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## Research



### Formulation And Evaluation Of Irbesartan Orally Disintegrating Films

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	<b>Abstract</b>
Published on: 26 Sept 2024	<p>Orally disintegrating films may accelerate the medication's onset of action, reduce dosage, and improve its efficacy and safety profile. It dissolves faster, is more stable, and lasts longer than other traditional dose forms. In order to create fast-dissolving films that dissolve in saliva rapidly and without the need for water, Irbesartan (IRB) was chosen for the sublingual route. The purpose of IRB oral disintegrating films was to increase patient compliance and bioavailability. The formulas were created with the intention of helping elderly, bedridden, and mentally ill people. IRB is used to measure the effect on the dissolution profile. The orally disintegrating films (ODF) were prepared using the solvent casting technique with water soluble polymers such as HPMC E3, HPMC E6, and Xanthan gum of various concentrations and PEG 400 as a plasticizer and an active ingredient. The medication dissipated rapidly, according to the results. This study suggests that an oral disintegrating film may be used to give IRB orally. ODF formulations dissolve smoothly and easily, releasing the entire medication within 20 to 30 minutes. Following disintegration, no remnant or particle matter was remaining. It was determined that the solvent casting method was effective in producing the quickly disintegrating IRB films. When there is no access to water, oral disintegrating films (ODF) have been effectively used with bedridden and psychotic patients as well as travelers. Prepared films demonstrated a higher rate of dissolution and a quicker start to action, which led to improved patient compliance, successful therapy, and increased use in the near future.</p>
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**Keywords:** Orally disintegrating films, Irbesartan, solvent casting technique, xanthan gum, HPMC.

## INTRODUCTION

Orally disintegrating tablets and Oro dissolving films are two of the fast-dissolving medication delivery technologies that have been developed as alternatives to traditional dose forms in order to help these individuals. Because oral medicine delivery has the highest compliance rate, especially among pediatric and geriatric patients,

it is considered the most practical, affordable, and safest drug delivery method. Any medication delivery system's ultimate purpose is to successfully deliver the drug to the body. Among the different dosage forms, the oral disintegrating dosage form is the most popular commercial product<sup>1</sup>. The film decreases the risk of choking and the fear of choking, is simple to make, easy to handle and administer, and has handy packaging. It also lessens the taste that is unpleasant. These thin polymer films are also known as melt-in-mouth dosage forms (MDF), mouth dissolving films (ODF), quick dissolving films (QDF), rapidly dissolving films (RDF), and oral dissolving films (ODF)<sup>2</sup>.

Some formulations were developed earlier that are Atorvastatin<sup>3</sup>, zolmitriptan<sup>4</sup>, levocetirizine dihydrochloride<sup>5</sup>, amlodipine besylate<sup>6</sup>, montelukast<sup>7</sup>, ondansetron<sup>8</sup>. HPMC (Hydroxy propyl methyl cellulose) is a non-ionic polymer that is white or creamy white, tasteless, odorless, and fibrous in powder form. Soluble in alcohol and water mixtures as well as ethanol and di-chloro methanol mixtures. HPMC is a popular ingredient in medicinal formulations<sup>9</sup>. Xanthan gum is found as a fine, odourless, cream- or white-colored powder that flows freely. It has good stability and viscosity qualities across a broad pH and temperature range, is nontoxic, and is compatible with the majority of other medicinal components<sup>10</sup>. Irbesartan is white to off white crystalline powder, practically insoluble in water, very slightly soluble in alcohol, methylene chloride, used to treat essential hypertension that is mild to moderate<sup>11</sup>. The goal of the current study was to create an oral disintegrating film that included the medication IRB, which is used to treat moderate to severe hypertension.

