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Original Article

IN VITRO AND *IN VIVO* EVALUATION OF EZETIMIBE FAST-DISSOLVING FILMS

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ABSTRACT

Objective: The goal of this investigation was to develop and evaluate Ezetimibe fast-dissolving films, which are used to treat hyperlipidemia and prevent cholesterol absorption.

Methods: The fast-dissolving Ezetimibe films were developed using the solvent casting method and included the following ingredients sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol, Polyvinyl pyrrolidone which act as film-forming agents polyethylene glycol 600 and sodium starch glycolate, which acts as a superdisintegrant and plasticizer;, citric acid and stevia powder, which serves as a saliva stimulant and sweetener.

Results: The fast-dissolving films of Ezetimibe prepared with PVP K30 released the drug up to 99.87% within 5 min, which showed the increased solubility, dissolution rate, flexibility and tensile strength of the films when compared to formulation prepared with sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol. The FTIR and DSC studies were conducted for pure drug, polymers and optimized formulation E11, which indicated that were no incompatibilities found between the drug and polymers used in the present studies. Scanning electron microscopy analysis was performed for pure drug, and optimized formulation E11 showed that they were no surface fractures and cracks in the films. The optimized formulation E11 was subjected to *in vivo* studies by using New Zealand Rabbits, and accelerated stability studies revealed that all the formulation is stable.

Conclusion: The current study reveals that fast-dissolving films formulated as a novel drug delivery technology can increase the solubility and dissolution rate of poorly water-soluble drug Ezetimibe.

Keywords: Ezetimibe, Solvent casting, Fast-dissolving films, Plasticizers and superdisintegrants

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INTRODUCTION

The oral route of drug administration is widely preferred among various drug delivery methods. Approximately 90% of medications are administered orally for the treatment of various disorders and diseases. This route of drug delivery is widely considered to be the safest, most practical, and most cost-effective method, resulting in higher patient compliance [1-4]. The medication can be administered in two ways: either as a whole tablet or by dissolving it. Once it enters the systemic circulation, it exerts its desired effect [5, 6]. The oral route of drug administration is considered the most significant mode of administering medicine for systemic impact despite significant advancements in drug delivery. This is due to factors such as self-medication, convenience of administration, and a lower level of discomfort compared to the parenteral route [7-10]. Fast-dissolving films represent an innovative category of drug delivery technologies designed to enhance the safety and efficacy of therapeutic molecules, ultimately promoting greater patient adherence. The sublingual drug delivery method involves the application of a film onto either the surface or underside of the tongue, providing a dependable means of administering medication. Upon placement on the tongue, the film undergoes rapid dissolution, facilitating the immediate release of the medication into the saliva. During the process of swallowing, saliva travels down into the stomach. It is worth noting that certain medications can be absorbed from the mouth, pharynx, and esophagus. In this particular scenario, it is crucial to prioritize the enhancement of tongue sensation, mitigation of choking hazards, and augmentation of drug absorption. In order to address the challenge of swallowing difficulties, researchers are currently working on the development of fast-dissolving drug delivery systems [11, 12]. The rapid dissolution of the film primarily occurs due to its significant surface area, which readily absorbs moisture upon exposure to a damp environment. The hydrophilic polymer employed for the production of FDF exhibits rapid dissolution when in contact with the tongue or buccal cavity, facilitating the drug's absorption into the bloodstream via the buccal mucosa. Quick-dissolving drug delivery systems were developed to enhance the bioavailability of medications with low doses and significant first-pass metabolism [13, 14].

Ezetimibe is a pharmaceutical compound classified as a cholesterol absorption inhibitor. It is primarily prescribed for the treatment of familial and primary hyperlipidemia. The mechanism of action involves reducing levels of total cholesterol, LDL cholesterol, Apoprotein B (Apo-B) cholesterol, and non-HDL cholesterol. In addition, individuals diagnosed with homozygous sitosterolemia have the option to utilize ezetimibe as a means to reduce elevated levels of sitosterol and campesterol, a condition known as phytosterolemia. The medication can be administered either as a standalone treatment or in conjunction with statins, which are HMG-CoA reductase inhibitors.

In the present study, the formulation of the Ezetimibe drug as an oral fast-dissolving film was investigated. Various film-forming agents, plasticizers, and superdisintegrants were employed to achieve improved solubility, dissolution rate, and enhanced therapeutic efficacy.

