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Original Article

QbD Approach for Developing Fast-Dissolving Films of Ondansetron Hydrochloride using HPMC E5 and Primojel

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ABSTRACT

Objectives: Purpose of present research study was to use Ondansetron to develop a film that dissolves quickly. **Materials and Methods:** HPMC E5 and Primojel were used in different ratios to prepare oral dissolving films. Technique used to prepare films was solvent casting. **Results:** Because of HPMC E5 cps, the film had an excellent thickness. The plasticizer glycerin showed good folding durability, elongation percentage, and tensile strength. Formulation F7 showed better oral sensation, folding capacity, and enhanced release of drug from formulation. The F7 had a quicker disintegration time of 31 sec and delivered 100% of the drug in 2 min. Percentage (%) and time of disintegration of drug thawed after 2 min (PD2) was calculated using polynomial equations created with Design Expert 7 software. To calculate the time of disintegration (Y1) and drug percentage dissolved in 2-min (Y2), the following formulas were utilised. For DT, Y1 is equal to 54.109 + 8.829 X1-19.828 X2-2.76 X1X2-0.169 X12+4.832 X22; for PD2, Y2 is equal to 59.98-1.769 X1+6.832 X2+ 0.39 X1X2+0.59 X12-3.59 PD22. Because the X1 coefficient in equation Y1 had a positive sign that predicts disintegration time increases as the HPMC content increases. In equation Y1 if X2 coefficient is negative it indicates when primojel concentration increases, the disintegration time decreases. **Conclusion:** Thus, using HPMC E5 and primojel, ondansetron mouth dissolving films were effectively prepared using a 3^2 Factorial Design. F7 formulation, which contains HPMC E5 (500 mg) and Primojel (5 mg), was deemed best formulation based on attractiveness.

Keywords: Ondansetron, HPMC E5, Primojel, 3^2 Factorial Design, solvent-casting, Fast-Dissolving Film, Disintegration Time.

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INTRODUCTION

In the past ten years, Oral Films (OFs) have gained recognition as cutting-edge dosage forms intended to improve the efficacy and safety of medicinal substances.[1] By making prescription drugs easier to use, these systems seek to increase patient adherence.[2] Advanced forms of OFs were first developed by a number of pharmaceutical companies. For instance, to meet unmet market demands, Lavipharm Laboratories Inc. has created a cutting-edge fast-dissolving medication delivery platform. Quick-DisTM, a patented intraoral delivery method from Lavipharm.[3] is a proprietary technology that includes a quick-dissolving thin, flexible film. The active medication is released from the Oral Films as soon as they are placed on the tongue, enabling it to dissolve in saliva.[4] A portion of the Active Pharmaceutical Ingredients (APIs) in saliva can pass through the pharynx, esophagus, and mouth when ingested, frequently leading to better bioavailability than with conventional tablets.[5] Because of its antiemetic and antinausea qualities, Ondansetron, a selective 5-HT3 receptor antagonist, is frequently indicated to overcome nausea and vomiting induced by chemotherapy.[6,7] It works by centrally and peripherally inhibiting serotonin receptors.[8] Despite its quick onset, ondansetron still has a modest oral bioavailability of about 60% because to first-pass metabolism and limited water solubility.[9,10] Furthermore, typical oral dosing is hampered by dysphagia, which is prevalent in both pediatric and geriatric populations. These drawbacks imply that the therapeutic benefits of ondansetron could be greatly increased by a mouth-dissolving film formulation that includes an efficient taste-masking ingredient.[11] For patients who have trouble swallowing, especially children, the elderly, and uncooperative patients, such a dose form

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would allow for a quicker onset of action while also enhancing convenience and compliance.

MATERIALS AND METHODS

Materials

Dr. Reddy's labs sent a complimentary sample of ondansetron. Loba Cheme Laboratories supplied the Hydroxypropyl Methyl Cellulose (HPMC E5), and all other compounds utilized were of analytical grade AR.

Methods

Method of preparing of fast-dissolving films

Formulae for the preparation of fast-dissolving films were shown in Table 1. Plasticizers and other water-soluble polymers were dissolved using ethanol. Using a magnetic stirrer, the homogenous mixed solution was agitated for 2 hr to remove any trapped air bubbles, and then it was left undisturbed for a while. Meanwhile, the drug with its excipients was dissolved and briskly swirled for 30 min. The two solutions were mixed together after the stirring was complete. Finally, the solution is cast into a petri plate to create a film. The petri-plates were kept at 60°C in a hot air oven for up to 1 hr. The film was carefully taken off of the petri-plate after drying, and then it was cut to the proper size.

