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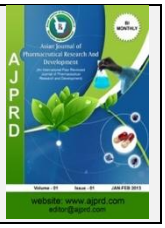

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Research Article

Formulation and Evaluation of Oral Fast Dissolving Film

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A B S T R A C T

The objective of present research work was to select cyclodextrins derivative for inclusion complex with Ezetimibe and formulate fast dissolving film to enhance pharmacokinetic and pharmacodynamic performance of drug.In this work, Hydroxypropyl Methylcellulose (HPMC) E5 and E15 were used as primary film-forming polymers in various combinations with pectin and glycerine as a plasticizer. The solvent casting method was employed to prepare the films. To improve the solubility and dissolution rate of Ezetimibe—a BCS Class II drug with low water solubility—inclusion complexes were developed using β-cyclodextrin, confirmed via FTIR, DSC, and XRD analyses. A 3^2 factorial design was implemented to systematically study the impact of formulation variables on key film characteristics such as disintegration time, drug content uniformity, folding endurance, and in vitro drug release. Among the formulations, batch F3 showed the most promising results, withRapid disintegration within 22 seconds, High drug content (98.87%), Superior tensile strength and folding endurance, Maximized drug release (above 95% within 5 minutes). The optimized batch followed first-order release kinetics, as validated by kinetic modelling (Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models).Stability studies of batch F3 under accelerated conditions demonstrated excellent physicochemical stability for up to 3 months, confirming formulation robustness.The study concludes that Ezetimibe-loaded oral films developed using HPMC E5/E15, pectin, and glycerine can serve as a patient-friendly, fast-dissolving alternative dosage form with improved bioavailability and therapeutic efficacy, opening avenues for innovative drug delivery systems in lipid-lowering therapy.

Keywords: Oral Fast Dissolving Film (OFDF), Ezetimibe, Hydroxypropyl Methylcellulose (HPMC), Inclusion Complex, Drug Release, Bioavailability.

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INTRODUCTION [1-12]

Oral drug delivery remains a preferred route for its ease of administration, patient acceptance, and the potential to enhance bioavailability, especially for medications undergoing first-pass metabolism. The introduction of ODF in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”. Oral Thin Films (OTFs) are likely to become a strong replacement for Oral Dispersible Tablets (ODTs). The demand for rapid onset of action and improved bioavailability has driven the development of dosage forms that quickly disintegrate and dissolve in the buccal cavity, facilitating direct absorption through the buccal mucosa into the systemic circulation. This approach proves particularly beneficial for individuals facing challenges in swallowing, including pediatric and geriatric patients, as well as those with limited liquid intake or conditions like dysphagia. The need for innovative formulations arises from the recognition that traditional oral dosage forms, such as capsules and tablets, pose difficulties for certain patient populations. Swallowing-related issues affect approximately 35% of the total population, with dysphagia presenting a significant hurdle in drug delivery and therapeutic efficacy. As an alternative method to overcome these limitations, orally disintegrating systems were developed, aiming for a fast release of the drug without water ingestion, also enabling drug absorption directly through oral mucosa to enter systemic circulation, avoiding first-pass hepatic metabolism. Orally disintegrating films (ODFs), also called Oro dispersible films, are thin polymeric films with the size of a postage stamp that quickly hydrate and adhere to the mucosa wetted by saliva, disintegrate their matrices and release active compounds for absorption.They also must provide acceptable taste and mouth-feel, with a short disintegration time (up to 1 min).

MATERIAL AND METHOD

MATERIAL

Ezetimibe (Molecular weight = 409) was received as a gift sample from MSN Hyderabad, (India). B- Cyclodextrinwas purchased from Research lab Chemicals Mumbai. HPMC E5, HPMC E15, Pectin, Saccharine, Citric acid, Glycerine, Methanol were obtained from SD Fine Lab Chemical, Mumbai, (India). Phosphate buffer saline at pH 6.8 was prepared as described in the Indian pharmacopoeia.

METHOD

Formulation of Fast Dissolving Film Using Ezetimibe by Solvent Casting Method:

Fast Dissolving Film of Ezetimibe was prepared using HPMC E5 and E15 as polymer by solvent casting method. The HPMC E5 and E15 were dissolved in 10 ml water by using magnetic stirrer.Drug was dissolved in polymer solution. Plasticizer and citric acid were added to polymer solution. Sweetener solution also added to polymer solution. The solution was allowed to stand for 30 min to allow deaeration to take place. The solution was casted on a Petri dish and dried at room temperature for 24 hr. The film was removed and cut into the required size of 3.1 x 1.8 cm².

Table 1: Formulation of oral fast Dissolving Film (Formulation Plan)

Formulation Batch	Inclusion Complex of Drug and Cyclodextrin (mg)	HPMC E5 (mg)	HPMC E15 (mg)	Citric Acid (mg)	Saccharine (mg)	Glycerine (ml)	Water (ml)
F1	33.33	300	300	100	50	2	10
F2	33.33	400	300	100	50	2	10
F3	33.33	500	300	100	50	2	10
F4	33.33	300	400	100	50	2	10
F5	33.33	400	400	100	50	2	10
F6	33.33	500	400	100	50	2	10
F7	33.33	300	500	100	50	2	10
F8	33.33	400	500	100	50	2	10
F9	33.33	500	500	100	50	2	10

PREFORMUALTION STUDY [13]

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients. The overall objective of Preformulation testing is to generate information useful to the formulator in developing stable dosage forms, which can be produced at large scale. A thorough understanding of physicochemical properties may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that there are no significant barriers to the compound's development.

Confirmation of Pure Drug:

The received sample of drug Ezetimibe was standardized by carrying out the following tests:

Description:

The Ezetimibe sample was evaluated visually for appearance and colour.

Melting Point Determination

Melting point determination of the obtained drug sample was done as it is a first indication of purity of the sample. Melting point of pure drug was determined by capillary tube method. The capillary tube was closed at one end by fusion and was filled with drug by repeated tapings.The capillary tube was placed in a Thiel's tube apparatus along with thermometer. The heat was provided to Thiel's tube with the help of burner. The rise in temperature was recorded with thermometer. The temperature at which the drug started melting was recorded.

Determination of Solubility [13]

In assessing the solubility of Ezetimibe, a semi-quantitative approach was employed. Incremental amounts of the drug were added to fixed volumes of solvents, including distilled Water, ethanol and methanol. Following each addition, the system underwent vigorous shaking and visual inspection for any undissolved particles.

