ORIGINAL ARTICLE

Fabrication, Development and Optimization of Mouth Dissolving Film of Ondansetron HCl by Natural Film Former

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Abstract

Aim: This study aimed to develop a mouth dissolving film of Ondansetron HCl. **Materials and Methods:** Solvent casting method is used, and various film forming polymers such as dried *cassia tora gum, konjac gum*, and PVP K30 in various concentrations were evaluated. The effect of independent factors, such as dried *cassia tora gum, konjac gum*, and PVP K 30 concentrations, on two dependent variables, such as disintegration time and percentage drug content, was examined using the 3^3 factorial design. The optimized formulation was identified based on a disintegration time of 5–30 s and a drug release exceeding 85%. Batches F5, F8, F-14, F20, F24, and F25 of the formulation show promising results. **Results:** As a result, each of these formulation batches were considered as optimized formulations and processes for *in vitro* dissolution testing. Batch F25 has a rapid disintegration time of 18.50 s and also the % drug release of 96.10% within 120 s. It contains 1% *cassia tora gum,* 1% *konjac gum*, and 1% PVP K30. **Conclusion:** From the results of this study, it can be interpreted that mouth-dissolving films of Ondansetron hydrochloride are feasible to prepare, provide quick onset of action, and have improved oral bioavailability using natural polymers.

Key words: Antiemetic, factorial design, Mouth dissolving film, natural film formers, solvent casting

INTRODUCTION

The oral route of administration is the preferred method for administering medications due to its low cost, simplicity, and high rate of patient compliance. However, the oral route seems to have some limitations such as hepatic first pass metabolism and degradation by gastrointestinal enzymes. Tablets and capsules are hard to swallow for some patients, particularly children and the elderly. Such patents are difficult to take in solid oral dosage forms.[1] In the 1970s, quick disintegrating mouth dissolving films (MDFs) were invented as a replacement to tablets and capsules for pediatric and geriatric patients. Mouth dissolving film is a new drug delivery system that was developed based on existing transdermal patch technology. Multiple approaches have been explored to deliver drug via transdermal routes to release the therapeutic agent to the particular location where it acts.[2]

Mouth dissolving oral films are a type of dosage form that are made with water soluble polymers that help the film hydrate more quickly in saliva, stick to the mucosal surface, and disintegrate in only a few seconds. This bypasses the hepatic first pass metabolism and increases the drug's bioavailability.[3]

Vomiting is a reflex action that expels gastric contents through the mouth, often triggered by motion sickness or chemotherapy-induced nausea.[3] Patients receiving chemotherapy often experience nausea and vomiting as a result of the treatment medications' potential for an adverse reaction.[4]

Ondansetron hydrochloride is a potent antiemetic drug that belongs to the 5HT3 receptor antagonist class. It is employed to relieve nausea and vomiting caused on by chemotherapy. Ondansetron hydrochloride has been shown to significantly delay the onset of nausea in cisplatin patients.[5] It is marketed in the form of standard tablets, but due to hepatic first pass metabolism, it has a poor bioavailability of 60% as well as

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a short plasma half-life of 3–5 h, requiring repeated dosing, which could cause side effects such as headaches, constipation, or diarrhea.[6] Mouth dissolving film is the best alternative dosage form for reducing dose frequency and bypassing hepatic first pass metabolism. The development of a mouth-dissolving film of Ondansetron hydrochloride was the aim of this investigation. The drug reaches the systemic circulation immediately after going through hepatic first pass metabolism, which is how the MDF works. Rapid absorption from highly vascularized oral mucosa, avoidance of first pass metabolism, increased medication efficacy, and ultimately enhanced patient compliance are only a few benefits of Ondansetron hydrochloride MDF. In this research investigation, the formulation parameters were optimized using factorial design software. All three variables were examined at three levels, −1, 0 and +1, using a 3^3 factorial design. After analysis, we have 27 different combinations. Response variables included disintegration time and drug content percentage.[7] The film was made using the solvent casting process, and its parameters including color, opacity, surface texture, pH of film surface, folding endurance, stiffness, rate of disintegration, percentage of drug content, and *in vitro* release of drugs were all examined.

Excipient properties

Konjac gum powder

Konjac (Lasioideaeamorphophallus) tubers, which are mostly farmed across Far East as well as Southeast Asia, are utilized to make *konjac gum*. It is a hetero-polysaccharide with both a glucose to mannose ratio of 1–3. It is made up of -D glucose and -D- mannose. As a result, it is known as a *glucomannan*. If heated, *Konjacglucomannan* dissolves quickly in an aqueous solution as well as being water-soluble under high shear.

Konjacglucomannan solutions become viscous as the concentration rises; they are remarkably stable in the presence of high salt concentrations but extremely sensitive to pH. Systems with lower pH have a negative impact on viscosity. Combined effects as create thermally reversible gels, *konjac* can cross-link with a variety of different polysaccharides, such as xanthan, carrageenan, and agar. While adding salt can prevent the production of the synergistic gel, adding sugar can increase the strength of the gel. This allows for control of the gel-forming ability.

In addition to controlling phase separation, imparting and controlling viscosity, improving spreadability, and extending shelf life, *konjac gum* provides a pleasant mouthfeel. Creates a reversible or non-thermo-non-reversible gel and, depending on the condition it has excellent water binding properties.

Cassia tora gumpowder

The two very similar-looking seeds, *Cassia tora* and *Obtusifolia*, are widely farmed throughout India. Native Americans gather *Cassia Tora/Obtusifolia* seeds, which are then processed by the industry to make *Cassia* splits, which are then utilised to make the powder.

About 75% of *cassia gum* is made up of polysaccharides, predominantly a linear chain of 1,4-D-mannopyranose units connected by 1,6-D-galactopyranose units. About a 5:1 ratio exists between mannose and galactose.

Characteristics

- Easy dispersion and viscosity with the increasing temperature.
- Exponential increase in viscosity with anincrease in concentration.
- Neutral Polysaccharide that is mostly not affected by the presence of other electrolytes.
- Good stability at a wide range of pH but unstable in a very strong acid ambient
- High stability in retorted processes.
- Good freeze thaw stability
- Interactivity with other hydro-colloids (carrageenan, xanthan gum and agar-agar). This can lead to a synergy and have a considerable effect on the consistency and elasticity with an improvement in stability when freezing/melting and provide a better resistance to gelatinization as well.

PVP K30

The pharmaceutical industry uses povidone, also known as polyvinylpyrrolidone, or PVP, as a synthetic polymer carrier for suspending and spreading medications. It can be used in many different ways, such as an adhesive for transdermal systems, a film-forming agent for ophthalmic solutions, a binder for tablets and capsules, and a flavoring agent for liquid and chewable tablets.