Evaluation of Oral Film Thicknesses

Film thickness was determined using micrometre screw gauge. To achieve uniformity, the thicknesses of the film are estimated at five different locations. Less than 5% should be the thickness of the oral film.

Folding Ability

To test the prepared oral film's capacity to fold, it is first sliced and then rapidly bent at the same place until it tears. The multiple times a film is folded at the same location and is deprived of sustaining any damage is a measure of its folding capacity. The topical folding endurance of the film was between 300 and 400.

Disintegrating Time (DT)

In a petri dish, a single film was placed on top of 2 mL of distilled water, and the amount of time it took for the oral film to dissolve was noted.

Weight Uniformity

Randomly ten oral films weight was assessed. Every film was weighed individually, and its weight was compared to the variance's average weight.

Assay

The test involved dissolving a 4 cm^2 portion of oral film in 50 mL of phosphate buffer pH 6.8 and spinning it. The filtrate obtained was diluted using the same buffer after this solution was run through a Whatman filter paper. The solution was examined using a UV spectrophotometer, and absorbance readings at 310 nm were taken.

In vitro dissolution test

The *in vitro* dissolving media (900 cc of phosphate buffer pH 6.8) was kept at 37±0.5 °C, and the basket was set to operate at 50 rpm. After being slit, a 4 cm^2 (2 cm*2 cm) film sample was placed in the basket. 5 mL of the sample were extracted every 2 min, and a corresponding volume of fresh buffer was added. The components that were extracted were filtered and examined using a UV spectrophotometer set to 310 nm.[6]

RESULTS

Ondansetron oral films were prepared as part of the study to treat nausea and vomiting. Films were made using 3^2 factorial designs with primojel as a disintegrant and HPMC E5. After primojel and HPMC E5, films containing 100 mg of ondansetron each was made using the formulas in Table 1. In each case, films were prepared using the solvent casting method. The films were clear and translucent. Additionally, the thickness remains constant. Additionally, the adaptability is good. The mechanical aspects of the films were satisfactory. The assay result showed that the drug had been properly added to the film. Each of the generated films was evaluated for its folding durability, drug content, disintegration time, dissolution and other dimension measurements (Thickness, weight variation). The physical attributes of the produced oral films were tabulated in Table 2. The films' exceptional mechanical strength was proved by their capacity to fold for over 300-400 sec. The content of the drug Ondansetron in the films ranged from 100±2%. Between 31 and 92 sec was the range of the disintegration times. The disintegration time decreases as the super disintegrant concentration rises (DT inversely proportional to concentration super disintegrants). In a phosphate buffer pH 6.8, the rate at which various films degraded was investigated. The various films' *in vitro* dissolving profiles are shown in Figure 1.

The dissolving results were analysed using zero and first order kinetics. First-order model's was stronger than the zero-order model's showed that the Ondansetron dissolution followed first-order kinetics. The values of the correlation coefficient (r) for the first-order model varied from 0.923-0.996.

An overview of the ondansetron oral dissolving film's dissolution properties is given in Table 3. The factorial design is one technique for determining and assessing the comparative significance of the elements involved in a development.

Additionally, any interactions between the chosen elements can be found. To create a factorial design, both parameter and response choices are required.

DISCUSSION

The proportion of Ondansetron oral dissolving films produced using the independent variables Primojel and HPMC E5 as per 3^2 factorial design. The planned dependent variables were the percentage of drug release after 2 min and the Disintegration Time (DT). A 95% Confidence Interval (CI), or $p<0.05$, was used to choose significant terms. Polynomial equations were developed for the Disintegration Time (DT) and the proportion of medication released after 2 min.

Three concentrations of X_1 (HPMC) and X_2 (Primojel) of 500, 600, 700 mg and 30, 40, 50 mg were used as bases to develop Ondansetron rapid dissolving film. According to the 3^2 Factorial, a particular combination of the two components, X_1 and X_2, was used to create a total of nine ondansetron fast-dissolving films. In order to identify the optimal combination and concentration required to produce the desired rapid release/dissolution of the medication, the importance of the combined activities of X1 and X2 was evaluated.

