Design and evaluation of ondansetron fast dissolving buccal Strip by Solvent casting Method

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ABSTRACT

This study's goals were to develop and enhance ondansetron fast dissolving film, which may help treat prevention of nausea and vomiting associated with emetogenic chemotherapy, post operation cancer and radiation therapy.

Materials and Methods: This film was prepared using the solvent casting method. Box Behnken design was used to optimize the impact of independent variables, including the number of polymers and active pharmaceutical ingredients (Hydroxyl propyl cellulose, starch, and Glycerin), the percentage of drug release, the disintegration time, and the film's thickness. Fourier-transform infrared spectroscopy used to drug compatibility. Equations of the results that sufficiently reflect the impact of the independent variables on the results were used to obtain the multiple regression analysis.3-D surface plots were utilized to relate the independent and dependent factors.

Results: All the formulations showed the acceptable Pre formulation and the post compression parameters Iike Physical Appearance and Weight variation, Thickness of film, surface pH, Dispersion, Folding endurance,moisture loss studies, Disintegration, Dissolution rate were found to be within specified limits.

In summary: From the data obtained from the formulation containing F3,Design of experiment it gives good response factors dependent and independent variable of Thickness of film 0.163mm,Disintergration time 18.20 sec and the Percentage drug release is of 97.98% at the end of 5min.

Key words: Ondansetron, Hydroxyl propyl cellulose, Starch, Glycerin, Solvent casting method, Box-Behnken design, stat–Ease Design software.

INTRODUCTION

The oral route of drug administration is considered the most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance, and acceptability[1].Approximately 60% of all dosage forms available are in the form of oral solid dosage forms, with tablets being the most preferred due to ease of manufacturing, transportation, and patient compliance[2].However, certain patient populations such as geriatric, pediatric, nauseous, bedridden, and noncompliant patients may experience difficulties in swallowing conventional oral dosage forms, leading to noncompliance and ineffective therapy[3].Dysphagia, or difficulty in swallowing, is a common problem associated with various medical conditions such as stroke, AIDS, thyroidectomy, Parkinson's disease, head and neck radiation therapy, and other neurological disorders, further complicating the administration of oral medications.

Table No.1: A typical composition contains the following ingredients

SI. NO	Ingredients	Concentration
1.	Drug	1-25%
2.	Water Soluble Polymer	40-50%
3.	Plasticizers	0-20%
4.	Fillers, Colours, Flavours Etc.	0-40%

AIM AND OBJECTIVES

- The aim of this study is to formulate oral films with fast dissolving of Ondansetron 8 mg
- Ondansetron, a serotonin 5-HT3 receptor antagonist, is a potent antiemetic drug that has an oral bioavailability of 60% due to hepatic first-pass metabolism and has a short half-life.

- Ondansetron is used mainly in the prevention of nausea and vomiting associated with emetogenic chemotherapy, post operation cancer and radiation therapy.
- It is also used to treat nausea and vomiting after surgery.
- The present study also aims to formulate and evaluation of ondansetron 8 mg with fast dissolving flim using Box-Behnken experimental design.
- In the present study, ondansetron films are prepared by the solvent casting method.
- Films will be subject to different evaluations such as:
    - Physical appearance and surface texture of film
    - Drug content
    - Weight Variation
    - Film thickness
    - Folding endurance
    - pH of the surface
    - Moisture loss studies
    - Dispersion test
    - Disintegration
    - In vitro dissolution studies

OBJECTIVES:

- Improved bioavailability.
- Patient compliance with treatment is improved.
- Immediately next to the action.
- Avoids first-pass hepatic metabolism.

DRUG PROFILE

Drug Name: ONDANSETRON

Molecular Formula:

C18H19N3O. HCL 2H₂O

PHYSIOCHEMICAL PROPERTIES

Mechanism of action:

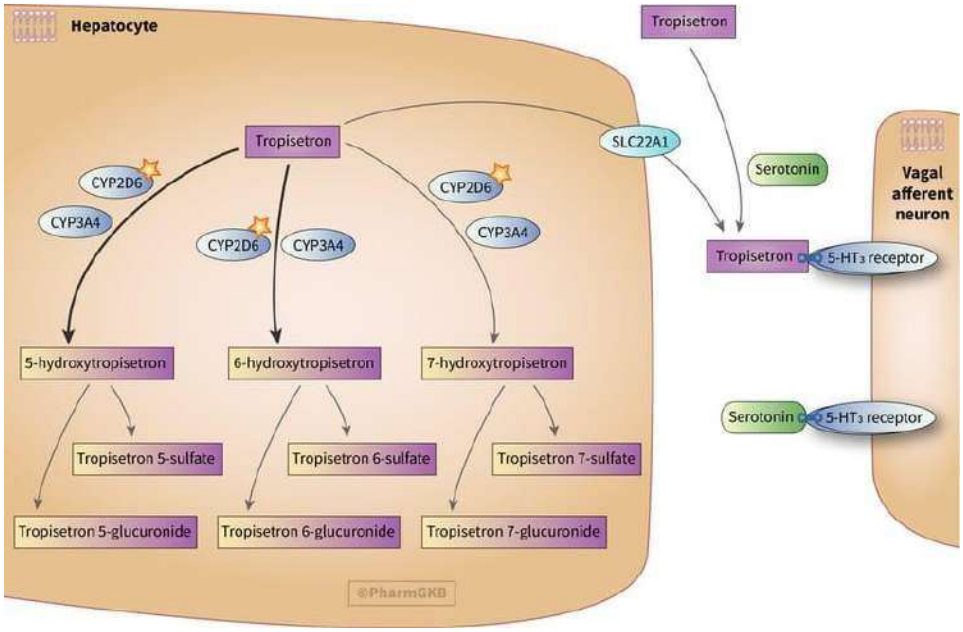


Figure 1: Mechanism of action

EXPERIMENTAL METHODS

1.1 PREFORMULATIVE STUDIES

Pre-formulation studies can be defined as a study of the physical and chemical properties of a single drug substance and when combined with excipients. Pre-formulation studies are designed to identify physicochemical properties and excipients that may influence formulation design, manufacturing method, and pharmacokinetic and biopharmaceutical properties of the resulting product. This is the first step in the rational development of dosage forms. Pre-formulation studies are needed to formulate the drug into a stable, safe and effective dosage form.