MATERIALS AND METHODS

Materials

Ezetimibe a gift sample from Alkem Laboratories Bangalore, sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol, Polyvinyl pyrrolidone were obtained from Yarrow chem, Ltd., Mumbai, stevia powder which is natural disintegrant obtained from High-pure fine Chem., Chennai.

Methods

Preparation of ezetimibe fast-dissolving films

Solvent casting method was used to make Ezetimibe fast-dissolving films. To obtain transparent solutions, film-forming polymers such as sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol and Polyvinyl pyrrolidone were dissolved in

aqueous solutions individually in 100 ml beakers. Specified amounts of Ezetimibe, sodium starch glycolate, stevia powder, citric acid and PEG 400 were weighed and dissolved in above aqueous solution, then well mixed to obtain a homogenous solution. The resulting solution was cast on a non-adhesive base plate and cured for 24 h under an infrared lamp. The films were trimmed into desired sizes once they had dried completely. Several attempts were conducted to improve the formula for making Ezetimibe fast-dissolving films [13-16]. The composition of Ezetimibe fast-dissolving films were given in table 1.

The resulting solution was cast onto a non-adhesive base plate and allowed to dry for 24 h under an infrared lamp. The films were sliced into the necessary sizes after they had fully dried. To optimize the method of preparation of Ezetimibe fast dissolving films, numerous studies were carried out.

Table 1: Composition of ezetimibe fast-dissolving films

Ingredients (w/w)	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12
Ezetimibe	10	10	10	10	10	10	10	10	10	10	10	10
Maltodextrin	20	20	20	20	20	20	20	20	20	20	20	20
NaCMC	80	90	100	-	-	-	-	-	-	-	-	-
HPMC E5	-	-	-	80	90	100	-	-	-	-	-	-
Polyvinyl alcohol	-	-	-	-	-	-	80	90	100	-	-	-
Polyvinyl Pyrolidone K30	-	-	-	-	-	-	-	-	-	80	90	100
PEG 600	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25
Sodium Starch Glycolate	5	5	5	5	5	5	5	5	5	5	5	5
Stevia powder	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Citric acid	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Water (ml)	5	5	5	5	5	5	5	5	5	5	5	5

NaCMC indicates sodium carboxy methyl cellulose, HPMC indicates hydroxyl propyl methyl cellulose, PEG indicates Polyethylene glycol.

Evaluation of physical parameters for ezetimibe fast dissolving films [17]

The Ezetimibe fast-dissolving films were evaluated for physical parameters such as Thickness uniformity, folding endurance, drug content uniformity. The results were given in table 2.

Thickness uniformity

At different places on the film, the thickness was measured using screw gauze with a minimum count of 0.01 mm. On the film, the thickness was measured at 3 distinct places, and the average was calculated. Results were given in table 2 [18].

Folding endurance

In terms of what is referred to as folding endurance, the film's flexibility is measured. The film's folding resistance was tested by repeatedly folding a small strip of it until it broke. The value of folding endurance is determined by how many folds of the film can be made without breaking. Results were given in table 2 [19].

Drug content uniformity

The films underwent UV-visible spectrophotometric testing to determine the uniformity of their drug content. From the cast film, films of the necessary sizes were sliced three times. Each cut film was put into a 100 ml volumetric flask and dissolved with a buffer with a pH of 6.8 pH phosphate buffer from this, 1 ml was pipette into a 10 ml volumetric flask, where it was added to the required volume to reach a 6.8 pH phosphate buffer Using a UV visible spectrophotometer, the absorbance of the resultant solution was determined at 296 nm against a blank. Using the standard graph, the percentage of drug content was determined. Results obtained were given in table 2.

It is challenging to mimic these natural conditions and measure using an appropriate approach when it comes to oral films since the disintegration and dissolution are difficult to determine if the oral films concurrently dissolve in a little volume of saliva. The media used in previous tests for dissolution and disintegration were in significant quantities and were n't physiologically present in the oral cavity. Independent approaches were provided for the assessment of disintegration and dissolution behaviour. Only a minimal amount of media was required for this procedure [20].

Diffusion studies by franz diffusion cell

The volume of the Franz Diffusion Cell is approximately 15 ml. A strip of film containing 10 mg of Ezetimibe is placed in the Franz Diffusion Cell, along with 10 ml of pH 6.8 phosphate buffer (pH of saliva). Place the cell on a magnetic stirrer, keep the medium at a temperature of about 400 °C and the speed of the bead in the cell at 50 RPM. Then, take out 1 ml of samples at intervals of 1, 2.5, 5, 10, and 15 min, make up to 5 ml with pH 6.8 phosphate buffer, and measure the absorbance in UV at 296 nm using pH 6.8 phosphate buffer as a blank. The drug release profiles for all the film formulations were shown in fig. 1, 2 and values obtained in table 3 [20].