## MATERIALS & METHODS

### Chemicals

Irbesartan was obtained as gift sample from Uni Chem laboratories Ltd., Mumbai. HPMC was purchased from Colorcon Asia Pvt. Ltd., Xanthum gum was purchased from Shilex Chemicals. PEG 400 was purchased from S.D. Fine Chem. Ltd., Mumbai. Aspartame was purchased from HI media Lab Pvt Ltd., Mumbai. Orange flavour was purchased from Pentagon trading company. Using the solvent casting method, IRB ODFs were made with several grades of Hydroxy Propyl Methyl Cellulose, such as HPMC E3, HPMC E6, and a natural polymer called xanthan gum. We set a formula with the following components:

### METHODOLOGY

#### Calibration of IRB

One hundred milligrammes of IRB precisely weighed, is added to a 100 millilitre volumetric flask. Using 6.8 pH phosphate buffer, which is the stock solution of 1 mg/ml, the volume was increased to 100 ml. Solutions with concentrations of 5, 10, 15, 20, 25, and 30 µg/ml were made by further diluting the stock solution appropriately (0.5, 1, 1.5, 2, 2.5, and 3 ml are taken from stock solution and dilute with 100 ml buffer) using 6.8 pH phosphate buffer. A standard graph was plotted and the absorbance of these solutions was measured using a UV-VIS spectrophotometer set to Lambda max 220 nm, with a blank of 6.8 pH phosphate buffer.

#### Fourier Transform Infrared (FT-IR) Spectroscopy

The drug's FT-IR spectra was captured with a JASCO 4100. The mid-IR 4000-400 cm<sup>-1</sup> spectral range was covered by the diffuse reflectance approach. The process entails utilizing a motor to disperse the sample in KBr (100 mg), then a compression gauge to triturate the materials into a fine powder bed inside the holder. For five minutes, the pressure was about five tons. The pellet was positioned along the light path, the spectrum was captured twice, and the distinctive peaks of the functional groups were deciphered.

#### UV Spectroscopy

Ten milliliters of water were added to a precisely weighed dose of 10 milligrams of medication. Phosphate buffer solution was made using 20 µg/ml of IRB solution from the principal stock solution. The range of 200–400 nm was scanned with this solution.

#### Formulation Design<sup>12</sup>

Using the solvent casting method, IRB ODFs were made with several grades of Hydroxy Propyl Methyl Cellulose, such as HPMC E3, HPMC E6, and a natural polymer called xanthan gum. We set a formula with the following components:

Drug	: Irbesartan
Solvents	: Methanol and Dichloro methane
Polymers/Film forming agent	: HPMC E3, HPMC E6 & Xanthan gum
Plasticizer	: PEG 400
Sweetener	: Aspartame

Flavoring agent : Orange flavor

The formulae of different formulations are as follows:

**Table 1: Formulation of Irbesartan ODF**

Ingredients (mg)	IF 1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9	IF 10	IF 11	IF 12
Irbesartan	75	75	75	75	75	75	75	75	75	75	75	75
HPMC E3	50	100	150	--	--	--	--	--	--	--	--	50
HPMC E6	--	--	--	50	100	150	200	--	--	--	--	150
Xanthan Gum	--	--	--	--	--	--	--	50	100	150	200	200
PEG 400	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	30	30	30	30	30	30	30	30	30	30	30	30
Orange Flavor	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S

*\* Processing solvents Dichloro methane, Methanol in the preparation of films, not present in the final formulation*

### Preparation of ODF

In the preparation of irbesartan ODF we used solvent casting method<sup>13</sup>. With the use of xanthan gum, HPMC E3, and HPMC E6, the ODF of IRB was created. Dichloromethane and methanol were combined in a 1:1 ratio to create the polymeric solution, which was then left for five to six hours to allow the polymer to swell. After IRB was dissolved in a specific amount of solvent, the drug solution was added to the polymeric solution mentioned earlier. The inclusion of plasticizers, such as PEG 400, came next. Flavor and sweetener were also added. The medication content can be made uniform by mixing for 15 to 20 minutes in a cyclo mixer. The mixture was placed into a ready mold and let to air dry for forty-five minutes. After the film was meticulously taken out of the mold, it was inspected for flaws and trimmed to the proper size so that each strip would have the appropriate dosage ( $2 \times 2\text{cm}^2$ ). Film samples that had cuts, air bubbles, or other flaws were not included in the investigation. Distilled water was used to dissolve the plasticizers and water-soluble polymers. To release all trapped air bubbles, the solution is agitated for two hours in a magnetic stirrer and then left aside. In the meantime, the medication and excipients were dissolved and vigorously agitated for 30 minutes. Both solutions were then combined after the stirring was finished. In order to create a film, the solution is finally cast onto an appropriate Petri plate. For one hour, the plates were stored at 60°C in a hot air oven. After drying, the film was carefully cut to the appropriate size and removed from the glass plate.