Povidone K30, whose chemical formula is (C6H9NO)n, is a white to slightly off-white powder. Povidone formulations are widely used in the pharmaceutical sector due to their ability to dissolve in both water-based and oil-based solvents. The k number represents the molecular weight of the povidone. Povidone with greater K-values (i.e., k90) are not typically injected due to their large molecular weights. Higher molecular weights result in the body's accumulation and prevent renal clearance.

MATERIAL AND METHODS

Materials

Ondansetron hydrochloride drug sample was purchased from SD chemicals, Nashik, *Konjacgum*powder and *cassia tora gum*powder were purchased from Amazon online shopping

site. PVP K30 purchased from SD chemicals, Nashik. Citric acid and other chemicals were purchased from SD chemicals, Nashik. All reagents were of analytical grade.

Pre-formulation studies

For identification and purity of drug melting point of drug was carried out and verified with reported reference.

Determination of λ max of drug carried out in distilled water, pH 6.8 buffers and pH 1.2 buffers, and observed λ max was recorded.

Calibration curve was carried by making different concentration of drug in pH 1.2 buffer solutions and analyzed in Ultraviolet (UV)-spectrophotometer (Jasco V-730) at 266 nm.

The compatibility in between drug and excipient compatibility was determined using FTIR spectroscopy analysis (Jasco FT/IR 4600) by ATR method in which drug and excipient sample directly place over ATR probe and sample were analyzed by scanning range of 500–4000 cm^{-1}.

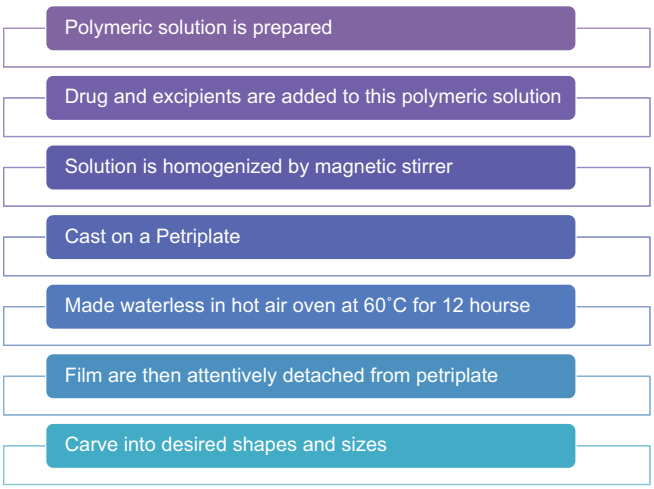
Mouth dissolving film formulation and development

The solvent casting approach has been shown to be the most reliable and advantageous method for the creation of an ondansetron hydrochloride MDF. The polymeric solution was made by measuring out how many polymers to dissolve in 20 mL of distilled water and whisking constantly until a clear liquid was formed. The drug, sweetener, and citric acid were then added in a calculated amount while this mixture was being constantly agitated on a magnetic stirrer. After that, the finished mixture was put into a Petri plate and dried in a hot air oven set at 60°C for 12 h. Subsequently, the film was meticulously extracted from the petriplate, examined for imperfections, and then chopped to the necessary dimensions (2×2 cm^2).

The graphical process of solvent casting and prepared films are shown in Figure 1.

Experimental design by full factorial

The MDF for Ondansetron hydrochloride was optimized using a 3^3 factorial design (Design expert 13). Furthermore, they investigated the effect of *cassia tora gum, konjac gum*, and PVP K30 concentrations on the physical and chemical test parameters of formulated MDFs. As independent variables, the amounts or concentrations of *cassia tora gum*factor 1, *konjacgum* factor 2, and PVP K 30 factor 3 were used. All three factors were tested at three different levels: −1, 0, +1, or 1%, 1.5%, and 2% w/v, respectively. Table 1 shows a 3^3 factorial design with 27 different combinations. Response



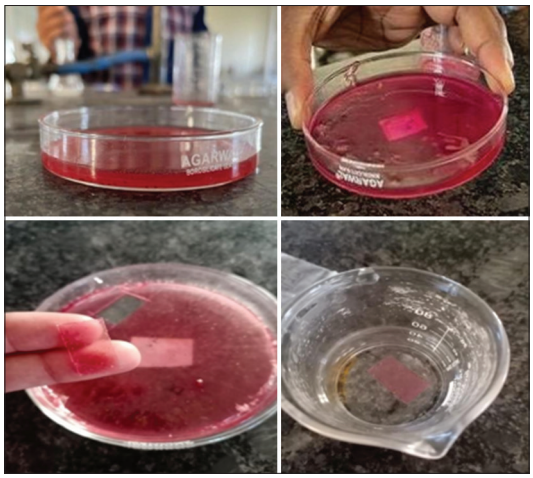


Figure 1: Graphical representation of solvent casting method

variables included disintegration time and percentage drug content.[7]

Calculation of dose of drug in each film

The dose of Ondansetron hydrochloride drug is 4 mg and in 2 cm diameter of film the quantity of drug is 4 mg. the following formula help in calculation of quantity of drug added in film.

$$\text{Drug to be added in each film} = \frac{\text{Dose of Drug per film} \times \text{Area of Petriplate}}{\text{Area of one Film}}$$

Here,

(1) Because the area of the petriplate is 9 cm^2, the diameter is 63.64 cm^2.
(2) A 2 cm film area results in a 4 cm^2 diameter.
(3) The quantity of drug which is to be present in 4 cm^2 of prepared film is 4 mg.
(4) The quantity of drug present in a 63.64 cm^2 area of petriplate is approximately 64 mg.

Table 1: Formulation batches

Formulation Code	*Cassia tora gum* (%w/v)	*Konjac gum* (%w/v)	PVP K-30 (%w/v)	CitricAcid (mg)	Sodium saccharin (mg)	PEG 400 (mL)	Drug (mg)
F-1	1	2	1.5	10	10	3	64
F-2	1.5	2	2	10	10	3	64
F-3	2	2	2	10	10	3	64
F-4	2	1	1	10	10	3	64
F-5	1	1	1.5	10	10	3	64
F-6	1.5	1.5	2	10	10	3	64
F-7	1.5	2	1.5	10	10	3	64
F-8	1	1.5	1	10	10	3	64
F-9	1	1.5	1.5	10	10	3	64
F-10	2	1	2	10	10	3	64
F-11	2	1.5	2	10	10	3	64
F-12	1.5	1.5	1	10	10	3	64
F-13	2	2	1	10	10	3	64
F-14	1.5	1	1	10	10	3	64
F-15	1	1.5	2	10	10	3	64
F-16	1.5	1.5	1.5	10	10	3	64
F-17	2	1	1.5	10	10	3	64
F-18	1.5	2	1	10	10	3	64
F-19	1.5	1	2	10	10	3	64
F-20	1	2	1	10	10	3	64
F-21	2	1.5	1.5	10	10	3	64
F-22	1	2	2	10	10	3	64
F-23	2	1.5	1	10	10	3	64
F-24	1	1	2	10	10	3	64
F-25	1	1	1	10	10	3	64
F-26	1.5	1	1.5	10	10	3	64
F-27	2	2	1.5	10	10	3	64

Evaluation of ondansetrin hydrochloride prepared mouth dissolving films

Physical appearance test

Physical evaluation visually done for uniformity of color, transparency and texture of film surface.[8]

pH of film surface

It was determined by digital pH meter by dissolving the film into 5 mL of phosphate buffer (pH6.8 buffer).