Dispersion test

A 200 ml of 6.8 pH buffer and a strip of film containing 20 mg of Ezetimibe are combined, stirred for three minutes with a glass rod, and then the mixture is run through a 22-mesh screen to determine whether the film passed the dispersion test.

***In vitro* diffusion studies**

All of the Ezetimibe fast-dissolving films were subjected to *in vitro* diffusion tests utilizing Franz diffusion cell apparatuses with pH 6.8 phosphate buffer as the dissolution medium. For each formulation, the dissolving studies took place over a 15-minute timeframe. Studies on dissolution were conducted in triplicate while maintaining sink conditions for all formulations. At regular intervals, a 5 ml aliquot of samples was taken, filtered, and measured spectrophotometrically at 296 nm. For each of the film formulations, the drug release profiles were displayed [20].

Evaluation of various *in vitro* dissolution parameters

The dissolution parameters such as T_{50}, T90, $DE5_{\%}$ and the first order rate constant were calculated from the dissolution data and the results can be obtained in table 3.

Depending on the results obtained by diffusion studies, some of the formulations were optimized and carried out for characterization.

I. R. spectral studies

BRUKER FTI. R was used to conduct I. R Spectral analyses on a few chosen films. Before they were put through dissolution tests, these studies on films were done to see whether there were any structural differences between the drug and the excipients used in the film formulations [21]. The FTIR graphs of the drug, polymers and optimized formulation E11 were seen in fig. 3-9, respectively and the interpretation were given in table 4.

Differential scanning calorimetry (DSC) studies

The DSC studies were conducted for pure drug, excipients and the optimized formulation E11 by using differential scanning

calorimeter (SHIMZDO and DSC-60). The samples were heated at a rate of 20 °C/min in a hermetically sealed aluminium crucible. The thermograms were shown in fig. 10-15 and data was given in table 5 [22, 23].

Scanning electron microscopy (SEM)

A thin layer of gold was applied to the samples using a sputter coater unit (SPI, Sputter, USA). Then, using a scanning electron microscope (model JSM-6390, Japan) operating at an accelerated voltage of 10kV, SEM photographs of pure drug and optimized formulation E11 was observed in fig. 16-17 [22, 23].

***In vivo* pharmacokinetic studies of ezetimibe fast dissolving films**

In the present study, Ezetimibe oral solution and Ezetimibe optimized formulation E11 was subjected to *in vivo* pharmacokinetic studies done in rabbits at Mahalakshmi agencies-Hyderabad maintained acclimation conditions for 7 d after taking permission from Institutional Animal Ethical Committee CPCSEA/ORG/ CH/2008/RegNo.1219. These formulations were administered to rabbits through oral route at a dose of 10 mg/kg body weight and plasma concentration of Ezetimibe was determined by UPLC method. Pharmacokinetic parameters such as concentration maximum (C_{max}), time of peak plasma concentration (T_{max}), Biological half-life ($t_{1/2}$), AUC ($_{o\text{-}t}$), AUMC ($_{o\text{-}t}$) and mean residence time (MRT) were calculated by using PK summit solutions software USA [24].

RESULTS AND DISCUSSION

Preparation of ezetimibe oral fast-dissolving films

The solvent casting method was used to produce Ezetimibe fast-dissolving films utilizing a variety of film-forming ingredients, sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol, Polyvinyl pyrrolidone. Total 12 formulations were prepared; among all the formulations the, formulation E11 was prepared with PVP K30 released 99.87% of drug within 5 min and shows that faster drug release and folding endurance. The formulation composition was given in table 1.

Evaluation of physical parameters for ezetimibe fast dissolving films [17-20].

The physical parameters like weight uniformity, drug content, film thickness and folding endurance were performed for all the Ezetimibe fast-dissolving films. The weight uniformity of all Ezetimibe fast-dissolving films prepared with Sodium carboxy methyl cellulose, HPMC E5, Polyvinyl Alcohol, Polyvinyl pyrrolidone were maintained in the range of 99 to 119 mg. The drug content of all Ezetimibe fast-dissolving films was maintained in the range of 9.47±0.01 to 9.89±0.25 mg. which indicates that the drug is evenly dispersed in all the Ezetimibe fast-dissolving film formulations. The film thickness of all Ezetimibe fast dissolving films formulations was maintained at the range of 0.030±0.034 mm. The folding endurance values for all the Ezetimibe fast-dissolving film formulations were maintained in the range of 99-101 folding, which indicates that the fast-dissolving film formulations were found to be stable and should good tensile strength. The dispersion test for all the prepared films was passed. The results of evaluated parameters such as weight uniformity, drug content, film thickness and folding endurance were given in table 2.