### Dose calculations

Length of glass plate = 10 cm.

Width of glass plate = 10 cm.

Area of the plate =  $100\text{ cm}^2$ .

No. of  $4\text{ cm}^2$  films present whole plate =  $100/4 = 25$  films.

Each films contains 3 mg of drug.

25 films contain 75 mg drug.

Labelled claim = 3 mg

### Drug - Polymer Compatibility Studies

To determine whether the medication and polymers were compatible, an FTIR research was conducted. IRB's infrared spectra was identified using the Fourier transform. KBr dispersion technique infrared spectrophotometer. With dried potassium bromide, the baseline correlation was carried out. Next, using an FTIR spectrophotometer, the spectra of a dried mixture of the drug and potassium bromide was run, and then the drug with other polymers. The careful selection of excipients, which are included to aid in administration, support the drug's constant release and bioavailability, and shield it from degradation, is essential to the formulation of a stable and effective solid dosage form. Compatibility studies are crucial if the excipients are novel and haven't been used in a formulation that contains the active ingredient. IRB's compatibility with Xanthan Gum, PEG 400, and HPMC was determined by Fourier Transform Infrared Absorption Spectral Analysis (FTIR).

**Thickness measurement<sup>14</sup>:** The film's thickness was measured five times using a micrometer screw gauge, and an average of three readings was determined.

**Weight variation<sup>15</sup>:** Using an analytical balance, the average weight of the mouths dissolving the oral films was calculated for each film.

**Folding endurance<sup>16</sup>:** The value of folding endurance is determined by the number of times the film could be folded in the same way without breaking.

**Drug content uniformity:** By evaluating the API content in each individual strip, content consistency is ascertained. 85–115% is the maximum content homogeneity<sup>17</sup>.

**Surface pH:** The film that was going to be tested was put in a Petri dish, wet with 0.5 milliliters of distilled water, and left for thirty seconds. After allowing one minute for equilibration and contacting the formulation's surface with the pH meter's electrode, the pH was recorded. For every formulation, an average of three determinations was made<sup>18</sup>.

**Assay of the Films:** The final solution's absorbances were measured at 220 nm wave length using a UV Visible spectrophotometer against a blank of 0.01N HCl. Using a conventional graph, concentrations were computed, and the formulation's total amount was determined.

**Percentage elongation<sup>19</sup>:** It was calculated by

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Initial length of strip}}$$

**Tensile strength<sup>20</sup>:** The greatest stress applied to the point at which the strip specimen breaks is known as its tensile strength.

**Scanning electron microscope:** With the use of scanning electron microscopy, the surface morphology of the optimized formulation was investigated<sup>21</sup>.

### ***In vivo* disintegration studies**

In this investigation, an ODF measuring 2 x 2 cm<sup>2</sup> that is necessary for medication administration was applied to the volunteers' tongues, and the amount of time it took for it to dissolve in the mouth was recorded.

### ***In vitro* Dissolution test<sup>22</sup>**

The developed ODF formulations were subjected to an in-vitro dissolving investigation utilizing an Electro lab dissolution rate test instrument in a USP type I (basket). Six duplicates of the release studies were carried out, and mean values were recorded.