Spectrophotometric Method for the Estimation of Ezetimibe

An ultraviolet-visible spectrophotometer was employed for the analysis of Ezetimibe. The spectrophotometric method for estimating Ezetimibe was developed in Methanolic Phosphate Buffer 6.8 pH.

Determination of λ Max [13]

In order to ascertain the wavelength of maximum absorption (max) of the drug, solution of the drug (10µg/ml) in Phosphate buffer pH 6.8 was scanned using spectrophotometer within the wavelength region of 400-200 nm against methanolic Phosphate buffer 6.8 as blank. Spectra and the absorption curve showed characteristic absorption maxima at λ max 232 nm for Ezetimibe.

Standard Calibration Curve of Ezetimibe in Methanolic Phosphate Buffer 6.8 [13]

1. **Preparation of Standard Solution**

   Drug (100 mg) was taken and to this 30 ml methanol (as co solvent) and 70 ml water.

Phosphate buffer 6.8 was added and shaken for about 20 min on ultra sonification to obtained a clear solution. To this sufficient amount of medium was added to make up the volume up to 1000 ml.

2. **Preparation of Working Solution:**

From above solution various dilutions were prepared to get concentrations of 5,10,15, 20 and up to 25 mcg/ml.

3. **Measurement of Absorbance:**

The absorbance of the various dilutions was measured against Methanolic phosphate buffer 6.8 as a blank at 232 nm using double beam UV visible spectrophotometer. The graph of absorbance v/s concentration was plotted and data were subjected to linear regression analysis.

Fourier Transform Infrared Spectroscopy for Analysis of Drug [14]

The FTIR spectrum of drug was recorded on an Infrared spectrophotometer by conventional KBr plate method. 5mg of drug sample was mixed with 500 mg of powdered potassium bromide. The mixture was passed with 25,000 psi pressure in a press to formed a small pellet. IR spectrum of drug was recorded in the frequency range 400-4000-1 cm.

Differential Scanning Calorimetry (DSC) Analysis of Drug [14]

Differential Scanning Calorimetry (DSC), accurately weigh and place the samples in hermetically sealed pans with pinholes. Set the DSC instrument to heat from 25°C to 400°C at a rate of 10°C per the under a nitrogen purge of 20 ml/min. Record the thermal behaviour of pure drug. Analyse the resulting thermograms for changes in thermal events to identify any interactions.

Compatibility Study of Drug and Excipients [15]

Fourier Transform Infrared Spectroscopy (FTIR) Study

Fourier Transform Infrared Spectroscopy (FTIR) Study Drug-excipient interaction studies were conducted using an FTIR spectrophotometer. The FTIR spectra of the drug and polymers were recorded on an infrared spectrophotometer within the frequency range of 400-4000 cm.

Differential Scanning Calorimetry (DSC) Study [15]

To determine the compatibility between drug and polymer using Differential Scanning Calorimetry (DSC), accurately weigh and place the samples in hermetically sealed pans with pinholes. Set the DSC instrument to heat from 25°C to 400°C at a rate of 10°C per the under a nitrogen purge of 20 ml/min. Record the thermal behaviour of pure drug and polymer mixture.Analyse the resulting thermograms for changes in thermal events to identify any interactions.

Calculation of Dose [16]

Ezetimibe 10 mg is a lipid-lowering medication used to reduce elevated cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol. The usual adult dose is 10 mg once daily, with or without food. It can be prescribed alone or in combination with statins or other lipid-lowering agents.

Phase-Solubility Studies [17]

Phase-solubility studies were performed according to the method reported by Higuchi and Connors. An excess amount of Ezetimibe (10mg) was added to the 10 ml of distilled water containing increasing concentration of β- CD solution at various concentrations (0.001-0.01 M) in 10 ml screw capped bottles. The contents were stirred for 72 hours at 37 °C on rotary flask shaker. After equilibrium, the samples were filtered through Whatman filter paper no. 42 and analysed spectrophotometrically for drug content at the wavelength of 232 nm using Double Beam UV Spectrophotometer Model No. UV 1800.

Preparation of Inclusion Complexes of Drug and Cyclodextrins

The complexes of β-CD and with EZE were prepared in the molar ratio of 1:1, 1:2, 1:3 (on the basis of phase solubility study) by different methods like Kneading Method. Physical mixture of β-CDs and EZE were prepared by simply mixing powders with a spatula for 15 min.

Kneading Method

Ezetimibe and the cyclodextrins were weighed in different ratio as shown in Table and transferred to mortar and kneaded for 45 min. using alcohol-water mixture in ratio 1:1, sufficient solvent was added to maintained paste like consistency. The resulting paste was then dried in oven at 50°C for 24 hours. The dried complexes were grounded in mortar for 2 min and passed through sieve no. 100. The prepared complexes were stored in glass vials and used for further studies.

Table 2: Composition of inclusion complex

Sr. No	Composition	Molar Ratio
1	Ezetimibe β-cyclodextrins	1:1
2	Ezetimibe β-cyclodextrins	1:2
3	Ezetimibe β-cyclodextrins	1:3

Characterizations of Complexes [17]

Fourier Transform Infrared (FTIR) Spectroscopic Analysis:

The FTIR spectra of pure drug and β-cyclodextrin, physical mixtures and inclusion complexes were taken by preparing KBr pellets using a FTIR Spectrophotometer.

Powder X-ray Diffraction (PXRD) analysis:

The physical state of drug in the various preparations was evaluated by powder X-ray diffraction study. Powder X-ray diffraction patterns of all samples were determined using X-Ray Diffractometer PAN analytical Spectris,a voltage of 40 µL and a current of 30 mA.

Differential Scanning Calorimetry (DSC) Analysis:

DSC scans of all powdered samples were recorded using DSC crucible Al 40uL, at of 100C /min heating rate, under

nitrogen environment. The temperature range used was 0-4000C.

Drug Content:

The percent drug content of each inclusion complexes was determined using powder equivalent to 10 mg Ezetimibe and was dissolved in 20 ml methanolic phosphate buffer 6.8 using the mechanical shaker for 20 min and to the solution obtained methanolic phosphate buffer 6.8 was added and volume was made to 50 ml. The solution was then filtered through Whatman filter paper no.42 and required dilutions were being made and absorbance was taken at 232nm using Double Beam UV Spectrophotometer.

EVALUATION OF FAST DISSOLVING FILMS [18-19]

Physical Appearance:

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

Weight Uniformity of Films:

Three films of the size 3.1 x 1.8 cm^2 were weighed individually using digital balance and the average weights were calculated.