Uniformity of weight of films

It was calculated by weighing each film individually, adding them all together, and then computed the average weight of the film. $n = 3$.

Folding endurance

This was done by doing the number of folds of film until it get broken down or formation of visible creaks it helps to evaluate brittleness of the film. Value of folding endurance recorded as how many times of folds essential to break the film.[9]

Determination of thickness of film

This was determined by measuring the individual film thickness by calibrated vernier caliper, all measurement done for 3 times.[10]

Determination of tensile strength

It can be defined as the point atfilm get breaks relative to the highest stress applied. In order to conduct this test, films were sandwiched between two paper clips, one of which was attached to the clamp of burette stand and the other to the weighing balance. By dropping the weight into the weighing pan, the film is tugged until it breaks. Applying the load at rupture divided by the cross sectional area of the film yields the tensile strength. $n = 3$.

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

Determination of time required for disintegration of film

In order to conduct this test, a petriplate containing 25 mL of pH 6.8 phosphate buffer was used. The time at which the film began to break was noted and recorded. Three times the test was repeated.

Determination of % drug content

The individual film used in this test had 4 mg of Ondansetron hydrochloride equivalent weight. It was dispersed in 100 mL of distilled water and shaken for approximately 10 mines before being filtered through a 0.45 m membrane filter. After that, a UV spectrophotometer was used to evaluate 1 mL of the sample at 310 nm after diluting it with 10 mL of distilled water (Jasco V730). Three times of each test were conducted.[11] following that, the drug content was calculated using the formula below:

$$\%\ drug\ content = \frac{Practical\ yield}{Theorotical\ yeild} \times 100$$

Determination of % drug release

The USP type II paddle apparatus was employed for this test, which was conducted at a temperature of 37 ± 0.5°C with phosphate buffer at pH 6.8 serving as the dissolution media. The samples were taken out at regular intervals of 0 s, 10 s, 20 s, 30 s, and 40 s to last 120 s, with the same quantity of new dissolution media being replaced to keep the sink condition. After then, absorbance was calculated at 310 nm with a UV-Visible spectrophotometer.[12]

FTIR of formulation

ATR technique was used to take FTIR spectra of mouth-dissolving film, and the spectra were run between 400 and 500 cm^{-1}. It was noted that there was no evidence of a drug-excipient interaction. Prior to the preparation of film, compatibility investigations of the pure drug ondansetronHCl with polymers were conducted. Figures 2-5 depict the IR spectra of the drug ondansetronHCl in both its pure and with polymers. The presence of all of ondansetronHCl distinctive peaks in the spectra suggests that the drugs are compatible with used polymers of films. It demonstrates that the there was no interaction found.

DSC thermal analysis

To analyze the complex formation and thermal stability of the medication in its formulation, DSC thermal analysis was performed. Research was conducted with Japan, Shimadzu, TA60 software, and DSC 60. The sample was weighed precisely, put on an aluminum plate, covered with an aluminum lid, and heated steadily at a rate of 5°C/min per minute between 0 and 250°C.

Stability study

The optimized formulation batch F25 were stored with proper packaging in environmental stability chamber for 1-3 months. The disintegration and dissolution tests were carried out to know any variation.

RESULT AND DISCUSSION

The objective was to produce a film that would dissolve in the mouth for Ondansetron hydrochloride. To optimize