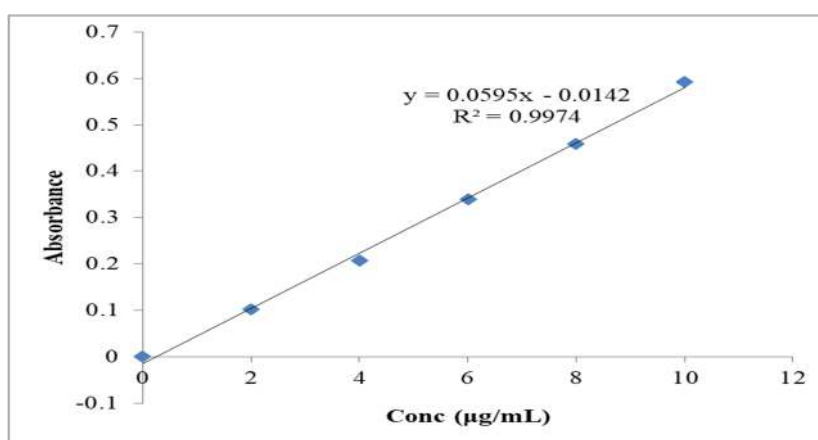
### **Release Kinetics<sup>23</sup>**

The findings from the invitro diffusion investigation were used to investigate the order and mechanism of drug release kinetics of IRB films. The kinetic models that were plotted included the zero order, first order, and Higuchi equations; the release was calculated using the Korsmeyer-Peppas equations.

## **RESULTS & DISCUSSION**

### **Calibration of IRB**

To make the stock solution, mix 50 mg of IRB with 100 ml of water. 10 milliliters of this stock solution were taken out and diluted with water to make 100 milliliters. A calibration curve was created using various concentrations (2–10 µg/ml) and the proper stock solution dilution. At 220 nm, the absorbance was measured. IRB was calibrated in a pH 6.8 pH phosphate buffer; the resulting curve is displayed in Figure 1.



**Fig 1: Standard Calibration Curve of IRB in 6.8 pH phosphate buffer**

## Calibration of 0.1 N HCl

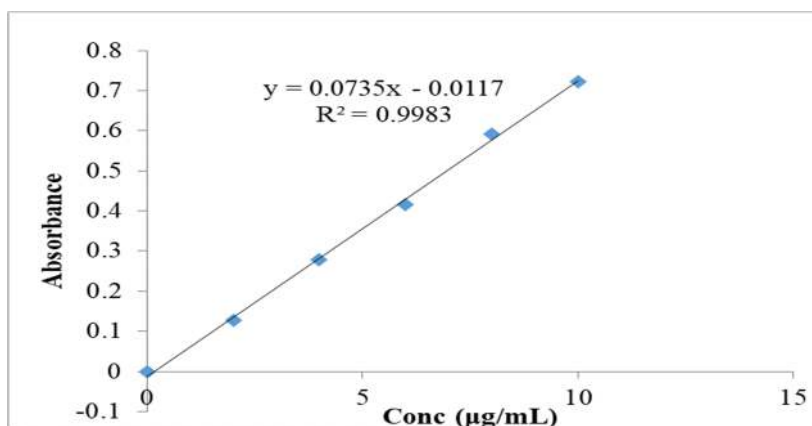


Fig 2: Standard Calibration Curve of IRB in 0.1N HCl

## Drug – excipient Compatibility Studies

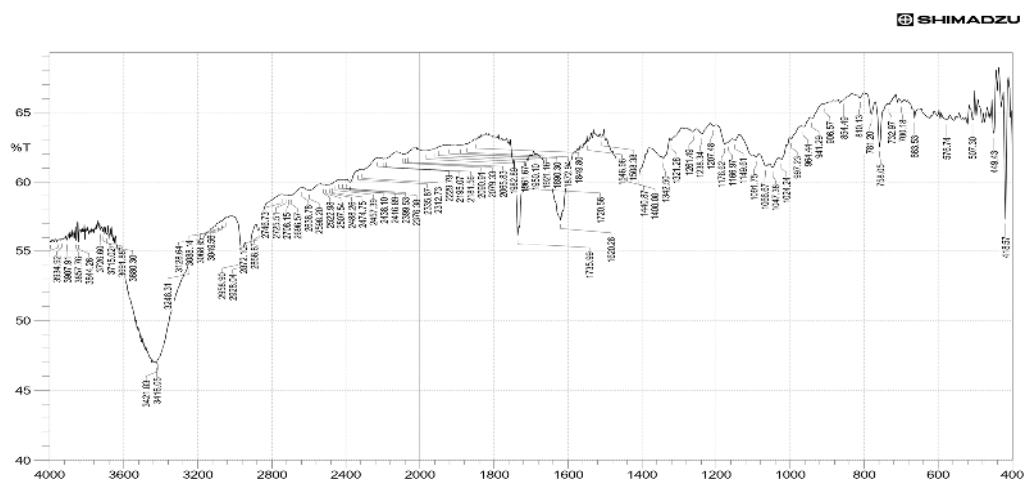


Fig 3: FTIR Spectrum of pure IRB.

