1	53	70.5
24	MDF-24	1	1	2	23.33	94.83
25	MDF-25	1	1	1	19.66	95.83
26	MDF-26	1.5	1	1.5	31	83.67
27	MDF-27	2	2	1.5	65.66	62.67

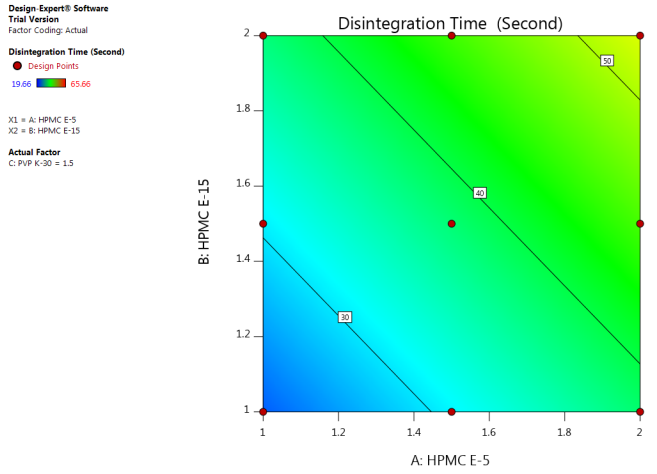

Figure 2: Two dimensional (2D) contour plot of response R1 (Disintegration time)

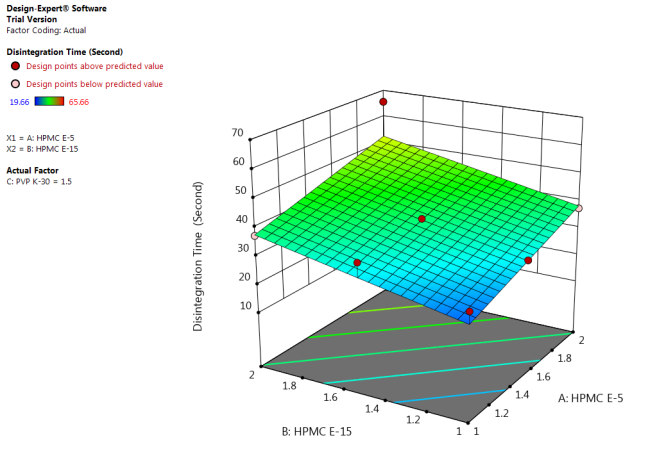

Figure 3: Three dimensional (3D) response surface plots for response R1 (Disintegration time)

of concentration of A, B, and C on disintegration time of the ondansetron hydrochloride MDFs.

Effects of Formulation Variables on % Drug Content

The drug content of prepared MDFs was found to be in the range of 55.50 ± 0.50 % to 95.83 ± 0.76 % (Reported in Table 3). Formulation MDF-5, MDF-24, and MDF-25 show the highest % drug content. On applying factorial design, the quadratic model was suggested by software and found to be F value 6.98, p-value <0.0009 and R^2 value of 0.5593, which implies that the model was significant. A p-value of less than 0.05 indicate that every model terms are significant. The model response R2 (% drug content) is as follows:

$$R2= +71.50- 4.64A- 7.41B- 3.61C+ 7.20B^2 \quad \text{Eq.- 2}$$

In above Eq. (2), – sign of factor A (HPMC E5), B (HPMC E15) and C (PVP K 30) has negative effect on drug content and + sign (B^2) indicate that it has positive effects on drug content. The combined effects of factor A, B and C was further interrupted with the help of contour plot (Figure 4) and 3D response surface plots (Figure 5) shown the effect of concentration of A, B, and C on % drug content of MDFs.

The % drug content of ondansetron hydrochloride MDFs was found to be dependent on concentration of polymers. As the concentration of polymers increases, the % drug content of the film decreases. MDF-5, MDF-24 and MDF-25 shows high % drug content above 90%.

Optimization of Formulation

After the application of 3^3 factorial experimental designs, the process was optimized for the response variables R1 and R2. If the disintegration time of the MDFs is high it may not provide rapid relief from the symptoms for which it is used. Also, if the drug content of the film is less, then the film may not release the required amount of drug into the systemic circulation to produce their effect. Hence the formulation showing disintegration time in the range (10-30 second) and desired % drug content more than 85% were to be selected as optimized formulations. Formulation MDF-5, MDF-8, MDF-14, MDF-20, MDF-24 and MDF-25 show all these desirable characteristics; thus, all these formulations were

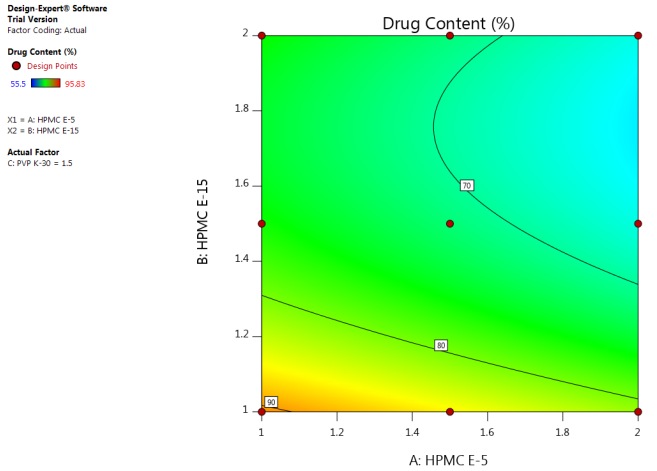

Figure 4: Two dimensional (2D) contour plot for response R2 (% Drug content)