***In vitro* diffusion studies of ezetimibe fast-dissolving films (n = 6)**

Diffusion studies were conducted on all the Ezetimibe fast-dissolving film formulations using Franz diffusion cell apparatus containing pH 6.8 phosphate buffer as dissolution medium [20]. The fast-dissolving film formulations E1-E3 which were prepared by using sodium carboxy methyl cellulose, showed an average drug release of 90.15 to 95.26 % within 15 min. The fast-dissolving film formulations E4-E6, which were prepared by using HPMC E5, showed an average drug release of 91.78-97.58 % within 15 min. The fast-dissolving film formulations E7-E9 which were prepared by using polyvinyl alcohol showed an average drug release of 93.69-98.96% within 15 min. The fast-dissolving film formulations E10-E12, which were prepared by using polyvinyl pyrrolidone showed an average drug release of 92.36-99.87% within 15 min. when compared to all the film formulations, the fast-dissolving film formulations that were prepared by using PVP K30 showed better drug release up to 99.87% within 5 min. The drug release profiles were showed in the fig. 18.

Table 2: Evaluation of physical parameters for ezetimibe fast dissolving films

Formulation	Weight uniformity (mg)	Drug content (mg/ film)	Film thickness (mm)	Folding endurance (no)	Dispersion test	Curling
E1	99	9.77±0.14	0.033	97	Passed	Absent
E2	108	9.52±022	0.030	98	Passed	Absent
E3	129	9.47±0.01	0.031	99	Passed	Absent
E4	100	9.85±0.12	0.032	98	Passed	Absent
E5	109	9.52±0.11	0.034	98	Passed	Absent
E6	120	9.36±0.23	0.035	97	Passed	Absent
E7	101	9.74±0.25	0.032	98	Passed	Absent
E8	117	9.88±0.32	0.034	99	Passed	Absent
E9	120	9.69±0.01	0.033	99	Passed	Absent
E10	101	9.78±0.13	0.032	98	Passed	Absent
E11	110	9.89±0.25	0.031	102	Passed	Absent
E12	119	9.57±0.28	0.032	99	Passed	Absent

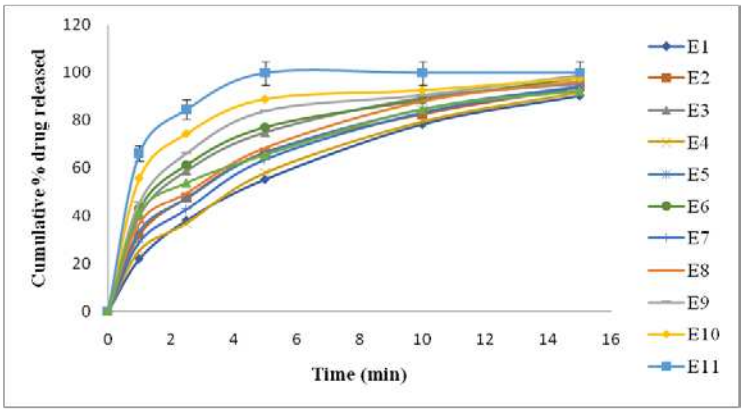

Fig. 1: Drug release profiles for ezetimibe fast dissolving films (E1-E11) (mean±SD; n=3)

Evaluation of various *in vitro* dissolution parameters

From the dissolution data, dissolution parameters such T50, T90, DE5%, and first-order rate constant were computed, and the results are shown in table 4. The optimized formulation E11 showed T50, T90, and DE 5% values of 1.4, 4.5, and 23.69%, respectively. All of the film formulations' first-order plots were linear. All of the film formulations were found to have first-order release rates that were linear, with R^2 values ranging 0.955 to 0.99. As a result, the rates of drug release from all film formulations were dependent on concentration and linear with the first-order release rate constant (K1).