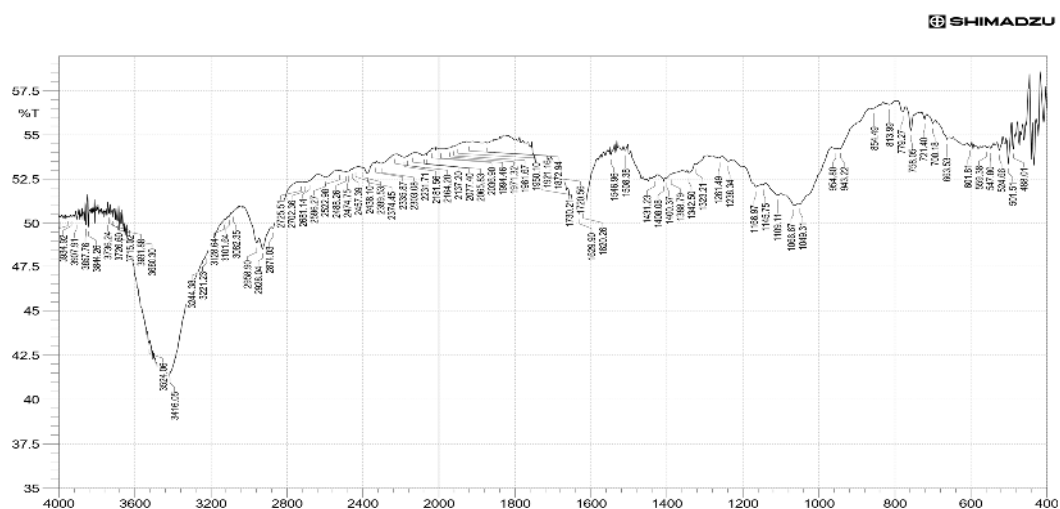


Fig 4: FTIR Spectrum of optimized formulation.

The acquired FTIR spectra are shown in Figure superimposed. The observations are consistent with the scientific literature, and the spectrum clearly displays the main characteristic bands linked to pure IRB. The principle peaks were observed at 2958.90  $\text{cm}^{-3}$  for (N-H stretching), 1735.99  $\text{cm}^{-3}$  for (C=O stretching), 1546.96  $\text{cm}^{-3}$  for (C=C stretching) and 1620.26  $\text{cm}^{-3}$  for (CN stretching). The absorption peaks of both the drug and excipients were observed indicating there was no interaction.

### Formulation of ODF

After IRB was dissolved in a specific amount of solvent, the drug solution was added to the polymeric solution mentioned earlier. Plasticizers, such as PEG 400, sugar, and flavors were added after this stage. The medication content can be made uniform by mixing for 15 to 20 minutes in a cyclo mixer. The mixture was placed into a ready mold and let to air dry for forty-five minutes. After the film was meticulously taken out of the mold, it was inspected for flaws and trimmed to the proper size so that each strip would have the appropriate dosage ( $2 \times 2\text{cm}^2$ ). Film samples that had cuts, air bubbles, or other flaws were not included in the investigation. HPMC E3 is used to manufacture ODF formulations IF1–IF3 at concentrations of 50–150 mg, respectively. The films made with a 100 mg concentration (IF2) were determined to have the finest formulation out of all of them. The medication release was delayed by an additional 150 mg-F4 concentration increase. HPMC E6 is used to create ODF formulations IF4–IF7 at concentrations ranging from 50–200 mg. The films made with a 100 mg concentration (IF5) were determined to be the finest formulations out of all of them. Xanthan gum is used to create ODF formulations IF8–IF11 at concentrations ranging from 50–200 mg. The films made with a 200 mg concentration (IF11) were determined to have the best formulation among them. Therefore, a formulation IF12 was created that has better qualities and a more effective drug release within 15 minutes, including half the quantities of the different polymers.