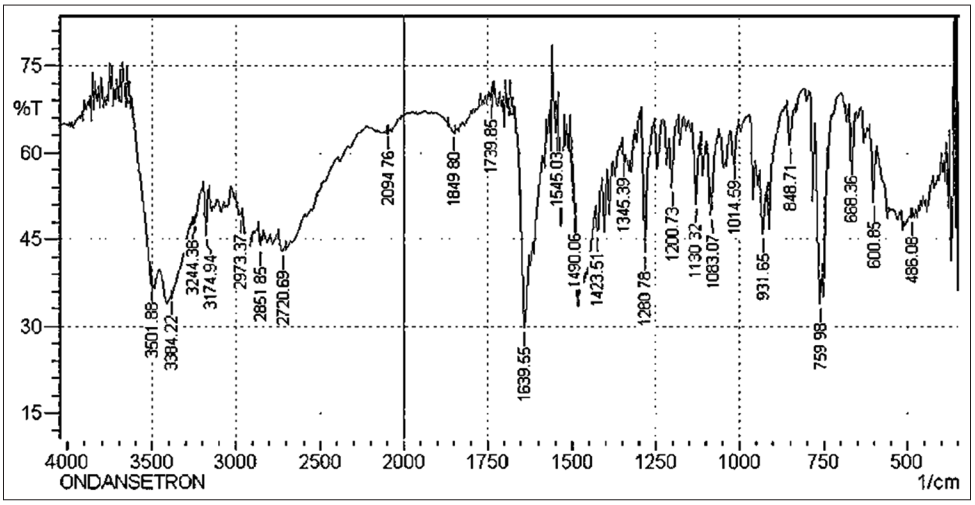


Figure 2: FTIR spectra of pure drug ondansetron hydrochloride

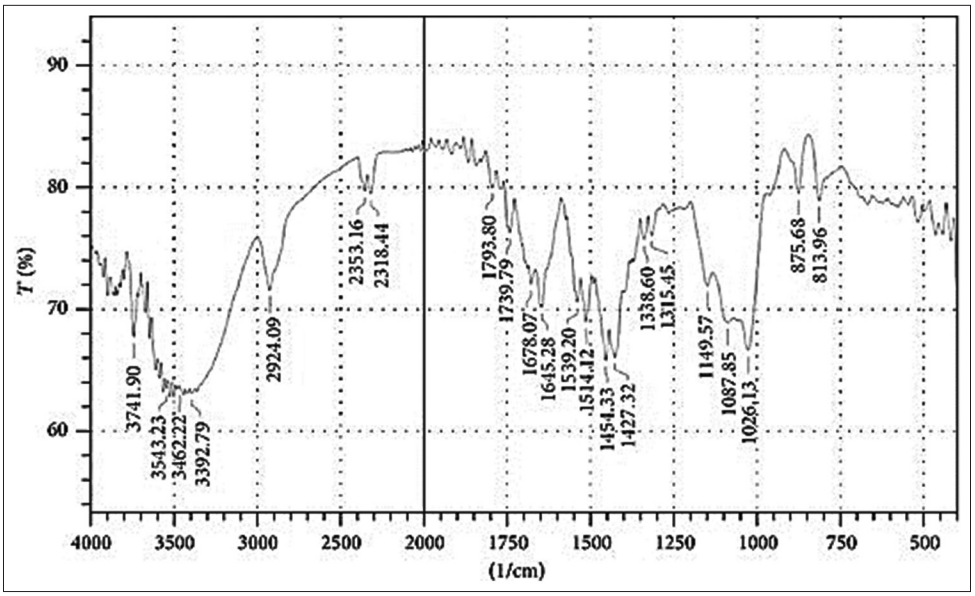


Figure 3: FTIR spectra of *Cassia tora* gum powder

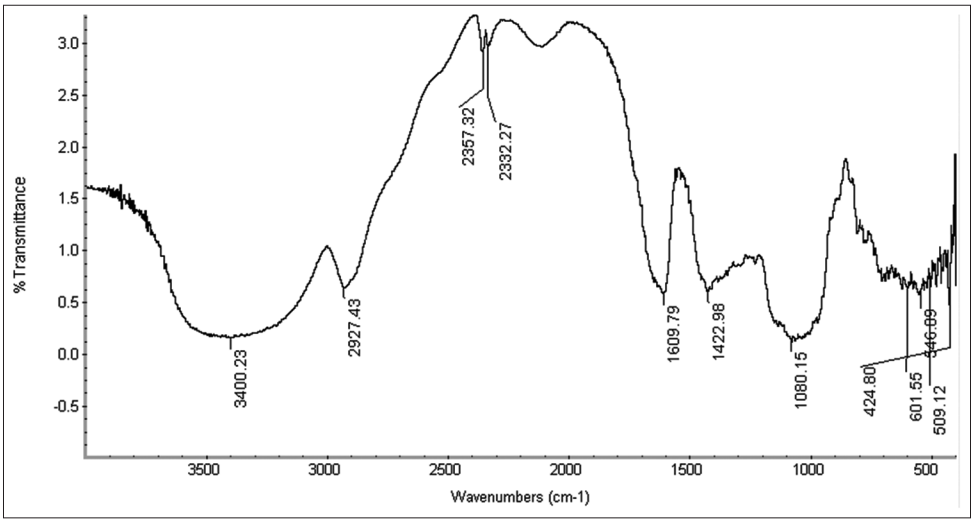


Figure 4: FTIR spectra of *Konjac gum* powder

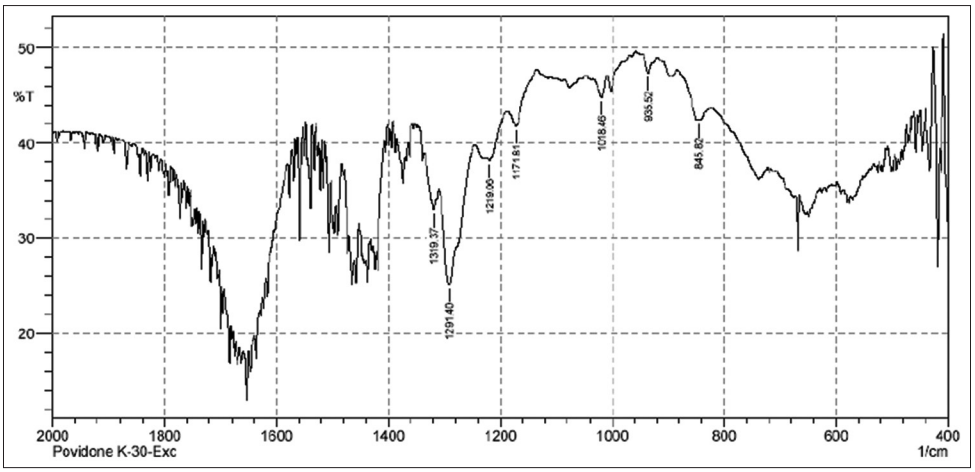


Figure 5: FTIR spectra of PVP K30

the factorial design, Design Expert 13 software was utilized. Solvent casting was used to successfully create Ondansetron hydrochloride MDFs, and the outcomes were evaluated.

Pre-formulation studies

For identification and purity of drug melting point of drug was carried out by capillary method in microcontroller based melting point apparatus and it was found to be 231–232°C which compiles with reference.

For λ max determination, the 100 ppm stock solution was prepared by taking 10 mg Ondansetron hydrochloride in distilled water, pH 6.8 buffer and pH 1.2 buffer, respectively, and UV spectra of 10 µg/mLof Ondansetron hydrochloride in 1.2 pH buffer was taken in the range of 200–400 nm and λ max was recorded it was found to be 266 nm as shown in Figure 6.

Calibration curve was carried by making 10 ppm, 20 ppm, 30 ppm, 40 ppm, 50 ppm concentration of drug in pH 1.2 buffer solution and analyzed in UV-spectrophotometer (Jasco V-730) at 266 nm was liner and R^2 was found to be 0.9997 as shown in Figure 7.

The compatibility in between drug and excipient compatibility was determined using FTIR spectroscopy analysis by ATR method. Small quality of ondansetron hydrochloride was placed over ATR probe prism and IR spectra wererun from 4000 to 500 cm^{-1} IR spectra is shown in Figure 2 and interpreted in Table 2. Small quality of *Cassia tora gum* powder was placed over ATR probe prism and IR spectra were run from 4000 to 500 cm^{-1} IR spectra is shown in Figure 3 and interpreted in Table 3. Small quality of *Konjac gum* powder was placed over ATR probe prism and IR spectra were run from 4000 to 500 cm^{-1} IR spectra is shown in Figure 4 and interpreted in Table 4. Small quality of PVP K30powder was placed over ATR probe prism and IR spectra were run from 4000 to 500 cm^{-1} IR spectra is shown in Figure 5.

Pure PVP K30's FTIR spectra (Figure 2) revealed a distinctive absorption band at 1658 cm^{-1}. The carbonyl group is to blame for this. The hygroscopic character of PVP K30 is revealed by the extremely broad band at 3440 cm^{-1}, which indicates the presence of moisture.

DSC thermal analysis

The thermal behavior of ondansetron hydrochloride shows crystallinity of ondansetron hydrochloride sharp endothermic peak observed at 221–222°C (Figure 8).

Determination of physical properties

All of the films were tested for color, transparency, and surface texture for visual appeal (Table 5). Conclusion: Formulated films were found to have a smooth texture, be transparent, and be free of air bubbles.