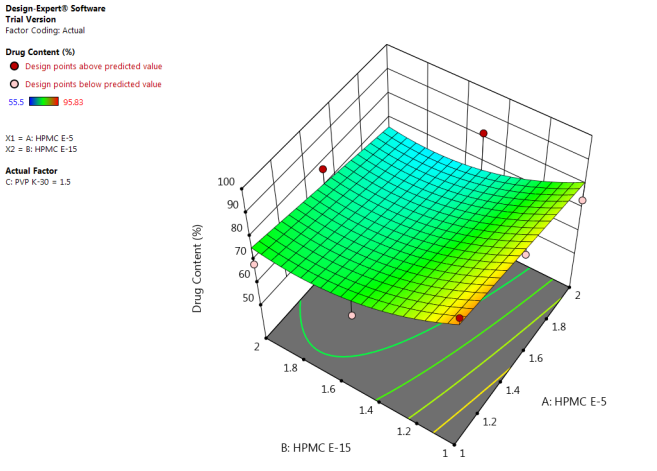

Figure 5: Three dimensional (3D) response surface plots for response R2 (% Drug content)

Table 4: *In vitro* drug release data of optimized Ondansetron Hydrochloride MDFs

Time	*% Drug Release*					
(Second)	*MDF-5*	*MDF-8*	*MDF-14*	*MDF-20*	*MDF-24*	*MDF-25*
0	0.00	0.00	0.00	0.00	0.00	0.00
10	67.95±0.76	68.16±0.78	62.33±0.23	60.57±0.78	65.44±0.65	73.44±0.44
20	69.58 ±0.88	66.96±0.67	64.55±0.56	62.55±0.55	68.67±0.34	75.55±0.69
30	71.45±0.98	68.55±0.45	65.32±0.76	64.77±0.65	71.89±0.15	77.21±0.99
40	74.80±0.78	69.54±0.10	67.32±0.62	65.43±0.21	73.45±0.56	78.43±0.55
50	76.42±0.34	72.65±0.51	69.23±0.66	68.36±0.44	75.83±0.67	80.12±0.77
60	79.11±0.10	75.33±0.67	71.43±0.56	69.66±0.44	78.67±0.41	82.±55±0.54
70	79.89±0.67	76.87±0.55	72.55±0.65	70.76±0.56	81.90±0.88	84.90±0.79
80	81.89±0.87	79.85±0.45	74.62±0.98	74.44±0.89	84.89±0.60	87.43±0.35
90	83.07±0.54	81.74±0.61	76.67±0.86	77.21±0.43	86.15±0.37	89.41±0.56
100	85.87±0.22	84.74±0.43	78.55±0.37	80.66±0.65	89.67±0.12	90.32±0.66
110	89.65±0.62	85.88±0.36	81.34±0.77	82.43±0.89	91.74±0.50	92.55±0.56
120	92.45±0.31	88.11±0.48	82.21±0.54	85.76±0.88	93.47±0.22	95.80±0.82

taken as optimized formulations and was subjected to i*n vitro* dissolution study to find out the drug release in phosphate buffer pH 6.8.

In Vitro Dissolution Study of Optimized MDFs

The *in vitro* dissolution study of all optimized MDFs was performed by using phosphate buffer pH 6.8 at 50 rpm. Maximum and minimum *in vitro* drug release were found to be 95.80 % and 85.76 %, respectively, over a period of 120 sec (2 min) and results are shown in Table 4 and presented in Figure 6. Among all the optimized formulations, the best formulation was found to be MDF-25, which containing HPMC E5 (1%), HPMC E15 (1%), and PVP K30 (1%). MDF-25 shows lesser disintegration time (19.66 seconds) and the highest % drug release (95.80%) within 120 second.

CONCLUSION

Mouth dissolving films (MDFs) is a novel dosage form for symptoms where the rapid onset of action of the drug is required, and at the same time, patient compliance is improved. It can be concluded that solvent casting technique is a simple and reproducible method for the preparation of MDFs of ondansetron hydrochloride. The results have shown that change in the concentration of the polymers has the potential to effects the disintegration time and drug content of MDFs. In combination with 1% HPMC E5, 1% HPMC E15 and 1% of PVP K30 was shown promising faster disintegration time (19.66 second) followed by rapid drug release within 120 sec (95.80%). From the present study one can conclude that ondansetron hydrochloride MDFs can be successfully prepared and it could provide quick onset of action with improved oral bioavailability and enhanced patient compliance and increased therapeutic efficacy when compared with other conventional oral dosage forms.

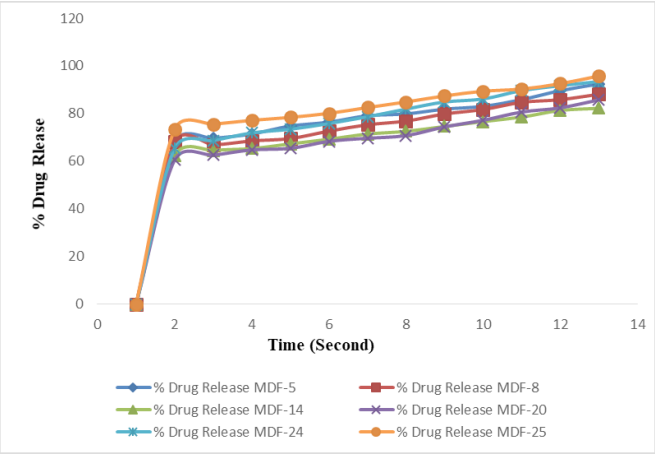

Figure 6: Percentage drug release profile of optimized ondansetron hydrochloride MDFs

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