1.1.1 ORGANOLEPTIC PROPERTIES OF THE MEDICINAL PRODUCT

The ondansetron sample was evaluated for its organoleptic properties such as colour, odour and appearance

1.1.2 SOLUBILITY DETERMINATION

Drug solubility was determined by adding approximately 5 mg of ondansetron to 10 mL of various solvents and sonicated for 10 min and visually checked for solubility and compared to the standard.

1.1.3 DETERMINATION OF THE MELTINHG POINT

The melting point of pure ondansetron was determined by an open capillary method. The capillary was sealed at one end with fusion and filled with ondansetron by repeated tapping. The capillary tube was placed in a melting point apparatus. The temperature is set to automatically increase the temperature. An increase in temperature was observed.

1.2 CONSTRUCTION OF THE STANDARD CALIBRATION CURVE FOR ONDANSÉTRON

1.2.1 Determination of λmax ondansetron

Ondansetron solution containing a concentration of 10 µg/ml was prepared with phosphate buffer pH 6.8 and the UV spectrum was obtained with a SHIMADZU spectrophotometer. The solution was scanned in the range from 200 to 300. The maximum absorbance was found at 253 nm.

The ondansetron standard calibration curve was prepared by dissolving 100 mg of accurately weighed ondansetron in a 100 ml volumetric flask and the volume was made up to 100 ml with phosphate buffer solution pH 6.8 to obtain a stock solution of 1000 µg/ml. From this stock solution, 10 ml was taken and diluted with 100 ml with phosphate buffer solution pH 6.8 to obtain a solution of 100 µg/ml. Different aliquots of ondansetron ranging from 0.2 to 1 ml were pipetted into different 10 ml volumetric flasks and the volumes were made up to 10 ml with 6.8 phosphate buffer to obtain a concentration of 2, 4, 6, 8, 10 µg. /ml. The absorbance of these drug solutions was measured at 253 nm. The calibration curve is plotted as concentration vs absorbance

DRUD -EXCIPIENT COMPATIBILITY STUDIES

Before formulating a drug substance into a dosage form, it is essential that it be chemically and physically compatible. Compatibility studies provide the necessary information to determine the nature of the drug substance and provide a framework for combining the drug with pharmaceutical excipients in the manufacture of a dosage form

One of the requirements for choosing suitable excipients or carriers for pharmaceutical formulation is their compatibility. Therefore, in the present work, a study was carried out using an infrared spectrophotometer to determine if there is a possible chemical interaction between the drug and the excipients.

Weigh 3mg drug was mixed with 100 mg of potassium bromide (dried at 40-50°C). The mixture was taken and compressed under a pressure of 10 tons in a hydraulic press to form a transparent pellet. The pellet is scanned at 4000-400 cm in an IR spectrophotometer. FT-IR peak correspondence

The FT-IR spectrum matching

Approach of the FT-IR data was used to reveal the chemical interaction between the drug and the selected polymers. The chemical interaction between the drug and the polymer can be identified by changes in the peak (characteristic wave numbers). A physical mixture of polymeric drug and drug and polymer was prepared and mixed separately with an appropriate amount of potassium bromide. About 100 mg of this sample was compressed to form a transparent pellet in a hydraulic press at a pressure of 15 tons. It is scanned at 4000-400 / cm. FT-IR spectra of the drug curve. The polymer and drug formulation were compared to detect any appearance or disappearance of peaks

1.3 FILM FORMULATION OF ONDANSETRON FAST DISSOLVING ORAL FLIM

1.3.1 Dose Calculation for Ondansetron Fast Dissolving Oral Films

The dose chosen for development is 8 mg. Ondansetron contains hydrochloride dihydrate of which each 10 mg contains 8 mg of Ondansetron equivalent. A film diameter of 1.5 cm was chosen for a single dose. Based on the surface area of the Petri plate, the required amount of medication for each batch was calculated. From the preliminary physical observation of the placebo prepared to

optimize the concentration and composition of the polymer films, the best compositions were used for the inclusion of Ondansetron. HPC and starch were dissolved in water with constant stirring. The calculated amount of ondansetron was dissolved in the polymer solution. After the drug was completely dissolved, sorbitol, orange booster and glycerin (plasticizer) were added and stirred to form a homogeneous solution. The solution is poured into a petri dish and then kept in a hot air oven at 50°C for 45 minutes. Further drying was calculated using a vacuum oven at 19°C applying vacuum. The film thus formed was cut into pieces with a diameter of 1.5 cm.