Fourier-transform infrared (FT-IR) spectroscopic analysis

The FTIR spectra of Ezetimibe exhibited principle peaks at wave numbers of 3256.04 cm^{-1} (C-H Stretching), 2655.23 cm^{-1} (C=O Stretching), 1642.11 cm^{-1}(C-H bending), 893.66 cm^{-1}(C-F Stretching, Aromatic). The FTIR spectra of sodium carboxy methyl cellulose exhibited principle peaks at wave numbers of 3001.58 cm^{-1} (C-H Stretching), 2125.36 cm^{-1} (C=O Stretching), 1478.22 cm^{-1}(C-H bending), 836.33 cm^{-1}(C-F Stretching, Aromatic). The FTIR spectra of HPMC E5 exhibited principle peaks at wave numbers of 3158.23 cm^{-1} (C-H Stretching), 2499.33 cm^{-1} (C=O Stretching), 1536.11 cm^{-1}(C-H bending), 901.26 cm^{-1}(C-F Stretching, Aromatic). The FTIR spectra of Polyvinyl alcohol exhibited principle peaks at wave numbers of 3337.25 cm^{-1} (C-H Stretching), 2036.11 cm^{-1} (C=O Stretching), 1755.12 cm^{-1}(C-H bending), 922.36 cm^{-1}(C-F Stretching, Aromatic). The FTIR spectra of Polyvinyl pyrrolidone exhibited principle peaks at wave numbers of 3381.02 cm^{-1} (C-H Stretching), 2827.33 cm^{-1} (C=O Stretching), 1788.66 cm^{-1}(C-H bending), 922.87 cm^{-1}(C-F Stretching, Aromatic). The spectra of optimized formulation E11 exhibited all the principle peaks present in the Ezetimibe pure drug. Thus, there was no appearance or disappearance of any characteristic peak, which shows that there is no chemical interaction between the drug and the polymer used [21]. The FTIR spectra of the drug, polymers and optimized formulation E11 were shown in fig. 3 to 9 and the interpretation were given in table 4.

Table 3: Evaluation of *in vitro* dissolution parameters for ezetimibe fast dissolving films

S. No.	Formulation	T_{50} (min)	T_{90} (min)	$DE_{5\%}$	First order	
					K (min^{-1})	R^2
1.	E1	4.9	14.9	17.56	0.163	0.955
2.	E2	4.5	14.4	18.33	0.181	0.961
3.	E3	4.0	14.0	21.03	0.156	0.952
4.	E4	4.7	14.7	17.10	0.234	0.987
5.	E5	4.3	14.1	18.55	0.226	0.9674
6.	E6	3.8	13.8	20.89	0.219	0.968
7.	E7	4.5	14.5	18.93	0.221	0.980
8.	E8	3.9	13.8	18.88	0.246	0.973
9.	E9	3.5	9.5	22.8	0.216	0.994
10.	E10	1.9	8.5	19.63	0.214	0.987
11.	E11	1.4	4.5	23.69	0.156	0.999
12.	E12	2.5	13.5	18.96	0.147	0.974