Thickness of Films:

Thickness of the films was measured using screw gauge with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

Folding Endurance of Films:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (approximately 3.1 x 1.8 cm) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

In Vitro Disintegration Time of Films:

In vitro disintegration time is determined visually in a Petri dish of 10 ml distilled water with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

Surface pH of Films:

Surface pH was determined to reduce the irritation of oral mucosa due to alkaline or acidic pH. It was kept in the range of salivary pH. Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode near the surface of films and allowing equilibrate for 1 min. Reading was recorded in pH meter.

Moisture Content:

This test is carried to evaluate the integrity of the film at dry condition. Film was weighted accurately and kept in a desiccator containing fused anhydrous calcium chloride. After 24h hr film was removed and weighted percentage moisture content of film was determined as follow:

$$\% \text{ Moisture content} = (Wa\text{-}Wb)\ Wb \times 100$$

Where,

Wa and Wb are the weights of film samples before and after drying.

Swelling Index:

After the determination of the film weight, the samples were allowed to swell in a phosphate buffer of pH 6.8 until 8 h. Increase in film weight (n=3) was determined at different time intervals by removing the film from the phosphate buffer and blotting with filter paper to remove excess water.

The percent swelling (%S) swelling was calculated by using the equation:

$$\text{Percent swelling } (\%S) = (Xt - X0/X0) \times 100$$

Where,

Xt is the weight of the swollen film after time t,

X0 is the initial weight of the film

Drug Content Uniformity Study of Films:

The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 3.1x1.8 cm^2 were cut from three different places from the casted films. Each film was placed in 10 ml volumetric flask and diluted with Phosphate buffer 6.8 up to 10 ml. The absorbance of the solution was measured at 232 nm using UV/visible spectrophotometer. The percentage drug content was determined.

In vitro Dissolution Study:

In vitro dissolution of mouth dissolving films was studied in USP XXIV dissolution test apparatus 900ml Phosphate buffer 6.8 solutions was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution medium was maintained at 37±0.2°C throughout the experiment. One film was used in each test. Samples of dissolution medium (1ml) were withdrawn by means of syringe. Solution was filtered with Whatman filter paper. Sample were withdrawn after 3,6,9,12 and 15 minute intervals of time and analysed fordrug release by measuring the absorbance at 232 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium.

Stability Studies [20]

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological Specifications. A drug formulation is said to be stable if it fulfils the following requirements,

• It should contain at least 90% of the stated active ingredient.

• It should contain an effective concentration of added preservatives if any.

• It should not exhibit discoloration or precipitation, nor develop a foul odour.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors

such as temperature, humidity, and light and enables recommended storage conditions, re-test periods, and shelf lives to be established. International Conference on Harmonization (ICH) specifies the length of study and storage conditions as,

1. Long-term testing 25°C ±2°C/60% RH 5% for 12 months.
2. Accelerated testing 40°C ±2°C/75 % RH 5% for 6 months.

RESULT AND DISCUSSION

Pre-Formulation Study

The result of Preformulation studies is given below

Description:

- **Colour:** White Powder
- **Odour:** odourless
- **Taste:** Tasteless

Determination Melting Point:

The melting point of the Ezetimibe drug sample was found to be164-166 °C which is within the reported range of 164-166 °C. It complies with the purity of the drug sample.

Discussion: Ezetimibe has the same melting point range as mentioned in the referred reference research index.

Determination of Solubility

Ezetimibe is Freely soluble in organic solvent like Methanol and Ethanol.

Discussion: The secured drug was showing the same solubility as the pure drug as per IP.

Spectrophotometric Method for the Estimation of Ezetimibe

Determination of λ max: -

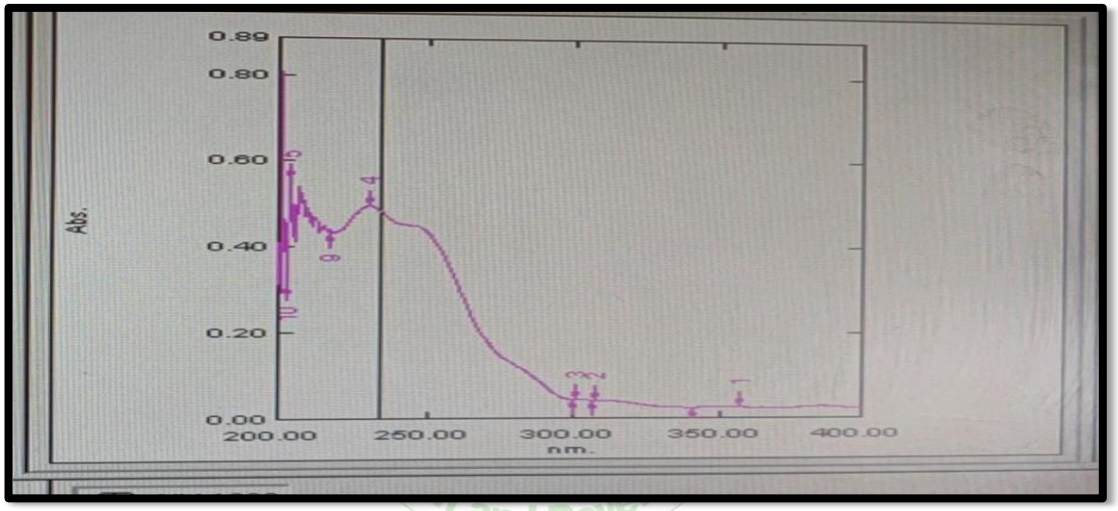

Figure 1: U.V Spectrum of Ezetimibe in Methanolic Phosphate Buffer pH 6.8

Discussion: The maximum absorbance of the Ezetimibe was studied and found to be 234 nm. Hence, the wavelength 234 nm is selected for estimation of drug content and analysis of drug in dissolution media. This is confirmatory analytical test for drug.