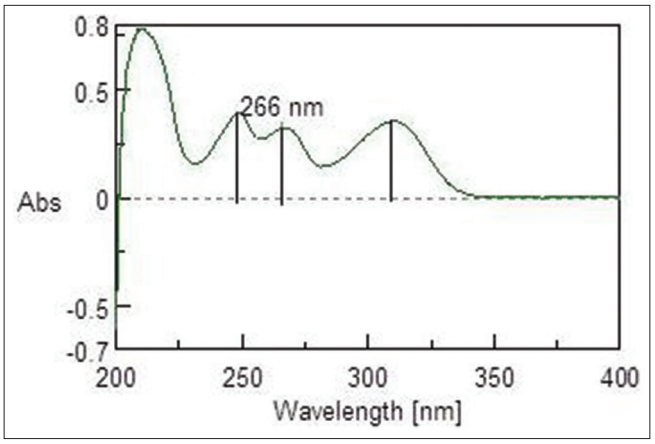


Figure 6: UV-Spectra of ondansetron hydrochloride

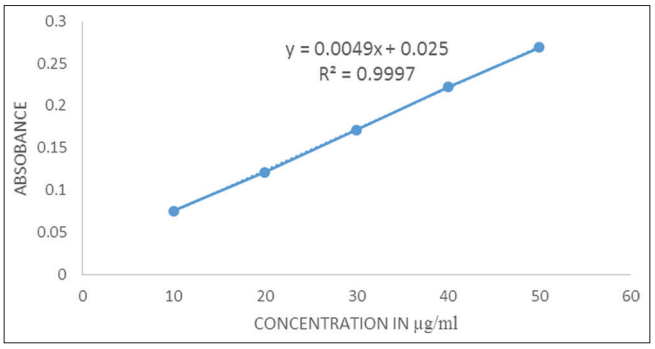


Figure 7: Calibration curve of ondansetron hydrochloride

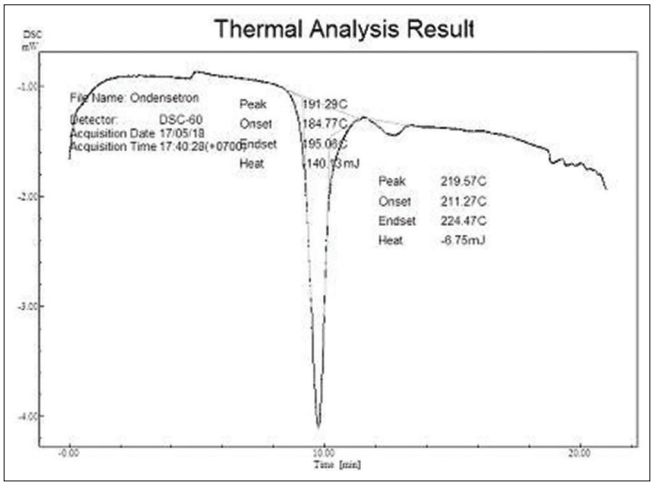


Figure 8: DSC thermogram of ondansetron hydrochloride

Determination of pH of film surface

The surface pH of formed films is displayed in Table 5. The film's surface pH was found to be between 6.45 ± 0.01 and 6.98 ± 0.06, suggesting that it is nearly neutral and that the MDF does not irritate the oral cavity's mucosal membranes.

Determination of uniformity of weight

The observations are reported in Table 5, and it was found that all films shows uniformity of weight between 99.00 ±

Table 2: Interpretation of FTIR of ondansetron hydrochloride

IR frequencies cm^{-1}	Functional groups
758 cm^{-1}	Ortho- disubstituted benzene ring
1280 cm^{-1}	Cyano group vibration(-CN)
1459 cm^{-1}	Methyl group(-CH3)
1531 cm^{-1}	Aromatic ring double bond(-C=C-)
1638 cm^{-1}	Cyano and keto group in 6 membered ring (-C=O,-CN)
3487 cm^{-1}	Hydroxyl group (-OH)
3410 cm^{-1}	

Table 3: Interpretation of FTIR spectra of *Cassia tora gum* powder

IR frequencies cm^{-1}	Functional groups
4813 and 875 cm^{-1}	Anomeric configurations (α and β conformers) and glycosidic linkages
1198 and 983 cm^{-1}	Stretching vibration of C–O in C–O–H bonds
1149 cm^{-1}	Bending vibrational modes of C–O, present in the pyranose ring
1134 and 983 cm^{-1}	C–OH bending
2800–3000 cm^{-1}	C–H stretching
3100–3500 cm^{-1}	O–H stretching vibration

Table 4: Interpretation of FTIR spectra of *Konjac gum* powder

IR frequencies cm^{-1}	Functional groups
3400.23 cm^{-1}	O–H stretch
2927.43 cm^{-1}	C–H stretch
1609.79 cm^{-1}	C=O stretch
1175.4 cm^{-1}	bridge O stretch
1080.15 cm^{-1}	C–O stretch

1.10 mg and 213.00 ± 0.70 mg. form results it was concluded that comparative gain in the weight of film was saw with increase in thickness of film.

Determination of film folding endurance

In accordance with the folding endurance data shown in Table 5, it was observed that all films had a folding endurance of more than 300 folds, proving that all formulations had adequate film-forming properties.

Determination of film thickness

Table 5 reports the findings of the film thickness measurement, which was made using a vernier calliper and found to be between 0.084 ± 0.32 mm and 0.305 ± 0.21 mm. Conclusion: As the concentration of the polymers increased, a proportionate increase in the film's thickness was observed. This might be as a consequence of the formation of a sufficient hydrogen connection between the plasticizer and the polymer, which gives the polymer flexibility to withstand fracture.

Determination of film tensile strength

The tensile strength results are shown in Table 5. According to the results, the tensile strength of the film falls as polymer concentration rises. The measured values imply that the ondansetron hydrochloride film's mechanical stress was adequate to withstand the stress during shipping.

Experimental design full factorial for formulation batches

Using design expert 13 software, the influence of independent variables on response was examined. Table 6 displays the formulation batches screen and 27 potential combinations generated by the software. Several models, including linear, 2FI, quadratic, and cubic, were fitted to the data; the best model was then recommended by software and tested using an analysis of variance. Also, regression polynomials were computed for each of the independent variables, after which each dependent variable's response (R) was used to generate a contour plot and a 3D surface graph, which were then stated as equations 1 and 2. The primary effects A, B, and C represent the average results of moving from low to high concentration by changing one factor at a time. To investigate nonlinearity, the polynomial terms B2 were included.

The effect of formulation variables on *in vitro* disintegration time

The prepared films' saw disintegration times ranged from 18.51 to 66.45 seconds, based on the film disintegration test findings displayed in Table 6. The fastest disintegration time is shown by the film F-27 formulation, which has the greatest concentrations of Cassia tora gum (2% w/v), Konja gum (2% w/v), and medium amounts of PVP K30 (1.5% w/v). The batch with the slowest rate of disintegration is batch F-25. After factorial design was employed, the program suggested a quadratic model, which was found to be significant with a model F = 9.45, $P = 0.0003$, and R2 = 0.5510 respectively. Any model term that has a $P < 0.05$ is deemed significant.