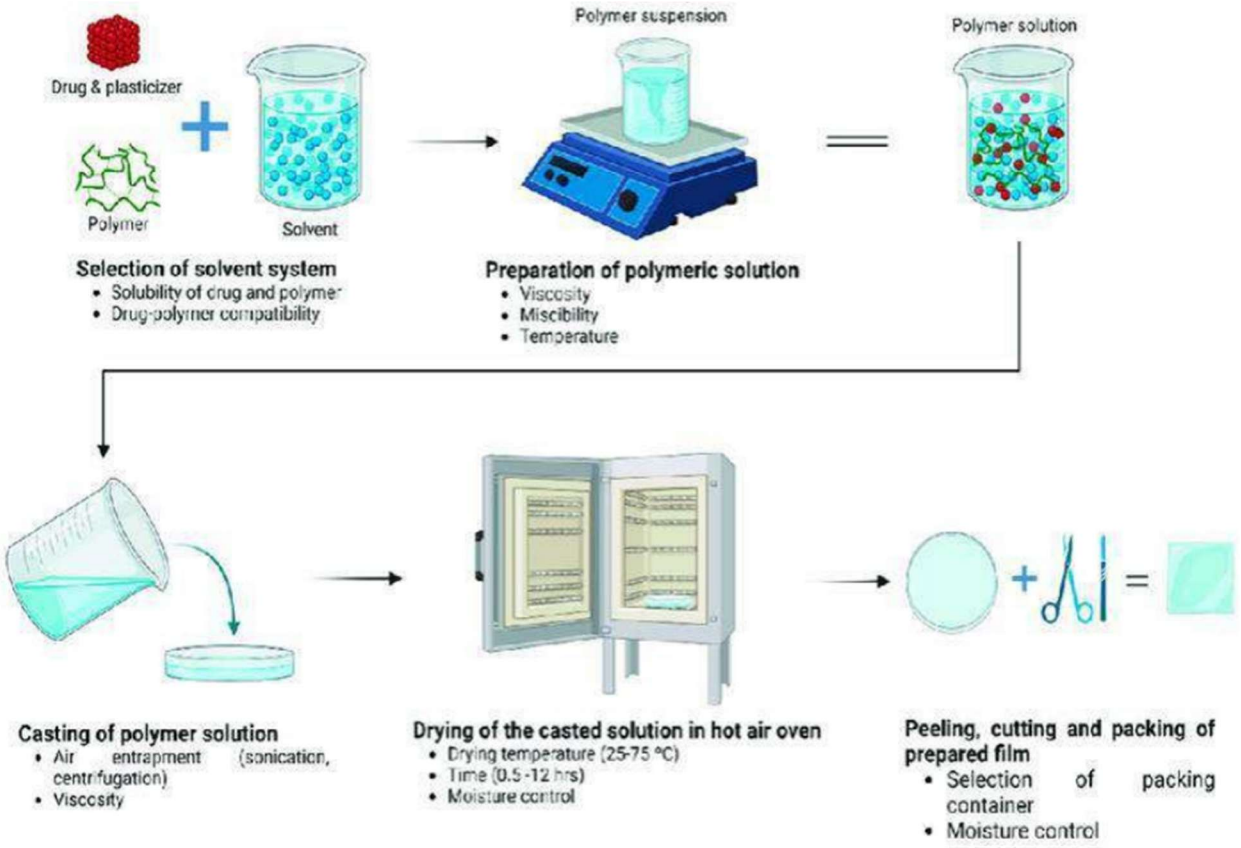


Figure No:2: Solvent Casting Method for preparation of film at Laboratory

1.4 DESIGN EXPERIMENTAL (DOE)

Response Surface Methodology is used to design and develop Ondansetron fast dissolving oral films. Computional design strategy by Box-Behnken design performed with three factors Hydroxy propyl cellulose, Starch and glycerin.The effect of dependent variables on the response, Thickness, Disintegration Time, Drug Release were studied to select the optimal formulation.

FORMULATION TABLE FOR ONDASTERON FAST DIISOLVING ORAL FILMSCHARACTERIZATION OF FILMS

1.4.1 Physical appearance and surface texture of films

These parameters were checked simply with visual infection of films and by feel or touch. The observation suggests that the films are having smooth surface and they are elegant enough to see.

1.4.2 Weight variation

Each film was weighed individually on electronic balance and average weight of three films was found. It is desirable that films should have nearly constant weight. It is useful to ensure that a film contains the proper amount of excipients and API.

1.4.3 Thickness

By using Digital vernier Calipers the thickness of the film was measured at five different places: an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

1.4.4 Folding endurance

Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking is computed as the folding endurance value.

1.4.5 Drug content

Drug content for all batches were determined by UV Spectrophotometric method. For this 2-2cm strip from each batch was cut and dissolved in 50 ml of phosphate buffer pH 6.8. The solution was filtered through Whatman filter paper and diluted by pipetting I ml of this solution to a 25ml volumetric flask with phosphate buffer pH 6.8. The resulting solution was measured spectrometrically at 253nm by using a Shimadzu spectrophotometer. Limit of content uniformity is 85-115%.

1.4.6 Surface pH

The film to be tested was placed in a Petri dish and was moistened with Iml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

1.4.7 Dispersion test

A film equivalent of 8 mg of Ondansetron was placed in 200ml of 6.8 pH phosphate buffer and was stirred for 3 min. Then the resulting solution was passed through sieve number 22. No residue was left hence the film passed the dispersion test.

1.4.8 Moisture loss studies

The percentage moisture loss study was carried out to check the physical stability and integrity of the films. In the present study the moisture loss capacity of the film was determined by placing de known weight and predetermined by placing size of the film in a desiccator containing hydrous calcium chloride for three days. The films were removed and reweight and the percentage moisture loss of the film was measured by using the following formula

Percentage moisture loss = initial weight-final weight/ final weight – 100

1.4.9 In vitro disintegration test

When a film starts to break or disintegrate it is called as disintegration time. The disintegration test for fast mouth dissolving film was carried out using single unit disintegration apparatus containing 900 ml of 6.8 phosphate buffer. The temperature was setted to 37.5±0.5°C. After reaching, the temperature film is placed on disintegration apparatus time required to start breaking is noted as disintegration time of particular film.

1.4.10 In vitro dissolution study

In vitro dissolution of fast dissolving film was studied in USP paddle dissolution test apparatus using 300 ml phosphate buffer at pH 6.8 as the dissolution medium. The temperature was maintained at 37±0.5°C and 100 rpm throughout the experiment. Iml sample was withdrawn for 30 sec and the same quantity was replaced with phosphate buffer of pH 6.8. The percentage of drug released was determined using UV visible spectrophotometer.

Table No.2: In vitro dissolution studies

APPARATUS	USP Dissolution apparatus type II
Dissolution Medium	Phosphate buffer pH (6.8)
Temperature	37±0.5 C
RPM	100 rpm
Vol. withdrawn and replaced	1 ml every 30 sec
λ max	253 nm
Blank solution	Phosphate buffer pH 6.8
Duration of Study	5 min
Volume of dissolution media	300 ml

1. RESULTS AND DISCUSSION

1.1 PREFORMULATION STUDIES

1.1.1 ORGANOLEPTIC PROPERTIES OF DRUG

The drug was identified based on the organoleptic properties. Ondansetron is an odourless, white to off white amorphous powder.

1.1.2 SOLUBILITY OF DRUG

Ondansetron was freely soluble in 0.1N Hcl, methanol and phosphate buffer pH 6.8. Sparingly soluble in ethanol. Slightly soluble in water.