Standard Calibration Curve of Ezetimibe

Table 3: Standard Calibration Curve of Methanolic Phosphate buffer pH 6.8

Sr. No	Concentrations (µg/ml)	Absorbance ± SD
1	5	0.14±0.01
2	10	0.25±0.02
3	15	0.37±0.024
4	20	0.49±0.25
5	25	0.6±0.26

Calibration Curve of Ezetimibe in Methanolic Phosphate Buffer pH 6.8

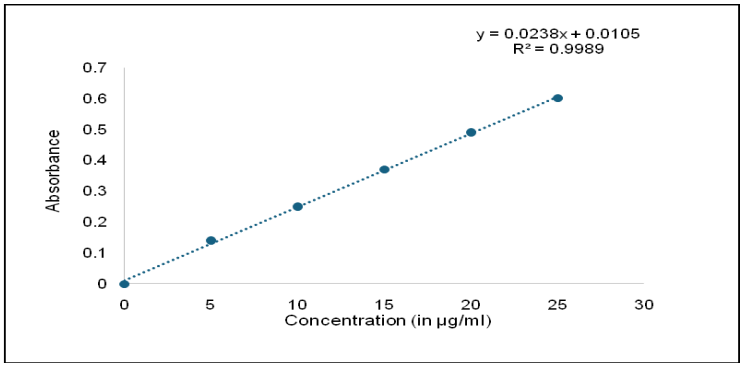

Figure 2: Standard Calibration Curve of Ezetimibein Methanolic Phosphate Buffer 6.8

Discussion: - From the standard curve, it was observed that the drug obeys Beer's law in concentration range of 2-20µg/mlin methanolic Phosphate buffer pH6.8. Drug showed good linearity with regression of coefficient (r^2=0.9989) and equation for this line obtained was found to be (y= 0.0238x + 0.0105) which is used for the calculation of amount of drug and dissolution study.

Fourier Transform Infrared Spectroscopy Analysis of Drug

The FT-IR spectrum of the Ezetimibe pure drug was found to be similar to the standard spectrum of Ezetimibe. Peaks of sample were matched with standard. The spectrum of Ezetimibe showed the following functional groups at their frequencies mentioned. The FTIR spectrum of Ezetimi be has shown in Figure.The peak obtained in FTIR of pure drug for group C=O, C-F, C-OH, C-N, Benzene, Propane were found to be1750cm^{-1},1000cm^{-1} 3200cm^{-1}, 300cm^{-1}, 1500cm^{-1}, 2850cm^{-1} From the figures it was observet hat peaks of pure drug showed in FTIR.

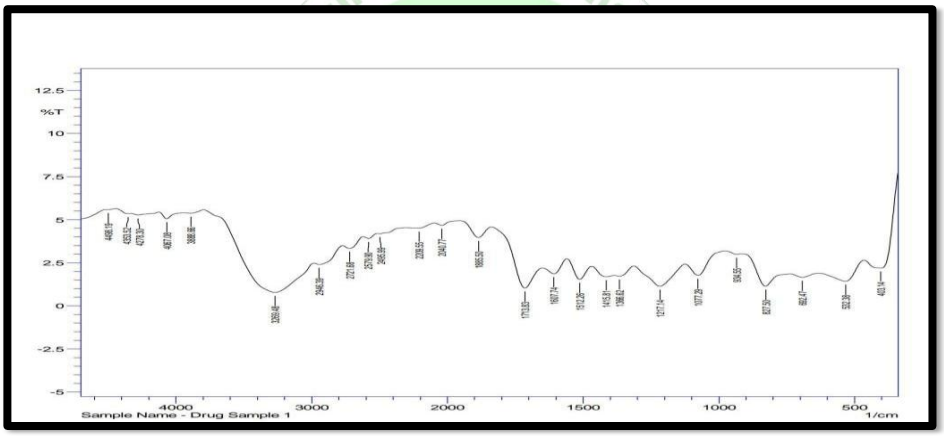

Figure 3: FTIR Spectrum of Ezetimibe

Discussion: - The spectra studied at 4000 to 400 cm. The FTIR of drug was found to be similar to the standard FTIR spectrum of Ezetimibe.

Differential Scanning Calorimetry (DSC) Analysis of Drug

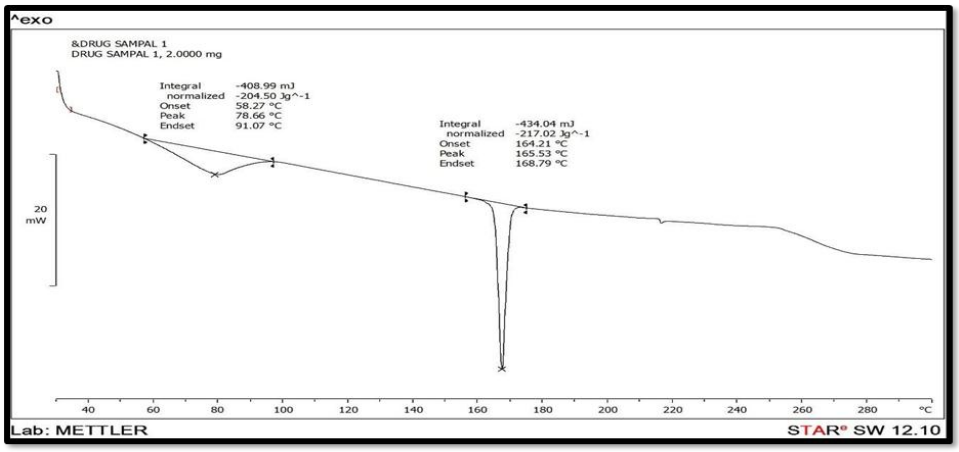

Figure 4: DSC of Pure Drug (Ezetimibe)

Discussion: - The endothermic peak with Tmax 163^0 - 166^0 C corresponds to the melting point of the ezetimibe. Drug-Excipients compatibility is being determined by DSC. The DSC study was carried out Differential scanning calorimeter (DSC 60) with thermal analyzer.

Compatibility Study of Drug and Excipients

Fourier Transform Infrared Spectroscopy (FTIR) Study

Compatibility Study of drug with polymers was performed. The spectrum of drug and excipient showed the following functional groups at their frequencies mentioned in was matched with the FTIR spectrum of pure drug (Ezetimibe).