The following is the model response Y1 Disintegration time:

$$Y1 = +36.85+6.94A+6.12B+3.02C \quad \text{Equation 1}$$

The concentrations of A (*Cassia toragum*mucilage powder), B (*Konjacglucoman mucilagepowder*), and C (PVP K30 concentration) have a beneficial impact on the disintegration time, according to equation 1. This implies that the rate of film disintegration is precisely proportional

Table 5: Physical observation of films

Formulation code	Color of film	Transparency of film	Surface texture	pH of surface of film	Film folding endurance	Film weight (mg)	Film thickness (mm)	Film tensile strength (Kg/mm²)
F1	Milky white	Translucent	Soft & Smooth	6.20±0.02	>300	174±0.98	0.149±0.12	0.521±1.12
F2	Milky white	Translucent	Soft & Smooth	6.45±0.04	>300	181±1.01	0.203±0.01	0.605±0.80
F3	Milky white	Translucent	Soft & Smooth	6.56±0.06	>300	173±1.04	0.205±0.25	0.755±0.15
F4	Milky white	Translucent	Soft & Smooth	6.81±0.05	>300	172±1.05	0.188±0.11	0.640±0.11
F5	Milky white	Translucent	Soft & Smooth	6.62±0.07	>300	145±1.14	0.084±0.32	1.011±0.14
F6	Milky white	Translucent	Soft & Smooth	6.67±0.03	>300	165±1.04	0.208±0.15	0.520±0.12
F7	Milky white	Translucent	Soft & Smooth	6.44±0.01	>300	180±1.07	0.186±0.07	0.466±0.15
F8	Milky white	Translucent	Soft & Smooth	6.38±0.05	>300	126±1.15	0.173±0.05	0.550±0.08
F9	Milky white	Translucent	Soft & Smooth	6.70±0.08	>300	134±1.17	0.174±0.18	0.651±0.09
F10	Milky white	Translucent	Soft & Smooth	6.72±0.07	>300	149±1.14	0.202±0.16	0.480±0.11
F11	Milky white	Translucent	Soft & Smooth	6.81±0.09	>300	175±1.04	0.251±0.21	0.788±0.14
F12	Milky white	Translucent	Soft & Smooth	6.85±0.05	>300	165±0.98	0.214±0.15	0.611±0.15
F13	Milky white	Translucent	Soft & Smooth	6.69±0.03	>300	179±0.87	0.255±0.08	0.619±0.45
F14	Milky white	Translucent	Soft & Smooth	6.75±0.04	>300	168±0.64	0.171±0.01	0.514±0.31
F15	Milky white	Translucent	Soft & Smooth	6.98±0.06	>300	144±0.45	0.201±0.09	0.490±0.19
F16	Milky white	Translucent	Soft & Smooth	6.85±0.07	>300	162±1.02	0.182±0.12	0.718±0.02
F17	Milky white	Translucent	Soft & Smooth	6.63±0.08	>300	213±0.78	0.214±0.15	0.861±0.08
F18	Milky white	Translucent	Soft & Smooth	6.48±0.02	>300	198±0.17	0.231±0.23	0.770±0.15
F19	Milky white	Translucent	Soft & Smooth	6.51±0.01	>300	145±1.36	0.148±0.17	0.901±0.13
F20	Milky white	Translucent	Soft & Smooth	6.74±0.07	>300	170±1.11	0.153±0.11	1.011±0.18
F21	Milky white	Translucent	Soft & Smooth	6.73±0.02	>300	184±0.95	0.211±0.15	0.762±0.08
F22	Milky white	Translucent	Soft & Smooth	6.45±0.01	>300	201±1.01	0.312±0.12	0.612±1.02
F23	Milky white	Translucent	Soft & Smooth	6.46±0.03	>300	178±1.07	0.218±0.05	0.461±1.08
F24	Milky white	Translucent	Soft & Smooth	6.76±0.05	>300	165±1.05	0.098±0.15	0.754±1.06

(*Contd*...)

Table 5: (*Continued*)

Formulation code	Color of film	Transparency of film	Surface texture	pH of surface of film	Film folding endurance	Film weight (mg)	Film thickness (mm)	Film tensile strength (Kg/mm2)
F25	Milky white	Translucent	Soft & Smooth	6.78±0.07	>300	99±1.10	0.096±0.18	1.08±1.02
F26	Milky white	Translucent	Soft & Smooth	6.68±0.09	>300	114±1.05	0.151±0.11	0.822±1.07
F27	Milky white	Translucent	Soft & Smooth	6.58±0.09	>300	113±1.02	0.142±0.13	0.832±1.17

Table 6: Formulation of batches of mouth dissolving film of on dansetron hydrochloride as per experimental design

Run	Formulation code	Factor 1 A: Cassia tora gum (% w/v)	Factor 2 B: Konjac glucomman mucilage powder (%w/v)	Factor 3 C: PVPK30 (%w/v)	Response 1 disintegration time (second)	Response 2 drug content (%)
1	F-1	1	2	1.5	36.13±0.21	67.17±0.11
2	F-2	1.5	2	2	47.16±0.52	63.83±0.45
3	F-3	2	2	2	36±0.01	82±0.48
4	F-4	2	1	1	42±0.26	68.47±0.14
5	F-5	1	1	1.5	26.61±0.74	94.85±0.33
6	F-6	1.5	1.5	2	47±0.12	62±0.15
7	F-7	1.5	2	1.5	35.11±0.14	72.5±0.47
8	F-8	1	1.5	1	23±0.21	90.77±0.05
9	F-9	1	1.5	1.5	37.36±0.14	65.27±0.78
10	F-10	2	1	2	42±0.87	69.61±0.98
11	F-11	2	1.5	2	63±0.15	68.63±0.45
12	F-12	1.5	1.5	1	36.33±0.64	67±0.61
13	F-13	2	2	1	54.33±0.11	53.55±0.07
14	F-14	1.5	1	1	26.33±0.47	89.18±0.12
15	F-15	1	1.5	2	33.66±0.18	64.51±0.47
16	F-16	1.5	1.5	1.5	39.33±0.14	74±0.77
17	F-17	2	1	1.5	36.31±0.07	71.43±0.12
18	F-18	1.5	2	1	40.23±0.46	72.63±0.85
19	F-19	1.5	1	2	26.35±0.14	88.73±0.44
20	F-20	1	2	1	25.46±0.34	84.54±0.66
21	F-21	2	1.5	1.5	38.23±0.32	85.13±0.47
22	F-22	1	2	2	46.53±0.07	66.47±0.33
23	F-23	2	1.5	1	52±0.84	72.54±0.44
24	F-24	1	1	2	24.63±0.46	91.13±0.78
25	F-25	1	1	1	18.51±0.05	96.83±0.41
26	F-26	1.5	1	1.5	30±0.77	81.97±0.60
27	F-27	2	2	1.5	66.45±0.03	65.47±0.07

to the increase in A, B, and C concentration. Ondensetron hydrochloride film disintegration time was discovered to be influenced by polymer content. The relative impact factor was determined using the coding equation by comparing the factor coefficients. With the aid of a contour map, the combined impacts of factor A, B, and C were further understood. The effects of the concentrations of A, B, and C on the disintegration time of the ondansetron hydrochloride film are shown in Figures 9 and 10, 2 & 3 D response surface plots.