1.1.3 MELTING POINT OF DRUG

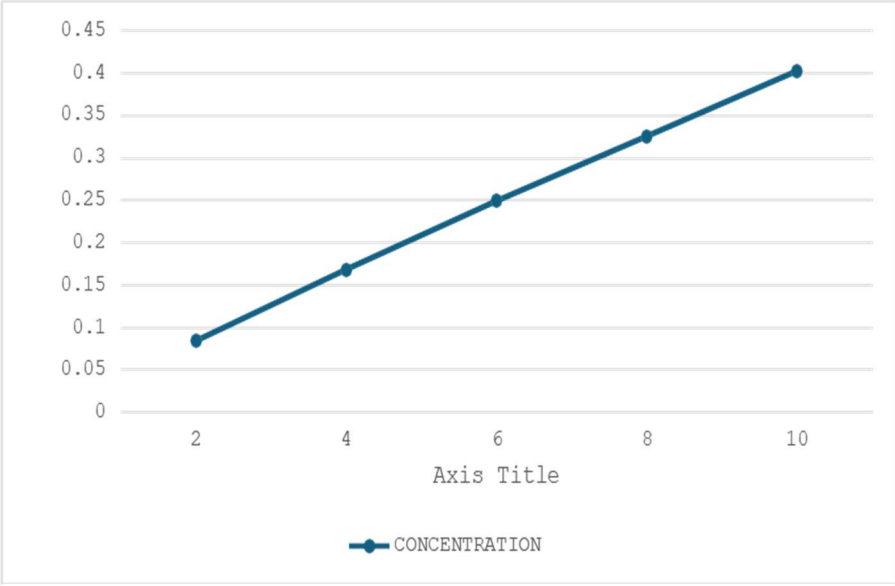
The melting point of the Ondansetron was found to be 231°C. The normal range of the melting point of Ondansetron is 231-232°C, which shows that the melting point of the drug was lying between the ranges. The melting point indicates the purity of the drug.

1.2 STANDARD CALIBRATION CURVE OF ONDANSETRON

For the preparation of the calibration curve samples were prepared from a stock solution (2, 4, 6. 8, 10 µg/ml). The absorbance of the samples was taken at 253 nm.

Table No.3: Absorbance data for calibration curve of Ondansetron

CONTCENTRATION (µg/ml)	ABSORBANCE (253)
2	0.084
4	0.169
6	0.249
8	0.327
10	0.402



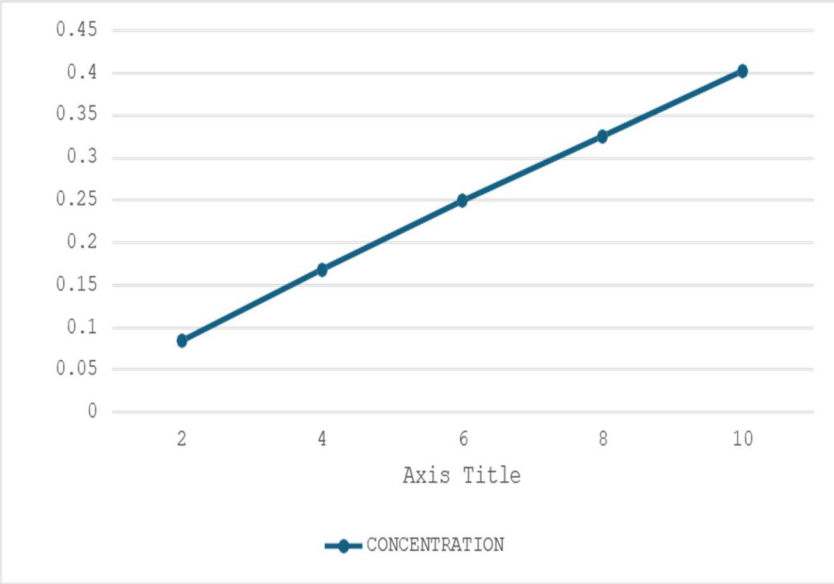


Figure No.3: Calibration curve of Ondansetron

Table No.4: Statistical data for calibration curve

SI. No	Parameters	Valve
1.	λmax(nm)	253
2.	Beer law limits	2-10
3.	Slope	0.040
4.	R2	0.999

1.1 DRUG-EXCIPIENTS COMPATIBILITY STUDIES

1.1.1 FTIR STUDY OF DRUG

Table No.5: FTIR spectrum of Ondansetron

Material	**Test wave number (cm^{-1})**	**Functional group**
Ondansetron	3403.57	N-H stretching
	2658.41	S-H stretching
	1635.09	C=H stretching
	1386.73	C-O stretching
	1280.69	S=O stretching
	1200.66 1107.94	C=S stretching
	780.45	C-H stretching

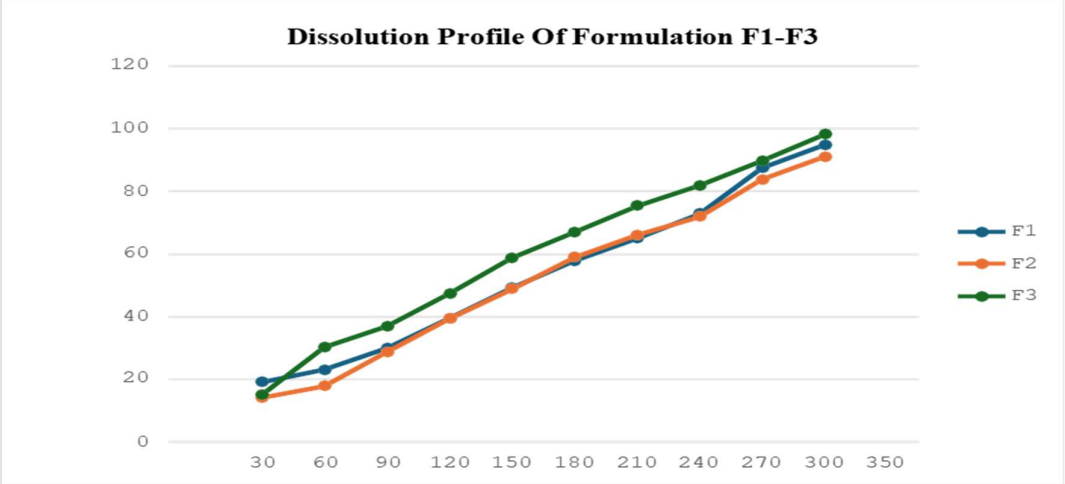


Figure No:4: In-vitro dissolution profile of ondansetron (F1-F3)