### Evaluation of ODF

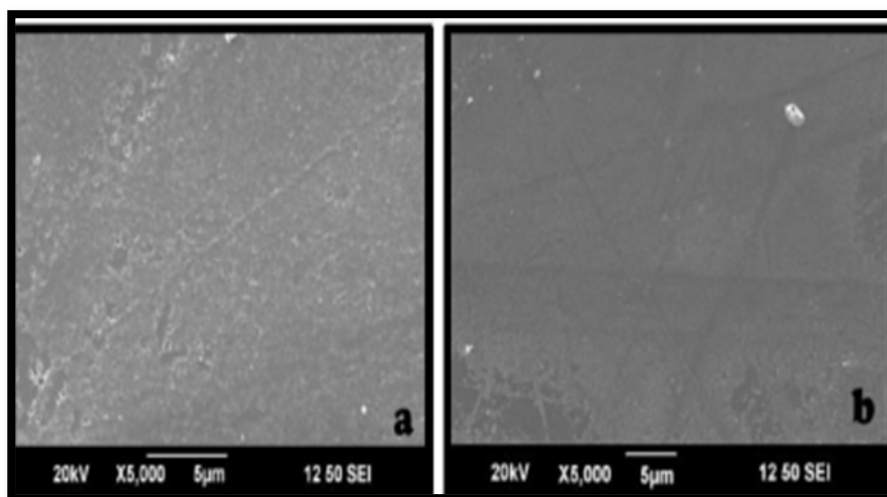
Thickness of the IRB formulation IF1–IF12 were determined to be  $89.78 \pm 0.62$ – $132.18 \pm 0.59$   $\mu\text{m}$  thick. The folding endurance value of IF1–IF12 was  $84 \pm 4$ – $180 \pm 14$ . Every film's surface pH was discovered to be between 6-7. The table displays the tensile strength of all formulations varies as  $49.28 \pm 0.31$ – $64.38 \pm 0.35$ . % elongation of all formulations' for IRB fast dissolving films ranges from  $9 \pm 2$ – $15 \pm 5$ . The disintegration time for IF1–IF12 was  $19 \pm 3$ – $28 \pm 5$  minutes.

**Table 2: Determination of Thickness, folding endurance and Surface pH of all formulations**

F. Code	Thickness ( $\mu\text{m}$ ) $\pm$ SD	Folding endurance	Surface pH	Tensile strength	Percentage elongation	In-vitro disintegration Time (sec)
IF 1	$89.78 \pm 0.62$	$84 \pm 4$	$6.13 \pm 0.11$	$51.21 \pm 0.21$	$9 \pm 2$	$19 \pm 3$
IF 2	$99.67 \pm 0.87$	$96 \pm 6$	$6.23 \pm 0.13$	$50.76 \pm 0.42$	$10 \pm 3$	$23 \pm 5$
IF 3	$110.31 \pm 0.97$	$103 \pm 7$	$6.21 \pm 0.07$	$49.28 \pm 0.31$	$12 \pm 4$	$20 \pm 4$
IF 4	$121.27 \pm 0.48$	$121 \pm 8$	$6.29 \pm 0.09$	$52.56 \pm 0.41$	$14 \pm 3$	$25 \pm 4$
IF 5	$132.18 \pm 0.59$	$123 \pm 6$	$6.18 \pm 0.10$	$60.51 \pm 0.16$	$13 \pm 6$	$22 \pm 5$
IF 6	$124.52 \pm 1.21$	$131 \pm 11$	$6.07 \pm 0.12$	$51.79 \pm 0.25$	$12 \pm 2$	$26 \pm 3$
IF 7	$102.29 \pm 0.84$	$139 \pm 9$	$6.31 \pm 0.11$	$52.83 \pm 0.31$	$11 \pm 1$	$21 \pm 4$
IF 8	$125.37 \pm 1.06$	$161 \pm 8$	$6.11 \pm 0.09$	$60.47 \pm 0.42$	$15 \pm 4$	$20 \pm 3$
IF 9	$129.79 \pm 0.81$	$180 \pm 14$	$6.21 \pm 0.08$	$62.31 \pm 0.13$	$11 \pm 2$	$21 \pm 1$
IF 10	$99.81 \pm 0.73$	$159 \pm 9$	$6.32 \pm 0.14$	$64.38 \pm 0.35$	$12 \pm 3$	$27 \pm 4$
IF 11	$119.63 \pm 0.72$	$147 \pm 7$	$6.29 \pm 0.11$	$55.39 \pm 0.16$	$9 \pm 2$	$28 \pm 5$
IF 12	$102.42 \pm 0.63$	$160 \pm 8$	$6.12 \pm 0.12$	$61.76 \pm 0.42$	$15 \pm 5$	$20 \pm 3$