Effect of formulation variables on % drug content

Table 6 presents the findings. The drug content of formed film was discovered to be between 53.55 ± 0.07% and 96.83 ± 0.41%. The formulations with the highest drug content are F-5, F-24, and F-25. When factorial design was used, the software proposed a quadratic model, which was found to have an F = 6.91, a $P = 0.0008$, and an R2 = 0.5951—signifying that the model was significant. Every model term is significant if the $P < 0.05$. Below is the model response R2 (% drug content):

$$Y2 = +70.40 - 3.51A - 7.11B - 3.23C + 7.37B2 \quad \text{Equation 2}$$

The (−) sign of factors A, B, and C has a negative impact on drug content, while factors B2's (+) sign indicates a positive impact. This was concluded from Equation 2. With the help of a contour plot, the combined impacts of factor A, B, and C were further understood. 3D response surface plots in Figure 11 that the impact of A, B, and C concentrations on the percentage of drugs in films is depicted in Figure 12.

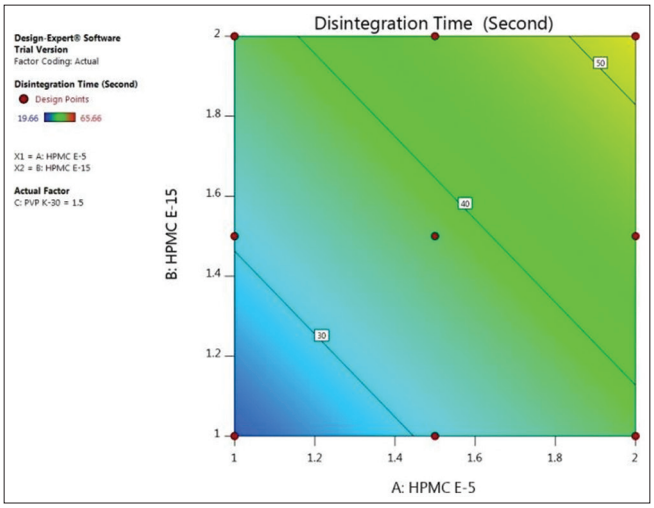


Figure 9: Two diamentional 2D counter plot response Y1 disintegration time

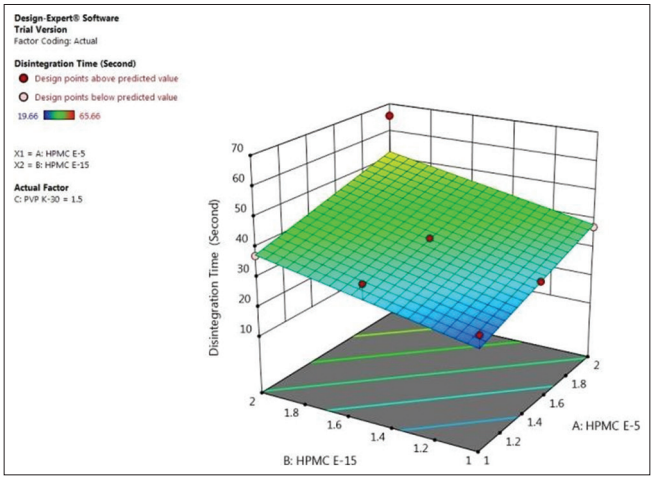


Figure 10: Three diamentional 3D response surface plot for response Y1 disintegration time

Ondansetron hydrochloride film drug content was found to be directly correlated with polymer concentration. The percentage of drugs in the film reduces as polymer concentration rises. The drug content in batches F-5, F-24, and F-25 is above 90%.

Formulation optimization by 3^3 factorial deign

Two response variables, Y1 and Y2, were taken into consideration to enhance the formulation process. Conclusion: If the mouth-dispersing film's disintegration time is long, there may be a chance that it would not provide immediate relief from the symptoms for which it is prescribed, and if its drug concentration is low, the film will release less medication into the bloodstream to have the desired effect. This leads to the conclusion that the formulations with a disintegration time between 10 and 30 seconds and a desired drug content of at least 85% were to be chosen as optimal formulations. Batches F-5, F-8, F-14, F-20, F-24, and F-25 of the formulation all exhibit all the predicted characteristics; therefore, all of the formulations were deemed to be optimized formulations and were processed further for an *in vitro* dissolution study to determine the release in phosphate buffer pH6.8.

In vitro dissolution study of optimized mouth dissolving film

It was calculated that the maximum drug release at 120 s would be 96.10 ± 0.82% and the minimum drug release would be 83.21 ± 0.05%. The results are listed in Table 7 and the release pattern is depicted in Figure 13. This test was conducted for all optimized film formulations in a phosphate buffer pH 6.8 at 50 rpm. The best batch of formulas among all optimized batches was determined to be F-25. This improved batch includes PVP K30 (1%), *Konjacgum* (1%), and *Cassia tora gum*(1%). The optimized batch F-25 demonstrates faster drug release (96.10 ± 0.82%) and a shorter disintegration time (18.51 ± 0.05 s) in within 120 s.

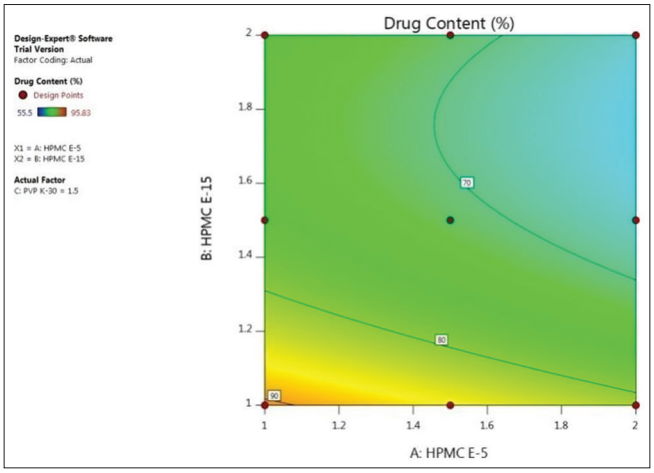


Figure 11: Two diamentional 2D counter plot for response Y2% drug content

FTIR of formulation

In the IR spectra of formulation all peaks of drug and excipients observed with slight shift of frequencies. Hence from Figure 14 it concludes there were no interaction between drug and excipients.