Table No.6: Determination of In-vitro dissolution study of different of the formulation of Ondansetron fast dissolving films (F4-F6)

Time (sec)	F4	F5	F6
30	14.49	13.60	13.91
60	18.90	19.78	17.01
90	29.56	28.55	28.48
120	37.38	39.65	39.67
150	45.32	45.53	48.76
180	58.65	59.48	58.32
210	66.72	66.87	65.24
240	73.84	75.28	78.24

270	79.89	86.46	83.89
300	86.92	95.76	90.15

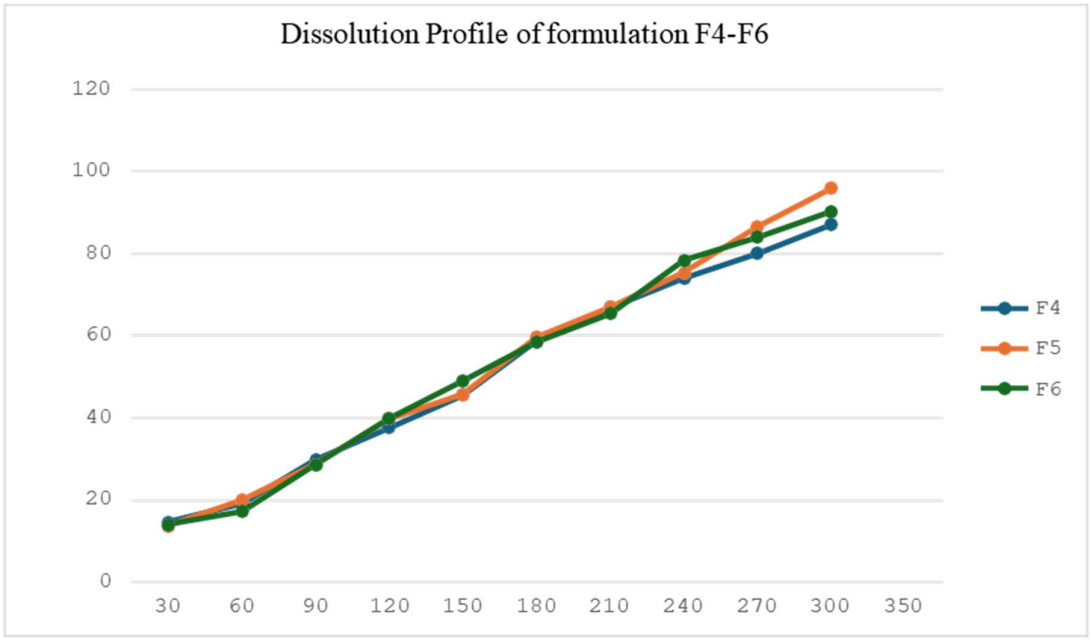


Figure No:5: In-vitro dissolution profile of ondansetron (F4-F6)

Table No.7: Determination of In-vitro dissolution study of different of the formulation of Ondansetron fast dissolving films (F7-F9)

Time (sec)	**F7**	**F8**	**F9**
30	21.78	15.94	13.56
60	31.66	26.22	16.76
90	44.58	35.41	24.54
120	52.31	47.81	33.67
150	65.87	55.56	37.68
180	73.95	64.21	45.54
210	79.70	71.29	58.65
240	84.28	78.45	69.22

270	91.39	87.46	79.33
300	96.38	94.66	88.59

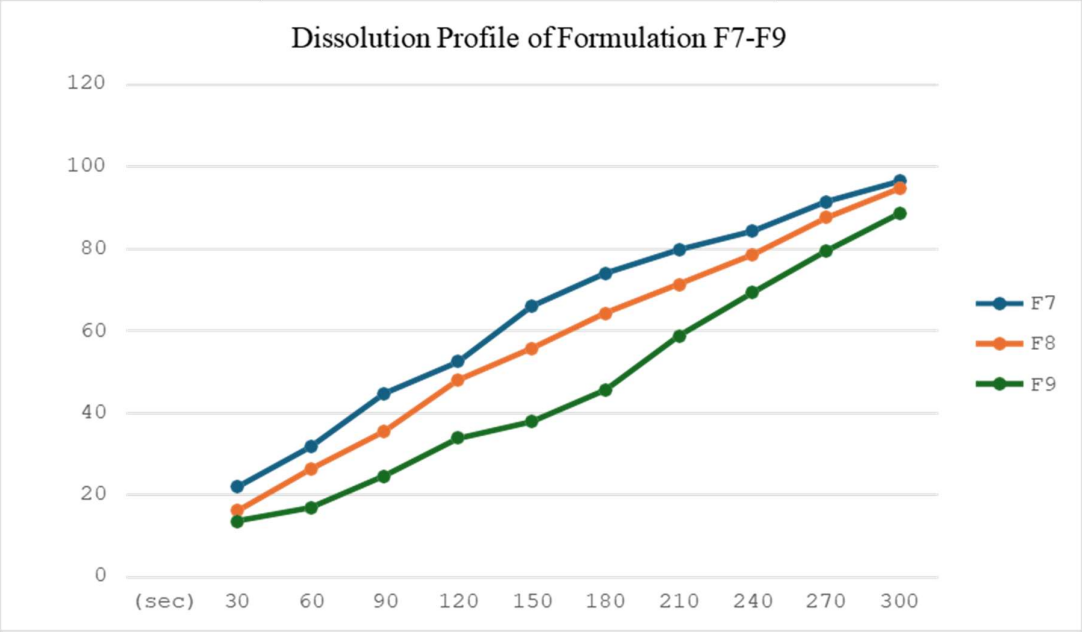


Figure No:6: In-vitro dissolution profile of ondansetron (F7-F9)

All the films were evaluated for their Drug release. The drug release estimation data for all the formulations were found to be 86.92% to 97.98% and the results was found to be within the limits. The drug release increases with the decrease in the concentration of polymer. Based on the dissolution studies formulation F3 were found to be promising and showed a drug release profile 97.98% respectively, when compared to the other formulations. The prepared films of all the formulations were evaluated and results shown in Table NO.23.