Three concentration levels of HPMC E5 were selected and assigned the following codes: 500, 600, and 700 mg. Three primojel concentration levels were chosen and arranged as follows: 30=-1, 40=0, and 50 mg=+1. The formulations for every experimental batch were given in Table 1. Polynomial equations (Equation-1) for Disintegration Time (DT) and percent drug dissolved 2 (PD2) were created using Design Expert 7 software. Response surface morphological plots for PD10 and disintegration time using X1 and X2 on both axes, respectively, were shown in Figure 2.[12]

Equation-1: $Y=b0+b1X1+b2X2+b12X1X2+b11X1^2+b22X2^2\ldots$

The dependent variable is Y, the anticipated coefficient for component X_1 is b_1, and the numerical mean response of nine batches is denoted by b_0. The principal impacts (X1 and X2) display the average result of changing one element at a time from its low to high value. The interaction term (X1X2) indicates that the answer varies when two parameters are changed simultaneously. The polynomial terms $X1^2$ and $X2^2$ are used to investigate non-linearity. The Disintegration Time (DT) and the percentage of drug released after 2 min (PD2) were calculated using the following polynomial equations.[13,14]

Y1= 54.109+ 8.829 X1-19.828 X2-2.76 X1X2-0.169 X12+4.832 X22 for DT

Y2= 59.98-1.769 X1+6.832 X2+ 0.39 X1X2+0.59 X12-3.59 X22 for PD2

The positive value for the coefficient of X_1 in the Y_1 equation indicates that disintegration time increases with HPMC content. The negative recommendation for the co-efficient of X2 in the

Table 1: Formulations prepared with varied formulas.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ondansetron in milligrams	100	100	100	100	100	100	100	100	100
HPMC E5 (mg)	500	600	700	500	600	700	500	600	700
Primojel (mg)	30	30	30	40	40	40	50	50	50
Glycerin (mL)	2	2	2	2	2	2	2	2	2
Citric acid (g)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sodium sacharin(mg)	25	25	25	25	25	25	25	25	25
Flavor (mg)	10	10	10	10	10	10	10	10	10
Ethanol (mL)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 2: Post compression parameters.

Formulation	Thickness (mm)	Folding Ability	Disintegration Time (sec)	Weight variation (mg)	Assay in %
F1	0.58	355	64	0.037	99.61
F2	0.55	373	80	0.055	99.22
F3	0.59	400	92	0.057	98.84
F4	0.51	350	50	0.046	99.61
F5	0.53	375	54	0.053	99.22
F6	0.52	393	58	0.056	98.84
F7	0.55	400	31	0.062	99.61
F8	0.57	376	38	0.064	99.22
F9	0.53	397	48	0.066	99.22

Table 3: Dissolution parameters.

Formulation	PD2 (%)	DT (Sec)	K1 (min^{-1})
F1	51.83	64	0.571
F2	49.83	80	0.407
F3	48.23	92	0.254
F4	63.25	50	0.625
F5	59.63	54	0.449
F6	58.25	58	0.345
F7	64.77	31	0.703
F8	63.33	38	0.469
F9	62.77	48	0.394

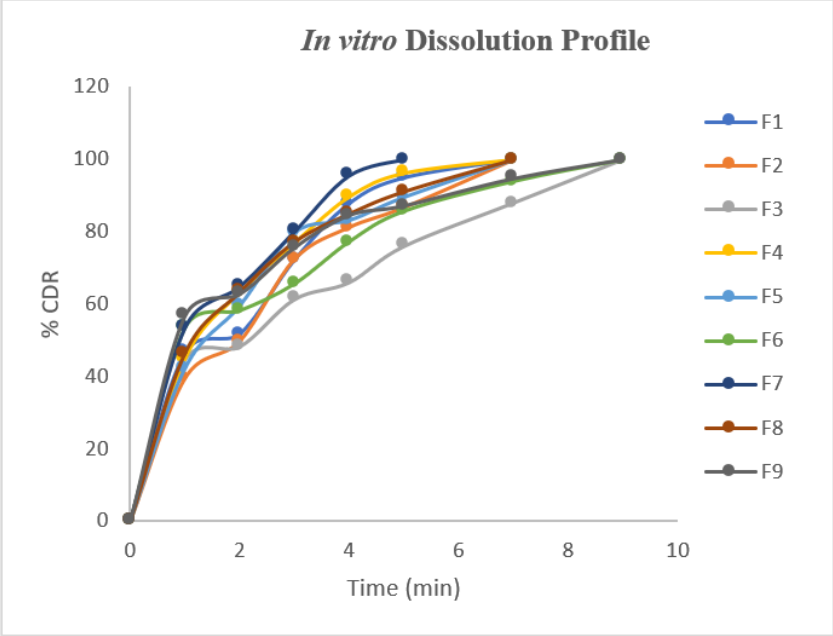

Figure 1: *In vitro* dissolution profiles for Formulations F1-F9.