DSC thermal analysis

DSC 60, with TA60 software, Shimadzu, Japan, were used in the studies. Precisely weighed samples were put on an aluminum plate, covered with an aluminum lid, and heated steadily at a rate of 5°C/min across the temperature range of 0–250°C (Figures 8 and 15).

From DSC thermogram, it was concluded that the formulation batch F25 shows melting point of ondansetron hydrochloride at 213°C–240°C with shorter endothermic peak it may happen because of effect of film former on physical properties of drug. It suggests that there were no interaction or degradation of ondansetron hydrochloride in film formulation.

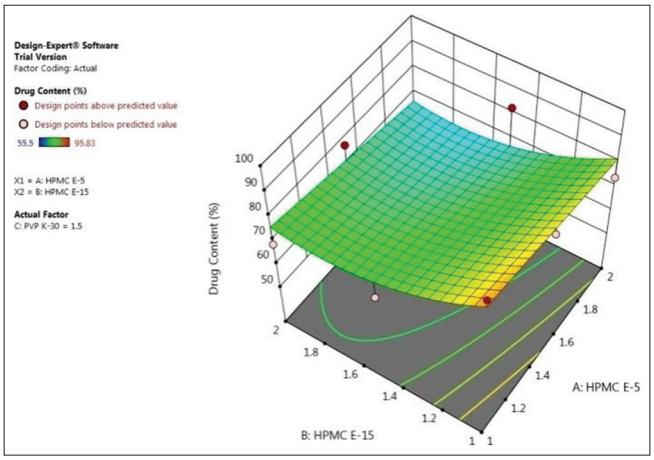


Figure 12: Three dimensional 3D response surface plots for response Y2% drug content

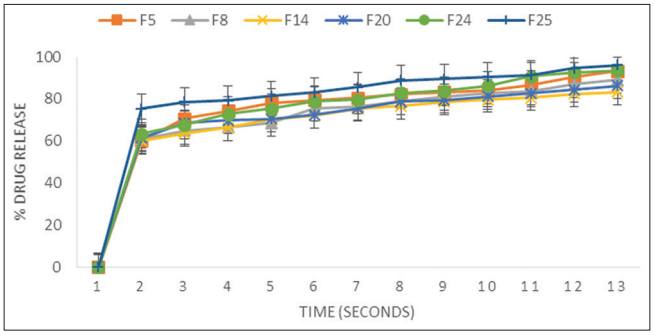


Figure 13: Dissolution profiles of optimized batches

Stability study

The optimized formulation batch F25 were stored with proper packaging in environmental stability chamber for 1-3 months and the disintegration time and dissolution study were carried out it was observed that there was no any major variation observed when compared with previous results of same batch F25. It suggests that prepared films of ondansetron hydrochloride are stable.

Table 7: Dissolution study data

Time Sec.	F5	F8	F14	F20	F24	F25
10	0	0	0	0	0	0
20	56	55	54	52	59	70
30	65	61	56	55	64	72
40	70	66	60	59	69	74
50	72	70	63	62	72	79
60	74	72	66	68	76	80
70	76	75	70	73	79	84
80	77	78	73	75	82	86
90	80	81	77	77	86	88
100	84	85	81	79	89	90
110	88	89	85	82	90	92
120	91	90	88	84	92	96

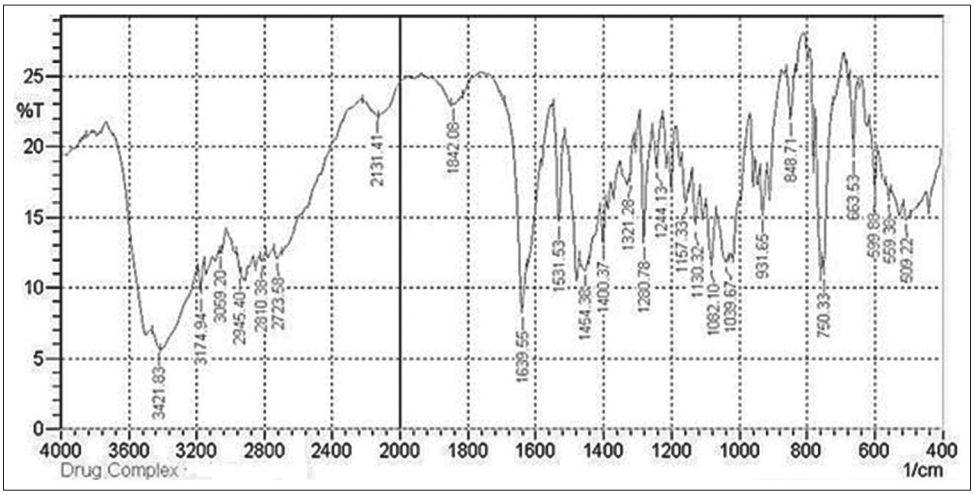


Figure 14: FTIR of formulation optimize batch F25

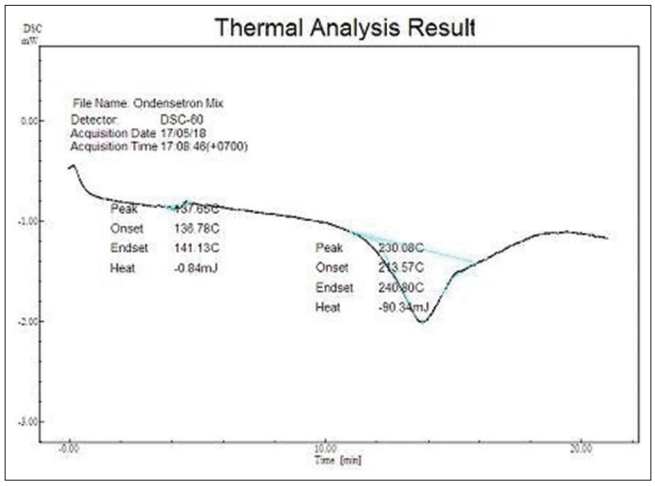


Figure 15: DSC Thermogram of formulation batch F25of mouth dissolving film

CONCLUSION

One of the patient-friendly dose forms for symptoms when a quick onset of the drug's effects is necessary, the MDF is the dosage form which full-fill this need. Based on the findings, it can be said that the solvent casting approach is an easy and repeatable method for producing an ondansetron hydrochloride mouth film. According to experimental findings, altering the polymer concentration may have an impact on the dissolution rate and drug content of films. In a formulation with a 1% concentration of *Cassia tora* gum, 1% *Konjac gum*, and PVP K30, the drug is released quickly within 120 s with (96.10 ± 0.82%) drug release. From the results of this study, it can be interpreted that mouth-dispersing films of Ondansetron hydrochloride are feasible to prepare, provide quick onset of action, have improved oral bioavailability, increase patient compliance, and have higher therapeutic efficacy when compared to other traditional oral dosage forms.

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CONFLICTS OF INTEREST

None.

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