### Surface morphology

The surface morphology of the IRB ODF sample was examined using scanning electron microscopy (SEM) at 20 kv and a magnification of X5000. The sample was made by breaking the films in liquid nitrogen, mounting it on aluminum stubs, and sputter coating it with platinum (JEOL 5400, Tokyo, Japan).



**Fig 5: SEM of Mouth dissolving film (a) upper surface and (b) lower surface**

#### Weight variation

Table 3 shows the weight variance of all formulations' varies between  $59.18 \pm 0.24$ – $69.31 \pm 0.27$ .

#### Drug Content Uniformity

The findings of the calculation of the percentage of medication content for various formulations are displayed in Table 3. With a drug content percentage of  $107.69 \pm 0.22$ , IF12 was deemed the best formulation when compared to the other formulation.

#### Assay

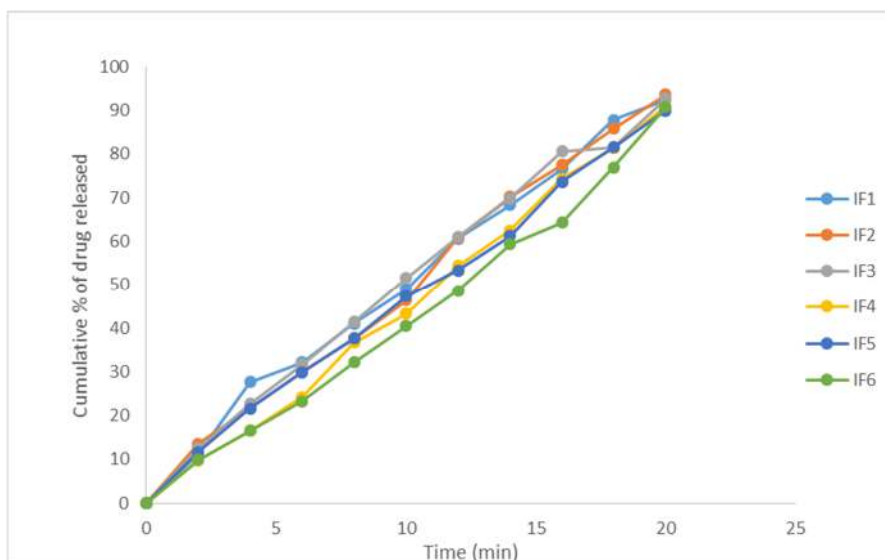
Using a UV spectrophotometer, this solution was examined. All of the formulations' assay results are displayed in Table 3, and the values are portrayed graphically in Figure.