1.1 OPTIMIZATION OF ONDANSTERON FAST DISSOLING ORAL FILMS

In the present study, response surface methodology with version 13 of Stat-Ease Design Expert software was used to prepare fast-dissolving oral films of

ondansetron. The Box-Behnken design is used to study the key formulation variables for the experimental design that affect the responses Thickness (Y1), Dissolution Time (Y2), Drug Release (Y3). The experimental study was carried out to investigate the effect of Hydroxyl propyl cellulose, Starch and glycerin on the above responses. According to the Box-Behnken model, a total of 9 formulations were prepared in a 3-factor, 3-response group with 5 focal points.

Table 8:

EXPERIMENT	DESIGN FACTORS			RESPONSES		
	A %	B %	C %	Thickness (mm)	Disintegration Time (sec)	Drug Release (%)
F1	35	27.5	15	0.236	25.12	94.67
F2	35	40	20	0.273	31.15	90.89
F3	20	27.5	20	0.163	18.20	97.98
F4	50	40	15	0.321	43.20	86.92
F5	20	40	15	0.213	23.42	95.76
F6	35	40	10	0.271	31.09	90.15
F7	35	15	10	0.193	21.22	96.38
F8	35	27.5	15	0.236	25.12	94.66
F9	50	27.5	20	0.292	37.39	88.59

1.1 STUDY OF EFFECTS OFFORMULATION FACTORS (X1,X2,X3) ON RESPONSES (Y1,Y2,Y3)

The different formulations of the experimental test and the observed responses are shown in table no. 32. The results clearly show that all response variables are highly dependent on the chosen formulation variables (independent variables) showing a large variation between the 9 groups.he three-dimensional response surface generated by the software and the corresponding two-dimensional contours illustrate the effects of independent factors on the responses studied. Response surface plots as a function of two independent factors at the same time are useful for studying their main effects and interactions at the same time.