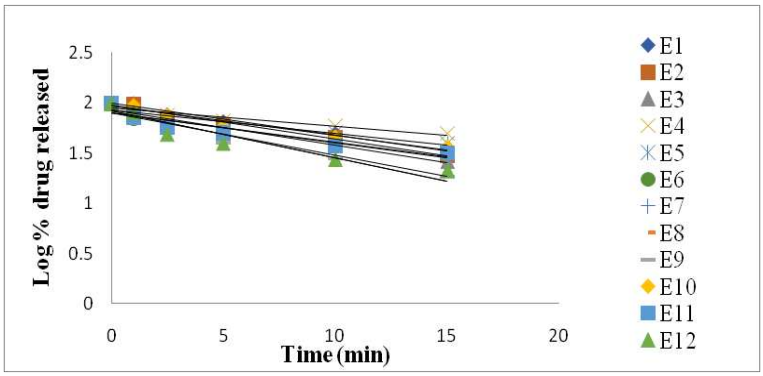

Fig. 2: First order profile for ezetimibe fast dissolving films E1 to E12

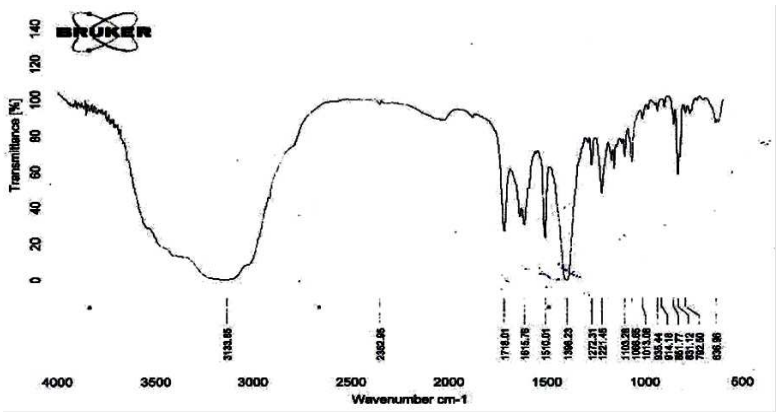

Fig. 3: FTIR spectrum of ezetimibe pure drug

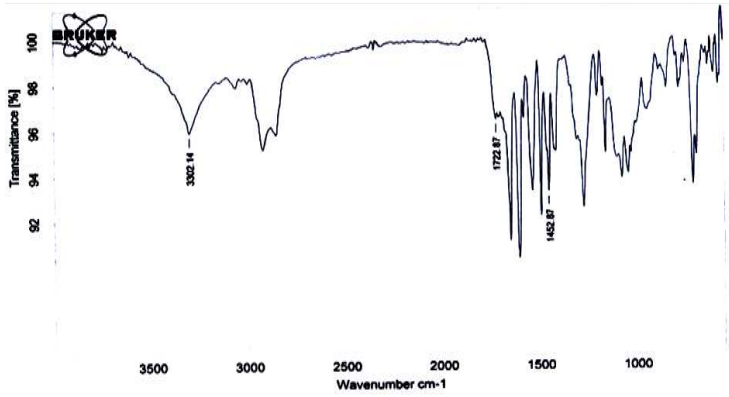

Fig. 5: FTIR spectrum of sodium carboxy methyl cellulose

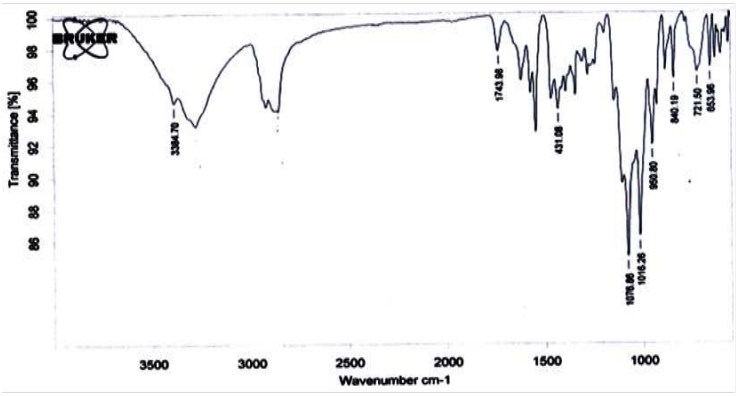

Fig. 6: FTIR spectrum of sodium HPMC E5

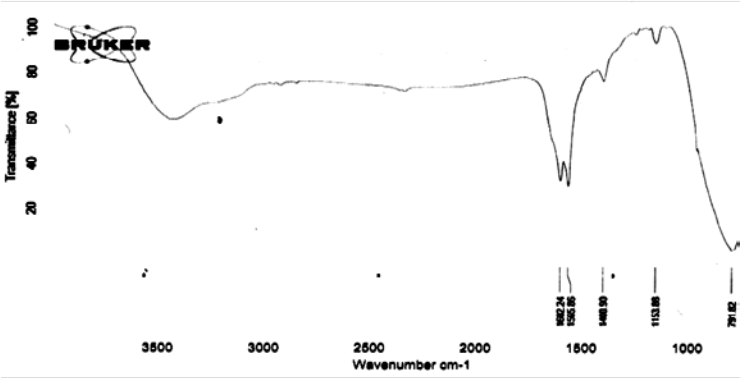

Fig. 7: FTIR spectrum of sodium polyvinyl alcohol

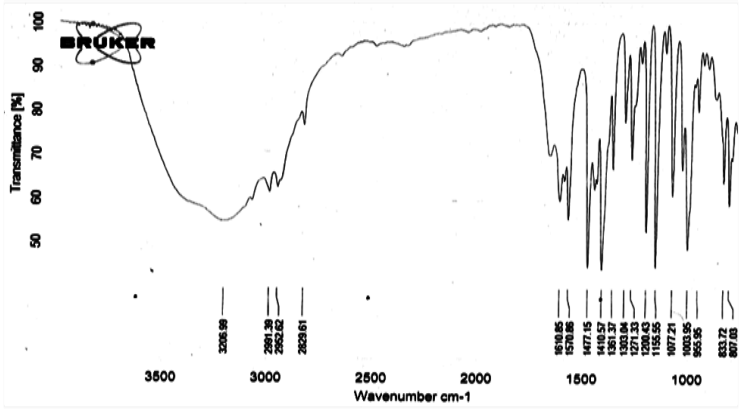