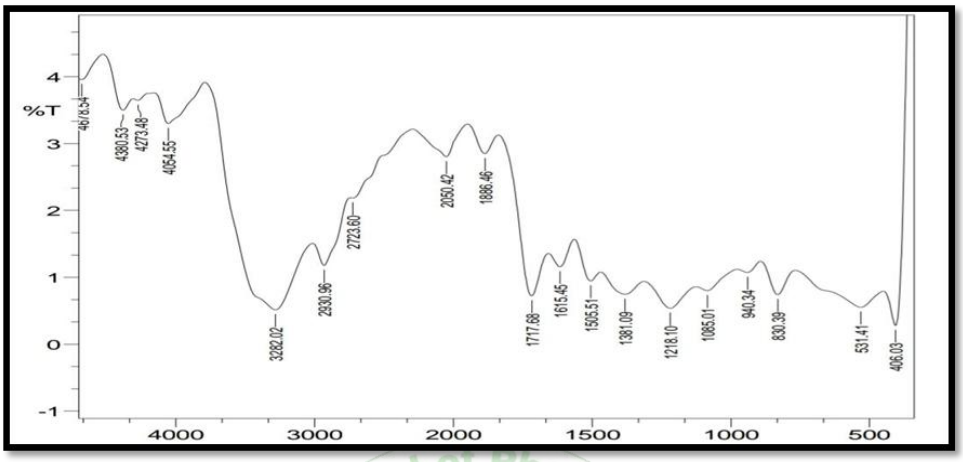

Figure 5: IR Spectrum of Drug and Polymer

Discussion: Drug excipient interaction study by FTIR spectroscopy was carried out as per standard procedure. FTIR spectra of physical mixture of Drug and polymers i.e. HPMC E5 and HPMC E 15. It was observed that the principal peak of the drug was found in the FTIR spectra of a drug as well as the FTIR spectra of a physical mixture of drugs and polymer. It was suggested that there was no physical and chemical interaction between drugs and polymers

Differential Scanning Calorimetry (DSC) Study

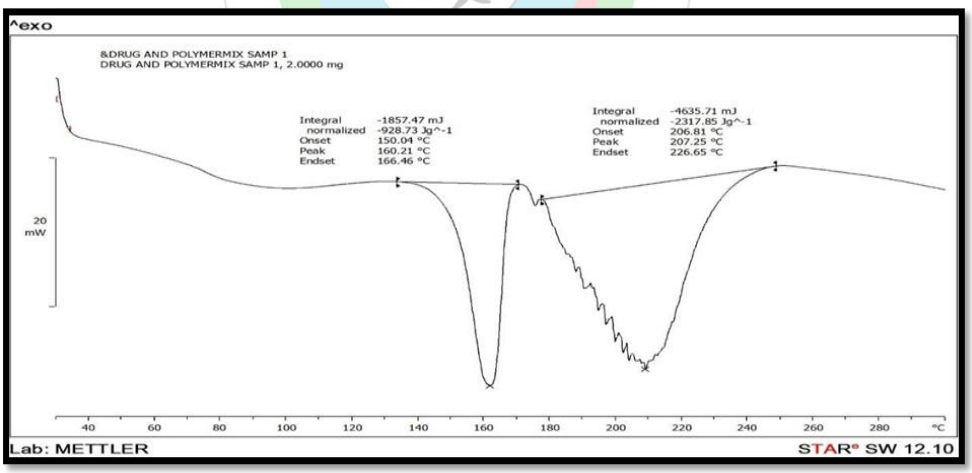

Figure 6: DSC of Pure Drug and Polymer

The Graph exhibits a sharp endothermic peak at 168.20°C. Physical mixture of Drug with polymers showed the presence of characteristic peaks of drug indicating physical compatibility between excipients.

Calculation of Dose

Ezetimibe 10 mg is a lipid-lowering medication used to reduce elevated cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol. The usual adult dose is 10 mg once daily, with or without food. It can be prescribed alone or in combination with statins or other lipid-lowering agents.

Phase-Solubility Studies:

The phase solubility method is useful for investigating an inclusion complexation of drug with cyclodextrin and its derivatives in distilled water because it gives not only the solubilizing ability of host molecules but also the stability constant of complexes with the help of phase solubility curve. From the phase solubility study. It was observed that B-CD showed Bs type phase solubility curve indicating limited solubility.

From (0.01 to 0.05M) B-CD concentration, the solubility of ezetimibe was suddenly increased linearly due to the

formation of soluble complexes. As the ascending portion of the phase solubility diagram may be considered as A, type phase solubility diagram, it is possible to determine the complex stoichiometry.

As the slope value is less than I in the distilled water it could be considered as formation of 1:1 complex on a molar basis.At the B-CD concentration value of 0.05 M, the solubility limit of this complexes is reached and so further addition of B-CD results in precipitation of the complexes.

The stability constant (Ks) of the 1:1 complex of drug with beta cyclodextrin was calculated by the ascending part of the diagram in Bs type solubility diagram and it was found to be 23.50

From these it could be concluded that ß-CD is the proper carrier for increasing solubility. Hence B-CD was taken for further study.From the phase solubility study it was observed that showed ratio 1.1 is enhanced the solubility of Ezetimibe. Solubility of Ezetimibe increased in all media in a linear fashion with increased concentration of HP-B-CD and M-B-CD and showed AL type phase solubility curve indicating that soluble complexes were formed and no precipitation was observed.

Table 4: Complex of Drug and Cyclodextrin Ratio to Molar Ration

Sr. No	Complex According to Molar Ratio	Absorbance	Concentration
1	1.1	0.57	23.50
2	1.2	0.47	20.14
3	1.3	0.40	16.36

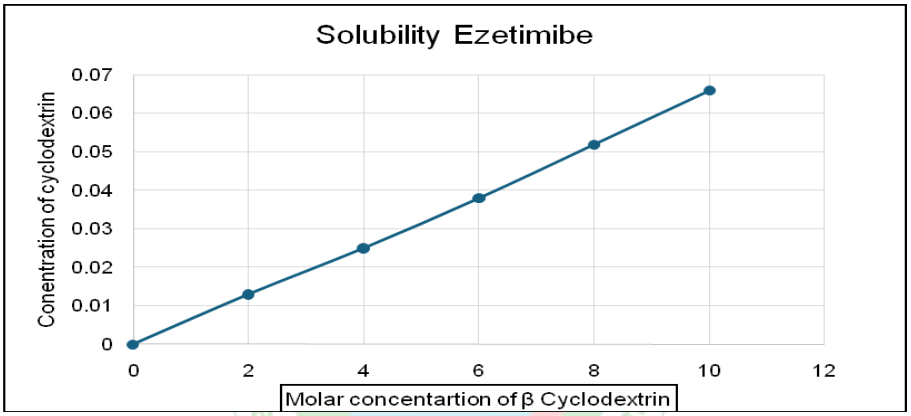

Figure 7: Phase Solubility Diagram of Ezetimibe and Cyclodextrin

Characterizations of Complexes

Fourier Transform Infrared (FTIR) Spectroscopic Analysis:

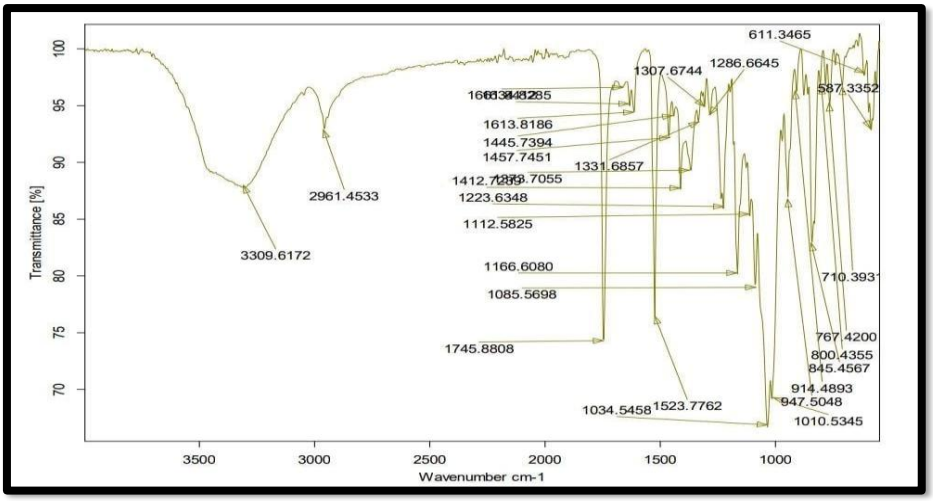

Figure 8: FTIR Spectrum of Inclusion Complexo f Ezetimib eand Cyclodextrin

Discussion: - The characteristic peak of ezetimibe and cyclodextrin complex such as OH-3309^{cm-1}& C-H 2961^{cm-1},C=O1745^{cm-1},C=C1613^{cm-1},C-O1260^{cm-1},N-O1523^{cm-1},C-Cl710^{cm-1}.Theresult of FTIR was showed were found to be retained in all inclusion complex showing only architectural fitting of the drug molecules in to the cyclodextrin without in chemical interaction.

Powder X-ray Diffraction (PXRD) analysis:

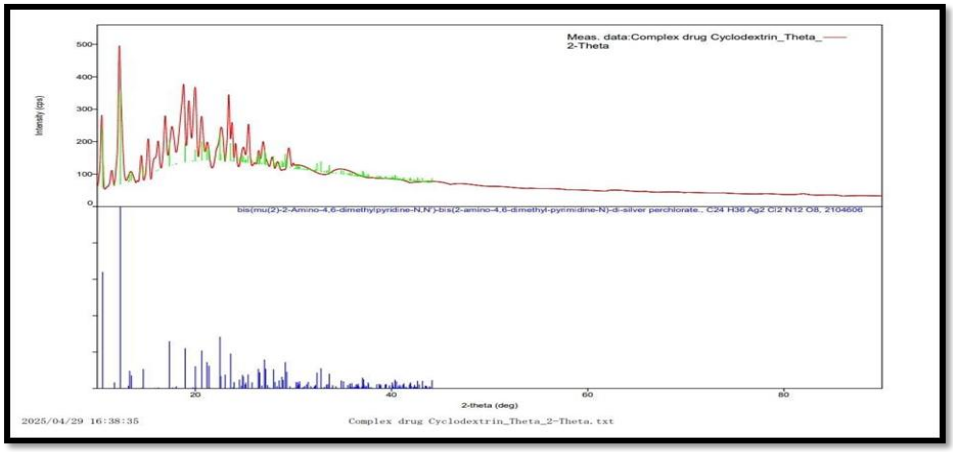

Figure 9: XRD of Inclusion Complex of Drug and Cyclodextrin

Discussion: - Characteristic peaks of ezetimibe lie between 2θ;6 to 30. Broadening of some of these characteristic speaks and complete disruption of remaining in the complexes shows changes in solid characteristic of the drug with subsequent reduction in the crystallinity.

Differential Scanning Calorimetry (DSC) Study

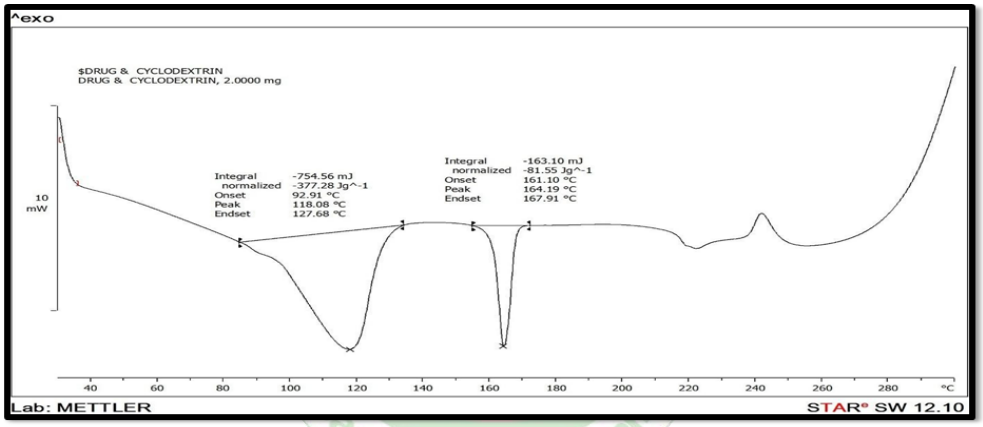

Figure 10: DSC Spectra of inclusion Complex Drug and Cyclodextrin

Discussion: - The endothermic peak with Tmax 163-166 corresponding to the melting of the ezetimibe. In the physical Mixture of ezetimibe with cyclodextrin as well as inclusion complex, there is no decreasing in the melting point.

Drug Content of Inclusion Complex:

Drug content of all the inclusion complex were in the range 59.40- 41.38%. This indicates the proper loading of drug in inclusion complexes and effectiveness by kneading method.

Table 5: Drug Content of Inclusion Complexes

Sr. No	Complex According to Molar Ration	% Drug Content
1	1:1	59.40±0.53
2	1:2	50.92±0.23
3	1:3	41.38±0.31

Calculation of Dose:

For the incorporation of the inclusion complex of drug and cyclodextrin complex which is incorporated in the film.