EFFECT OF PROCESS VARIABLE ON THICKNESS

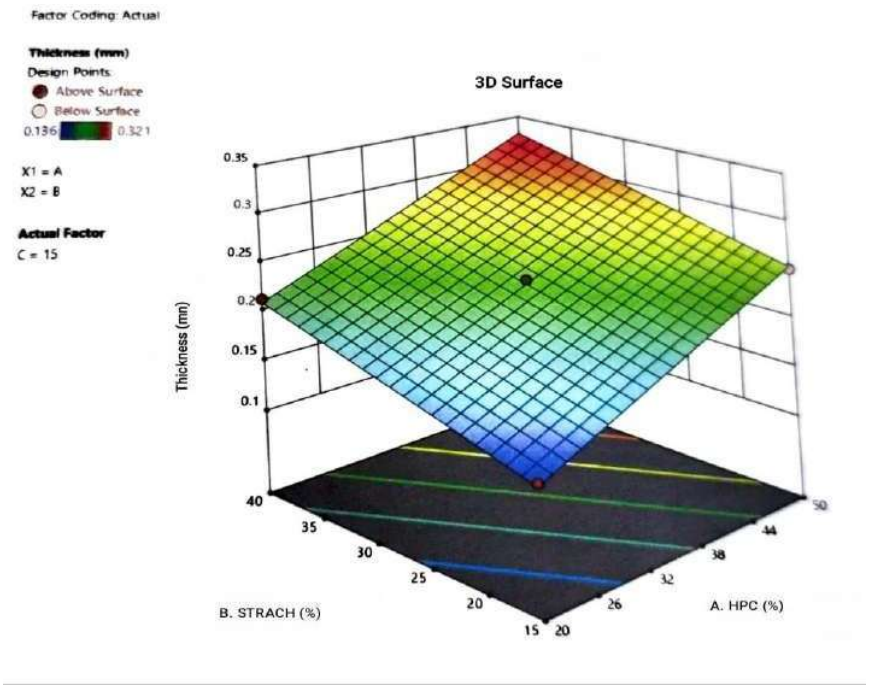


Figure No:7: RSM Plot for Thickness

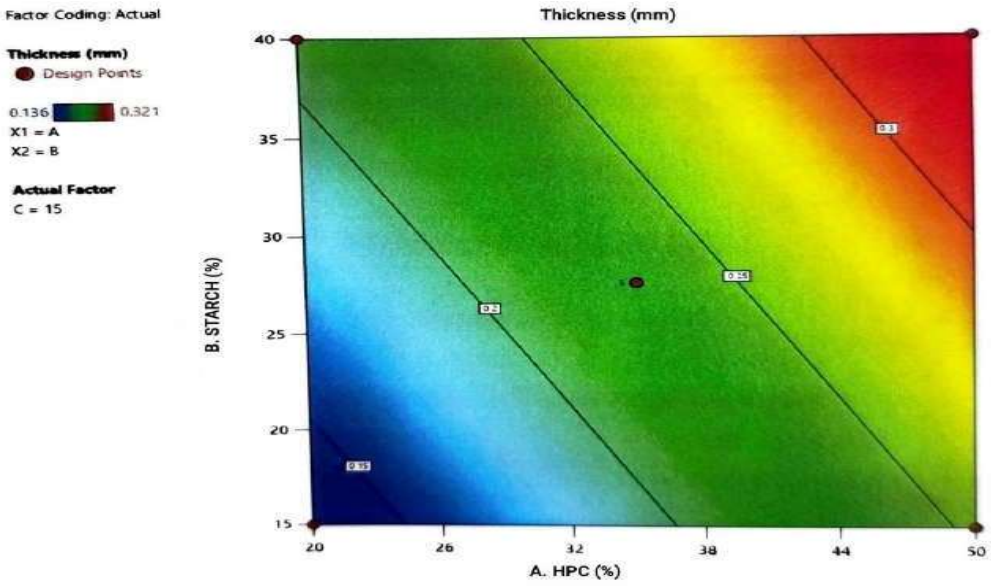


Figure No:7: Contour Plot For Thickness

1.1.1 EFFECTS OF PROCESS VARIABLE ON DISINTEGRATION TIME

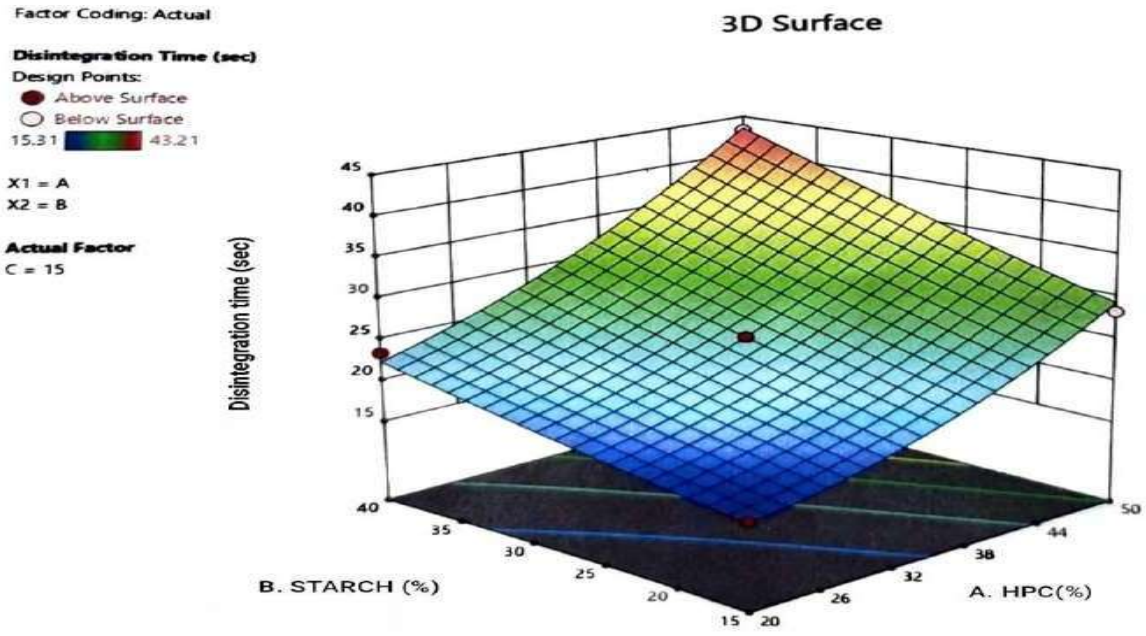


Figure No:8: RSM Plot for Disintegration Time

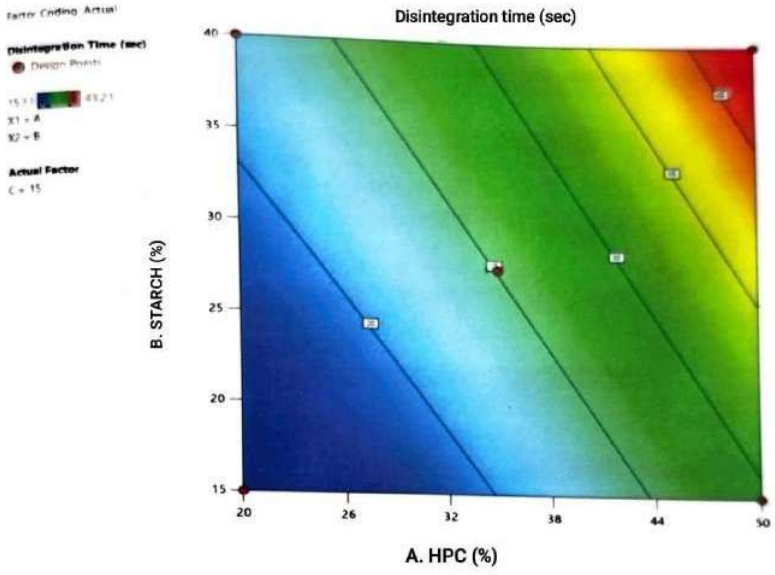


Figure No:9: Coutour Plot for disintegration Time

1.1.1 EFFECT OF PROCESSVARIABLE ON IN VITRO DRUG RELEASE

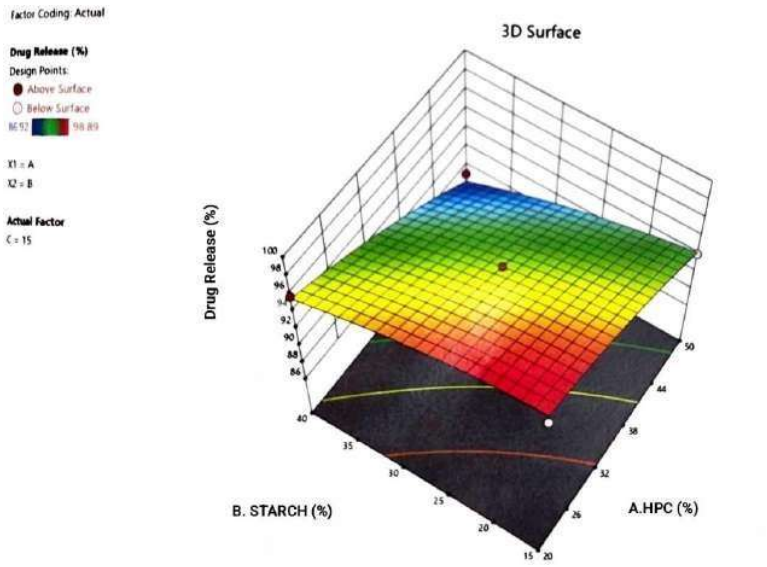


Figure No:10: RSM Plot for In-vitro drug release

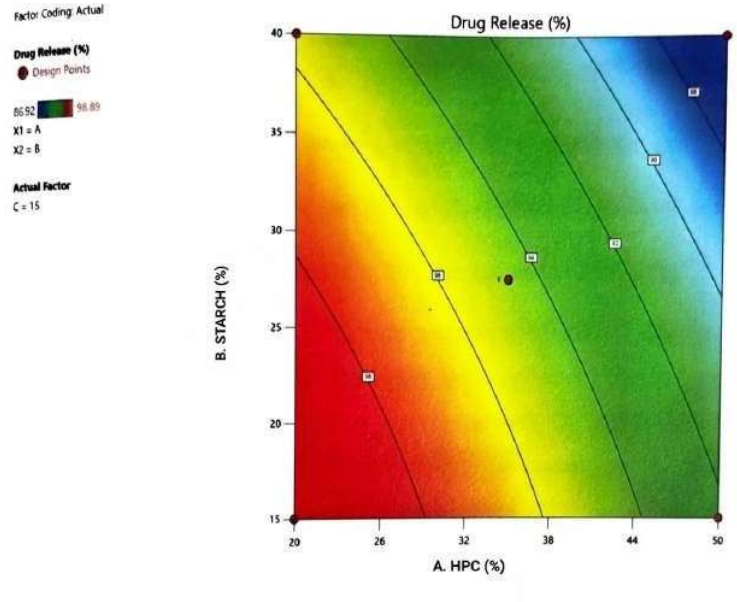


Figure No:11: Contour plot for In-vitro release

STABILITY STUDIES:

The best formulations, F3, were chosen for three-month stability experiments at 25ºC/60% RH and 45ºC/75% RH based on the outcomes of in-vitro drug release. The methodology outlined in section four was followed for conducting the stability studies. Physical appearance, weight variation, drug content, and in-vitro drug release were all assessed for the chosen formulations Physical appearance, Moisture loss studies, Dissolution, Drug content, and Disintegration time did not significantly alter throughout the course of the trial, according to the data. Stability tests conducted after three months showed no appreciable drug degradation. The resulting compositions were stable chemically and physically.

TEST INTERVAL	Initial	1st MONTH	2nd MONTHS	3rd MONTHS
Description	White, Smooth, Uniform and flexible	White, Smooth, Uniform and flexible	White, Smooth, Uniform and flexible	White, Smooth, Uniform and flexible
Weight Variation (mg)	66.62 mg	66.65mg	66.69mg	66.70mg

Moisture loss studies (%)	1.13	1.15	1.15	1.16
Disintegration (Sec)	18.20 sec	18.36 sec	18.45sec	18.49sec
Dissolution (%)	97.98	97.92%	97.90%	97.88%
Drug content (%)	99.55	99.52 %	99.50%	99.48%

Table No:9: Stability Studies for formulation F3

SUMMARY AND CONCLUSIONS

Oral films are beginning to gain popularity and acceptance as a new drug delivery system due to patient compliance. A fast-dissolving oral dosage form, usually about the size of a postage stamp, that dissolves or rapidly dissolves in the oral cavity, resulting in a solution or suspension without the need for drug administration.

Typically, geriatric, paediatric, nauseated, bedridden, and noncompliant patients have difficulty swallowing conventional oral dosage forms and do not take their medications as prescribed. The fast-dissolving oral dosage form is suitable for geriatric patients and bedridden patients who do not wish to take a strong dosage form.

The fast-dissolving films are easy to administer and allow an immediate start of the drug action, because the films are taken sublingually. Since the sublingual mucosa is relatively permeable and, due to its thin membrane, the rapid absorption of the drug with high perfusion and immediate availability is possible, which leads to the rapid onset of the drug's action. Since the drug is absorbed directly into the systemic circulation, the degradation in the gastrointestinal tract (GI) and the effect of the first step can be avoided. These points make this formulation very popular and acceptable among paediatric and geriatric patients and patients who fear choking.