Fig. 8: FTIR spectrum of sodium polyvinyl pyrrolidone

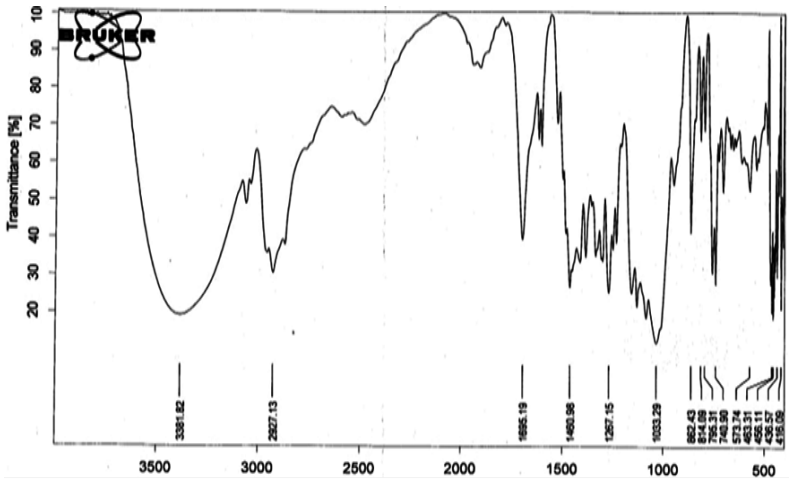

Fig. 9: FTIR spectrum of optimized formulation E11

Table 4: Interpretation of FTIR spectrum

Functional group	Wave number (Cm^{-1})					
	Pure drug	Na CMC	HPMC E5	PVA	PVP	E11
C-H Stretching	3256.04	3001.58	3158.23	3337.25	3422.01	3381.02
C=O Stretching	2655.23	2125.36	2499.33	2036.11	2722.01	2827.33
C-H Bending	1642.11	1478.22	1536.11	1755.12	1812.52	1788.66
C-F Stretching, aromatic	893.66	836.33	901.26	922.36	888.36	922.87