The dose calculation is followed as:

Calculation Drug Loading (%w/w) in complex

$$\text{Drug Loading (\%)} = \frac{Amount\ of\ Pure\ Drug}{Amount\ of\ complex} \times 100$$

$$= \frac{10}{30} \times 100$$

= 33.33%

The complex containing 33.33% w/w of ezetimibe; hence it is concluded that 33.33 mg of complex is equal to 10 mg of ezetimibe

EVALUATION OF FAST DISSOLVING FILMS:

The formulations were subjected to evaluation parameters as mentioned below:

Table 6: Evaluation of All the Formulation Batches

Formulation Batches	Physical Appearance	Weight of Film	Thickness (nm)	Folding Endurance	DI Time (Sec)
F1	Transparent	99.5±0.12	0.18±0.01	186±2	1 min 16sec±0.31
F2	Transparent	93.6±0.32	0.19±0.02	187±5	1 min 17sec±0.29
F3	Transparent	93.1±0.43	0.17±0.01	183±3	1 min 14sec±0.25
F4	Transparent	94.01±0.34	0.20±0.02	190±5	1 min 25 sec±0.30
F5	Transparent	95.3±0.44	0.22±0.03	197±3	1 min 32 sec±0.28
F6	Transparent	96.6±0.36	0.26±0.03	201±6	1 min 39 sec±0.27
F7	Transparent	97.6±0.42	29±0.03	198±7	1 min 50 sec±0.32
F8	Transparent	98.3±0.44	0.32±0.04	210±5	1min 58 sec±0.34
F9	Transparent	99.5±0.40	0.35±0.02	220±4	2 min 05±0.36 sec

Table 7: Evaluation of All the Formulation Batches

Formulation Batches	Surface pH of Film	Moisture Content %	Drug Content	Swelling Index %	In- Vitro Dissolution Study
F1	6.80	1.28±0.02	70.74±0.63	33.04±0.2	85.33±0.5
F2	6.80	1.70±0.02,	85.96±0.43	37.65±0.3	83.31±0.85
F3	6.80	1.07±0.03	86.35±0.76	39.45±0.5	87.35±0.67
F4	6.80	1.80±0.04	63.15±0.56	35.06±0.6	68.35±0.67
F6	6.80	2.13±0.03	73.25±0.60	59.13±0.8	57.35±0.85
F7	6.80	2.15±0.05	55.50±0.45	69.11±0.7	50.25±0.77
F8	6.80	2.74±0.03	50.49±0.36	71.22±0.6	47.38±0.42
F9	6.80	2.51±0.13	40.37±0.76	78.33±0.3	32.42±0.23

Table 8: In vitro Drug Released of F3 Formulation

Sr. No	Time (in min)	Cum. Drug Released (in mg)	% Cum. Drug Released	% CD Remaining	Log % CD Remaining
1	0	0	0	100	2
2	3	0.015±0.85	9.51±0.13	90.49±0.84	1.956601±0.01
3	6	0.024±0.83	22.45±0.9	77.55±0.90	1.889582±0.03
4	9	0.026±0.87	57.34±0.84	42.66±0.93	1.630021±0.05
5	12	0.029±0.90	77.33±0.85	22.67±0.78	1.355452±0.08
6	15	0.031±0.86	98.3±0.52	1.7±0.32	0.230449±0.04

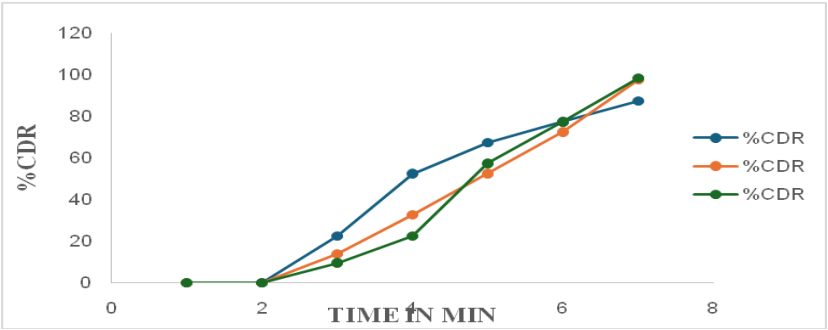

Figure11: Plot % Cum. Drug Retained Vs. Time for Formulation F1, F2 and F3

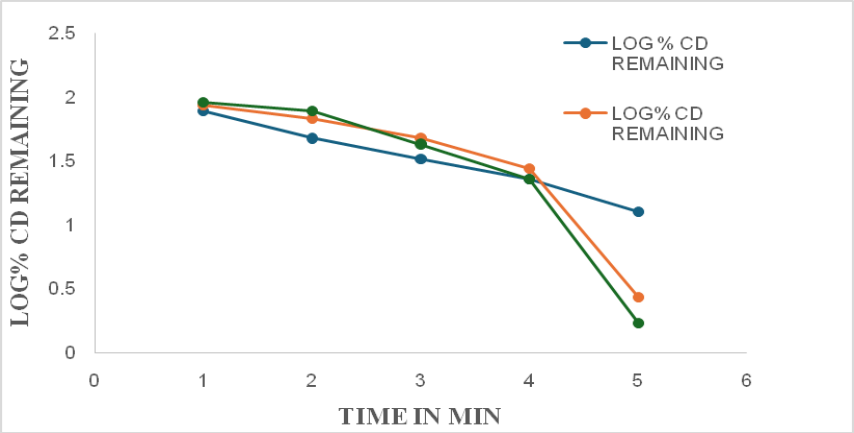

Figure 12: Plot of Log % Drug Released Vs. Time for Formulation F1, F2 and F3

Kineties of Drug Release

The kinetic treatment reflected that the release data of all the formulations showed higher R^2 values or first order plot indicating that release of drug follows first order kinetics as shown in Table

Table 9: Kinetics of Drug Release

Formulation Batch	Zero Order R^2	First Order R^2	Higuchi Model R^2	Kores Meyer Peppas Model R^2	Hixson Crowel Model R^2	Best Fitted Model
F3	0.8695	0.9853	0.9145	0.9358	0.8742	First Order Kinetic

Discussion: From the result kinetics batch F3 has First order kinetics as best fitted model with regressioncoefficient 0.9853 with Log% cumulative drug released at 15 min 98.3%.Drug released study shows drug released from F3 batch is by first order kinetic model.

STABILITY STUDY

The stability studies of optimum formulation revealed that there is no significant reduction in drug content, Disintegration time, Appearance was observed over period of 28 days.