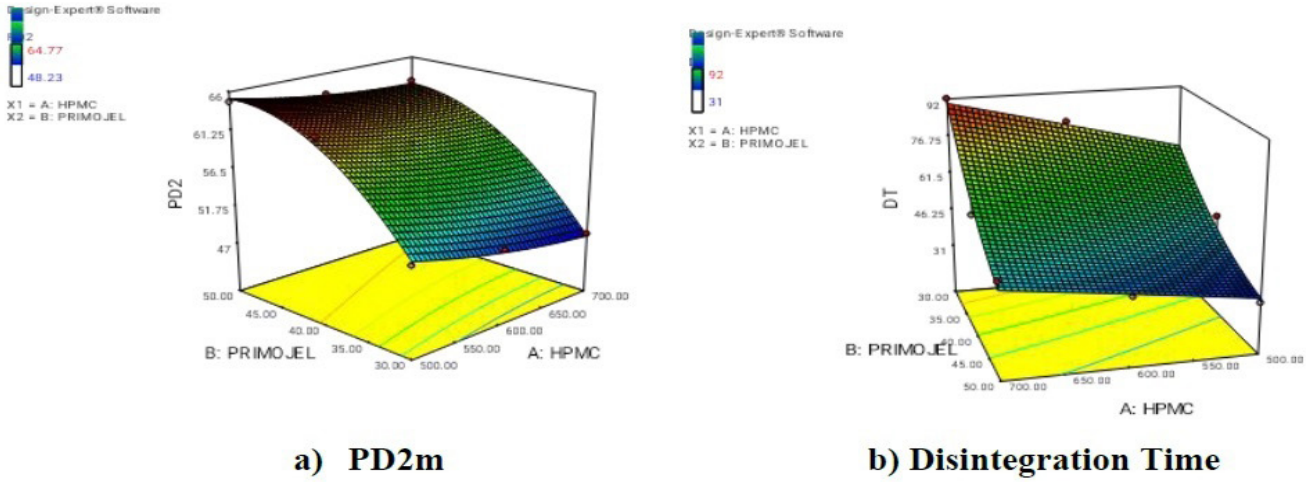

Figure 2: Response Surface Morphological Plots for PD2 and DT.

Y1 equations indicates that the disintegration time decreases as primojel concentration rises. These results indicate that a higher concentration of super disintegrant shortens the disintegration period of the dosage form and that the drug release pattern can be changed by selecting the appropriate X1 and X2 levels. Response surface plots were presented to show how X1 and X2 affected the Disintegration Time (DT) and the percentage of drug release after 2 min (PD2), proving that the derived equations for the dependent variables are true. Because of this, Ondansetron quick dissolving films were successfully prepared using 32 Factorial Design with HPMC E5 and Primojel.

CONCLUSION

The major objective of this work was to use ondansetron along with common ingredients including flavor, polymers, plasticizers, sweeteners, and saliva stimulants to make a fast-dissolving film. Rapid dissolving films prepared by casting solvent. Because of HPMC E5 cps, the film had an excellent thickness. The plasticizer glycerin showed good folding durability, elongation percentage, and tensile strength. The enhanced formulation (F_7) showed quick drug release, folding endurance, and good mouth feel in addition to strong mechanical properties. The F_7 had a quicker disintegration time of 31 sec and delivered 100% of the drug in 2 min. For the effective treatment of nausea, vomiting, emesis, and other related conditions, Formulation F_7 was helpful.

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ABBREVIATIONS

ODF: Oral Dissolving Films; **FD:** Factorial Design; **nm:** Nano Meter; **CC:** Cubic Centimetre; **mL:** Milliliter; **%CDR:** Percentage cumulative drug release; **DT:** Disintegration time; **PD2:** Percentage Drug Release after 2 Min.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Current research investigation meticulously optimizes factors/ independent variables on the response/dependent variables for the development of ondansetron oral dissolving films for the effective management of emesis, vomiting using response surface technique. Through systemic experimentation, the current research investigation identifies the composotion of HPMC E5, Primojel, directly impacting the film properties. Furthermore the investigation reveals HPMC E5 500 mg and Primojel 50 mg produced promising desired release characteristics. This strategic approach elucidates the interplay between factors in facilitating improved rates of diffusion and improved therapeutic outcomes.

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