Initial testing of polymers and plasticizers was performed with placebo to optimize the concentration of polymers and plasticizers. Fast-dissolving oral films of Ondansetron have been successfully formulated using the solvent casting method with hydroxypropyl cellulose and starch. Glycerin is used as a plasticizer to improve mechanical properties. Sorbitol and orange enhancer were used to improve the taste of the films.

All formulations are rated for. Physical appearance, weight change, thickness, drug content, moisture loss studies, dispersion test, folding stability, surface pH, dissolution time and in vitro dissolution studies.

Compatibility studies with Fourier transform infrared spectroscopy (FTIR) showed that there was no significant interaction between the drug and the excipients used.

The standard calibration curve for ondansetron was studied using a pH 6.8 buffer. It was found at 253 nm. The linearity was found y -0.040x and the R^2 value was indicated as 0.999 respectively. All films were evaluated for physical appearance and found to be white, smooth, uniform and flexible. The weight depends on the concentration of the polymer. The weight variation was found from 64.65mg to 68.37 mg .In all cases, The calculated standard deviation values are very low, suggesting that the prepared films were uniform in weight. The bending strength of all the formulations was measured by hand and found to be 254 to 356. It exhibits good flexibility. The flexural strength results show that the film does not break.

The thickness increases with the increase in polymer concentration. The thickness was found to be

0.163 ± 0.03 mm to 0.321± 0.01 mm and the results were found to be within the limits. The drug content evaluation data for all the formulations were found to be 97.37 ± 0.26 to 99.55 ± 0.18. The drug content was uniform in all film formulations, indicating uniform drug distribution. The surface pH of all films was found to be neutral. The films passed the dispersion test and no residue remained. The moisture loss of the films was found to be from 1.13 ± 0.01 to 2.74 ± 0.01. Less moisture loss in the formulations helps the films remain stable, brittle and not completely dry.

The dissolution time Increases with increasing polymer concentration. The disintegration time of all formulations was found to be from 18.20 ± 1.20s to 43.20 ± 1.25s. The drug release evaluation data for all the formulations were found from 86.92% to 98.89% and the results were found within the limits. Drug release increases with decreasing polymer concentration.

The results of the investigation revealed that the combination of two or more polymers at the appropriate levels can result in a fast dissolving film with improved characteristics compared to the mono polymer film. Some limitations such as high disintegration time, low folding stability, poor appearance, etc. can be improved by formulating multipolymer films compared to the corresponding mono polymer films.

Based on the evaluation parameters, formulation F3 showed optimal performance compared to other formulations, therefore formulation F3 was selected. Based on the encouraging results, fast dissolving ondansetron films can be considered suitable for clinical use where a more rapid onset of action for a dosage form is desired and ease of administration. The preparation method has become simple and requires a minimum of excipients, which makes the product cost-effective.

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