Table 10: Stability Study for F3 Formulation

Stability (Room Temp)	Appearance	Drug Content	Disintegration Time
0 Day	Transparent	86.35±0.74	1 min 14 sec±0.35
7 Days	Transparent	86.35±0.56	1 min 14 sec±0.31
14 Days	Transparent	86.35±0.76	1 min 14 sec±0.29
21 Days	Transparent	86.35±0.45	1 min 14 sec±0.25
28 Days	Transparent	86.35±0.32	1 min 14 sec±0.23

Table 11: Stability Study for F3 Formulation

Stability (45 ± 2^0,75±5%RH)	Appearance	% Drug Content	Disintegration Time
0 Day	Transparent	86.35±0.68	1 min 14 sec±0.32
7 Days	Transparent	86.35±0.61	1 min 14 sec±0.29
14 Days	Transparent	86.35±0.59	1 min 14 sec±0.25
21 Days	Transparent	86.35±0.55	1 min 14 sec±0.22
28 Days	Transparent	86.35±0.51	1 min 14 sec±0.20

Stability study at room temp 45 ± 2^0 , 75±5% RH was carried out for 0-28days. At room temp% Drug constant was found to be 86.35±0.68 and disintegration time was about 1 min 14 sec. At 45 ± 2^0, 75 ± 5^0, RH drug content was found to be 86.35±0.68 and disintegration time was about 1 min 14 sec±0.35

No significant changes were observed on drug content and disintegration time at room temp and 45 ± 2^0, 75 ± 2^0 RH. Hence formulation F3 was found to be stable for 28 days.

CONCLUSION:

The optimized batch **(F3)** containing polymer HMPC E5 and HMPC E15 shows that good stability at various storing

condition temp 45± 2^0, 75±5% RH, At 45±2^0,75±5^0 RH. Hence Formulation **(F3)** was found to be stable for 28 days.

SUMMARY AND CONCLUSION

SUMMARY

For the preparation of oral fast dissolving film containing Ezetimibe was selected as active ingredient. It is antihyperlipidemic agent and used commonly cardiovascular drug. It is prescribed in hyper cholesterol and also in the combination of statin for the effective reduction of cholesterol. The sample of Ezetimibe was standardised by carrying out various analytical identification test (Determination of λ max, FTIR, and DSC Study) and various pre formulation parameter such as Physical description study, Determination of solubility and melting point determination.

For the preparation of Oral fast dissolving film HPMC E5, HPMC E15 as a polymer, Glycerine as a Plasticizer, Citric acid as a saliva stimulating agent, Saccharine as a sweetening agent selected. All the polymer and chemicals pass the identification test as per describe in IP. The drug-excipients Compatibility study was carried out by using FIIR spectrophotometer and Differential scanning calorimetric, it was observed that there was no physical and chemical interaction between drug and polymers

Standard Calibration Curve of Ezetimibe in Methanolic Phosphate Buffer pH 6.8 was plotted in concentration range of 2.0-20 µg/ml it was observed that it follows Beer's law and shown good linearity with regression of coefficient (r = 0.9989) and equation for this line obtained was found to be y = 0.0238x. Formulation of oral fast dissolving film was prepared by using various other processing excipients such as and it was prepared HPMC E5, HPMC E15, Glycerine, Citric acid and Saccharine by Solvent casting method.

Preliminary Trial for Formulation of oral fast dissolving film was design by Seeing of Various polymers (Pectin, HPMC E5, HPMCE15) evaluated for post formulation study (Thickness, weight variation, Folding endurance, Surface pH, Disintegration time) and prepared OFDf, it was observed that from post formulation study of preliminary trials batch that study that all formulation shows good result.

Factorial design was selected to optimized oral fast dissolving film, for these two independent variables was selected such as HPMC E5 (X1) and HPMC E15(X2) and dependent variables for 3 factorial designs. It was observed from post formulation study of factorial batch, all these

formulations show good result of thickness, weight variation, folding endurance, Surface Ph, Drug content. It was also observed that the result is depend upon concentration of polymer. All this formulation shows rapid actions.

By forming the inclusion complex of drug and cyclodextrin by taking the ratio according to their molar ratio 1.1, 1.2, 1.3 in which contain 100 of ezetimibe and 200 mg of cyclodextrin. After forming the complex by kneading method we were characterised the complex of FTIR, DSC. It was also observed that there is no interaction of ezetimibe and cyclodextrin. By forming the complex, we should increase the solubility of drug (1.1= 23.50, 1.2= 20.14,1.3= 16.36). It was observed that the solubility of 1.1 ration were increased and taking the inclusion complex of drug and cyclodextrin 1.1

Kinetic of drug release was applied to dissolution data of factorial batch. It was observed **F1, F2, F3, F5, F8, F9** has best fitted to First order kinetics. While **F4, F6, F8** has best fitted to Higuchi order release.

From evolution of oral fast dissolving film formulation for factorial batch, formulation F3 has shown (Transparent Appearance, Weight uniformity 93.1±0.23, Thickness 0.17±0.01, Folding endurance 183±2, in vitro disintegration time 1 min 14 sec ± 0.30, Surface pH. 6.80, Moisture content 1.07, Swelling index 39.45, Disintegration time (87.35±0.68) at 15 min.

Hence, from above it was concluded that formulation, oral fast dissolving film formulation (F3) containing HPMC E5 (500), HPMC E15 (300), Citric Acid (100), Saccharine (50mg) glycerine (2 ml), which could be most promising oral fast dissolving film containing inclusion complex of drug and cyclodextrin. Stability study at room temp 45±20 ,75±5% RH was carried out for 0-28days. At room temp % Drug constant was found to be 87.35±0.68 and disintegration time was about 1 min 14 sec. At 45±20,75±50, RH drug content was found to be 87.35±0.68 and disintegration time was about 1 min 14 sec±0.35. No significant changes were observed on drug content and disintegration time at room temp and 45±20,75±20 RH. Hence formulation F3 was found to be stable for 28 days.

CONCLUSION

The study successfully developed fast dissolving films of Ezetimibe using HPMC polymers and inclusion complexation with β-cyclodextrin to enhance solubility. The optimized formulation (F3) showed rapid disintegration, good mechanical properties, high drug release following first-order kinetics, and stability over 28 days. Thus, HPMC E5 HPMC E15 based oral films with inclusion complexes offer an effective drug delivery system for improving bioavailability and patient compliance**.** The inclusion complex of Ezetimibe with β-cyclodextrin (β-CD) was successfully prepared to enhance the drug's aqueous solubility and stability, which are crucial for improving its bioavailability in oral drug delivery systems**.**

From above it was concluded that formulation, oral fast dissolving film formulation F3 containing HPMC E5 (500), HPMC E15(300), Citric Acid (100), Saccharine (50mg) glycerine (2 ml), which could be most promising oral fast dissolving film, formulation for inclusion complex of drug and cyclodextrin

It was concluded that from various evaluation parameters result of optimized gastro retentive matrix tablet (F3) could fast action within in 3 min

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