**Table 3: Determination of Weight variation, Drug Content Uniformity and Assay**

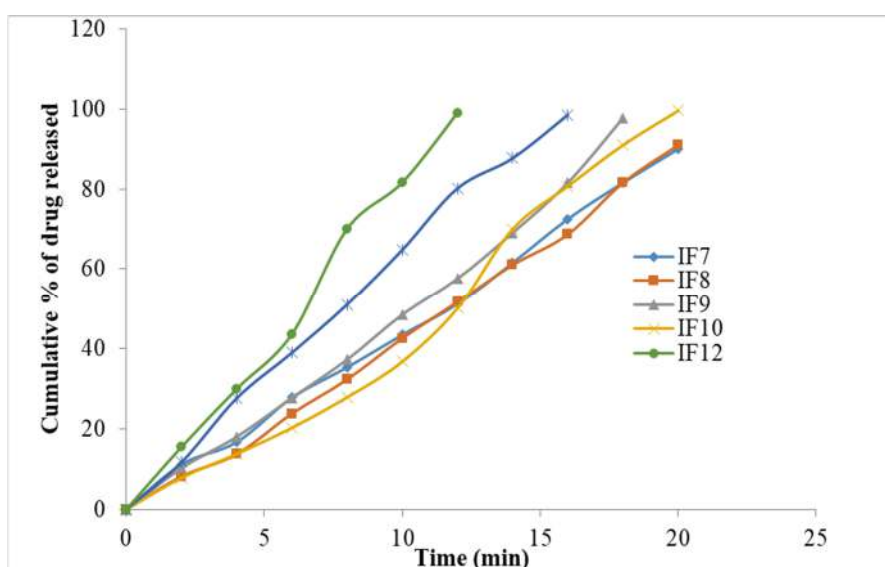
F. Code	Weight variation	Drug Content Uniformity	Assay
IF 1	$60.29 \pm 0.18$	$90.82 \pm 0.32$	$96.17 \pm 0.02$
IF 2	$61.37 \pm 0.35$	$91.38 \pm 0.22$	$97.37 \pm 0.06$
IF 3	$64.21 \pm 0.26$	$99.47 \pm 0.19$	$96.52 \pm 0.04$
IF 4	$62.13 \pm 0.21$	$102.53 \pm 0.29$	$97.73 \pm 0.06$
IF 5	$60.38 \pm 0.31$	$109.51 \pm 0.31$	$98.59 \pm 0.03$
IF 6	$66.58 \pm 0.26$	$110.31 \pm 0.23$	$96.42 \pm 0.02$
IF 7	$65.36 \pm 0.15$	$100.48 \pm 0.39$	$97.63 \pm 0.05$
IF 8	$68.28 \pm 0.23$	$99.64 \pm 0.21$	$97.48 \pm 0.03$
IF 9	$69.31 \pm 0.27$	$91.83 \pm 0.27$	$98.23 \pm 0.04$
IF 10	$59.18 \pm 0.24$	$110.36 \pm 0.15$	$96.62 \pm 0.06$
IF 11	$64.55 \pm 0.32$	$104.43 \pm 0.29$	$98.74 \pm 0.09$
IF 12	$67.62 \pm 0.31$	$107.69 \pm 0.22$	$99.69 \pm 0.11$

#### In-vitro dissolution

The media, 900 ml of 0.1 N HCL, was kept at  $37 \pm 0.5$  °C with the basket spinning at 100 rpm. Every two minutes, 5 milliliters of the sample were removed, and the same volume was replaced with brand-new 0.1 N HCL. After being extracted, the samples were filtered and subjected to 220 nm UV spectroscopy analysis. The figure 6-7 displays the percentage cumulative drug release for IF1 to IF12. Ultimately, after just 12 minutes, the formulation IF12 which contained half of the optimal concentrations of HPMC E3, E6, and xanthan gum released 99.13% of the medication. It thus is considered to be the best formulation.



**Fig 6: Invitro dissolution studies of formulations (IF1-IF6)**



**Fig 7: Invitro dissolution studies of formulations (IF7-IF12)**

#### Application of Release Rate Kinetics to Dissolution Data

To investigate the kinetics of drug release, many models were employed. To study the mechanism of the dosage form's drug release rate kinetics, the obtained data was fitted to several release models: first-order, zero-order, Higuchi, and Korsmeyer-Peppas.

#### Stability Studies

To evaluate the stability of the medication formulation, stability experiments were conducted in accordance with ICH guidelines. A polyethylene-laminated aluminum packaging contained the optimized IF12 formulation. For three months, the samples were stored at 4°C and 75% RH.

#### CONCLUSION

It was determined that the solvent casting approach was effective in producing the fast-dissolving IRB films. Orally disintegrating films (ODF) have been effectively used for patients who are immobile, schizophrenic, or traveling in areas without access to water. IRB films underwent quality control testing, including kinetic studies, stability studies, disintegration time, surface pH, folding endurance, SEM, thickness, weight fluctuation, and in-vitro diffusion. At accelerated stability conditions, the optimized formulation IF12 was found to be stable.



Improved dissolving rate and quick start of action were demonstrated by prepared films, which led to improved patient compliance, successful therapy, and increased popularity in the near future.

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