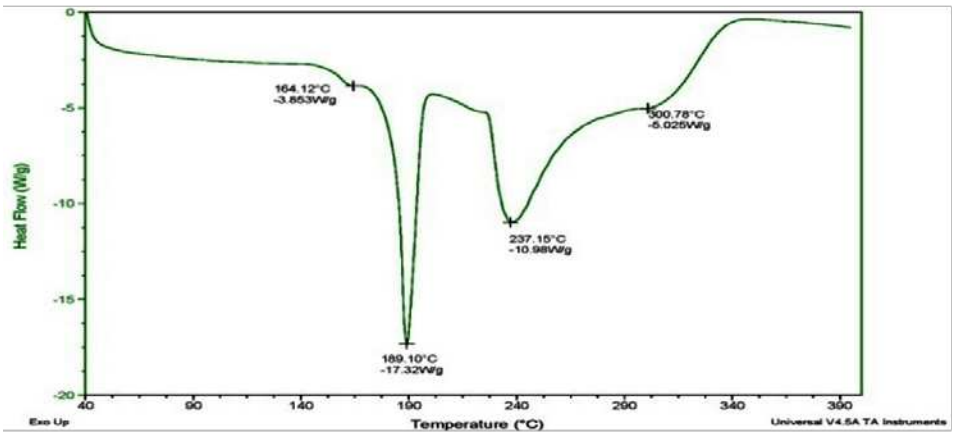

Fig. 10: DSC spectrum of pure drug ezetimibe

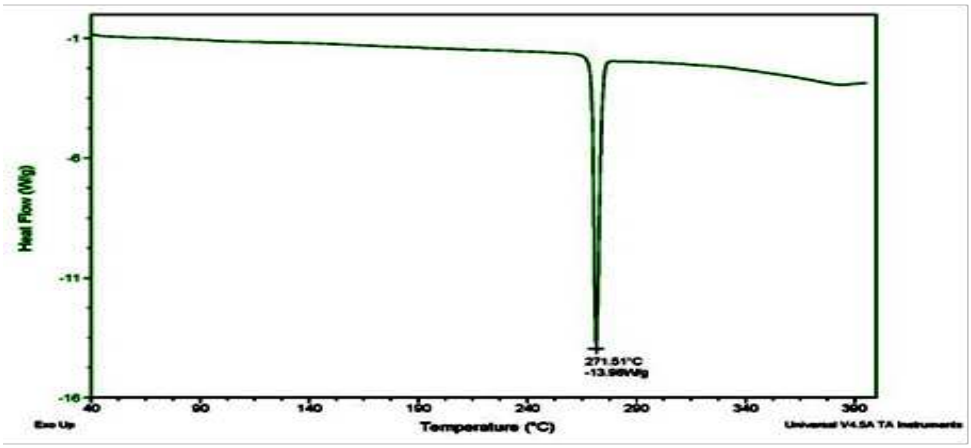

Fig. 11: DSC spectrum of sodium carboxy methyl cellulose

Differential scanning calorimetry

DSC thermographic peak for Ezetimibe was observed at temperature 164.12 °C as sharp endothermic peak. The DSC thermographic peak for sodium carboxy methyl cellulose was observed at 271.33 °C as sharp endothermic peak. The DSC thermographic peak for HPMC E5 was found at 220.13 °C as broad endothermic peak. The DSC thermographic peak for polyvinyl alcohol was found at 183.31 °C as sharp endothermic peak. The DSC thermographic peak for polyvinyl pyrrolidone was found at 103.66 °C as broad endothermic peak. The DSC thermographic peak for optimized formulation E11 was found at 128.99. °C as broad endothermic peak, 219.33 °C as sharp endothermic peak and 234.60 °C as sharp endothermic peak. The results revealed that there were no major interactions between the drug and the polymers during the coating process. The DSC endothermic peaks were shown in fig. 10 to 15 and data was given in table 5 [22, 23].

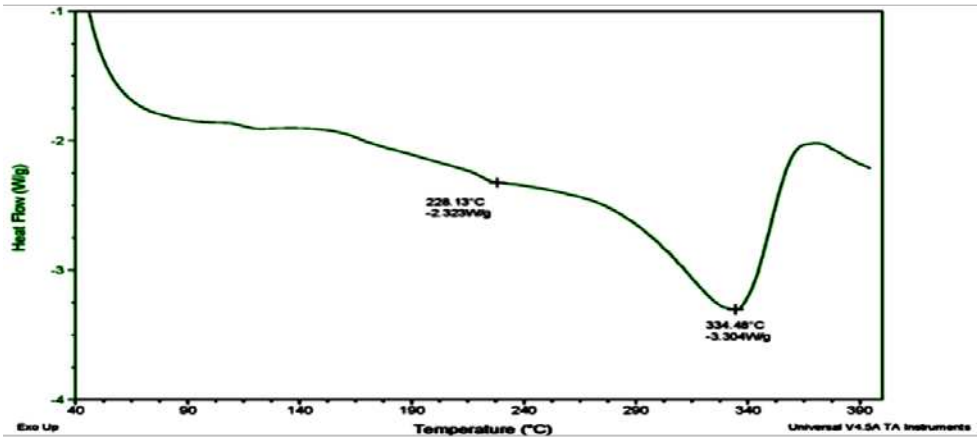

Fig. 12: DSC spectrum of HPMC E5

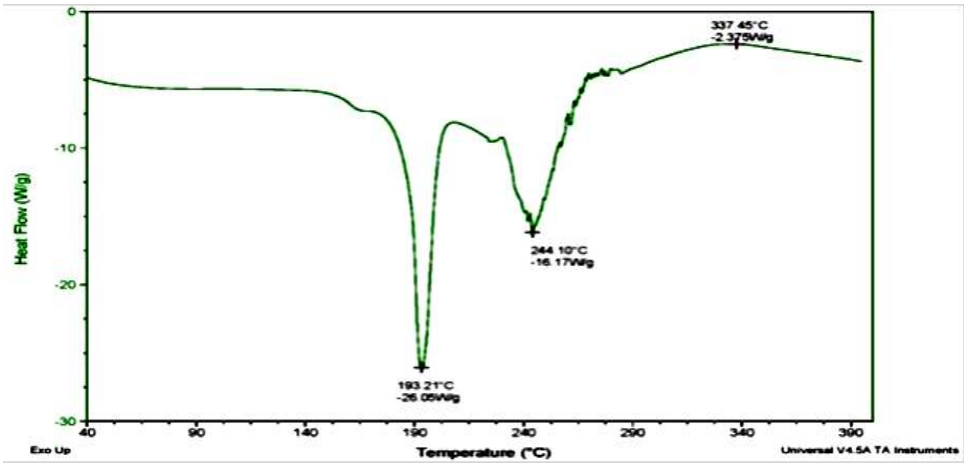

Fig. 13: DSC spectrum of polyvinyl alcohol

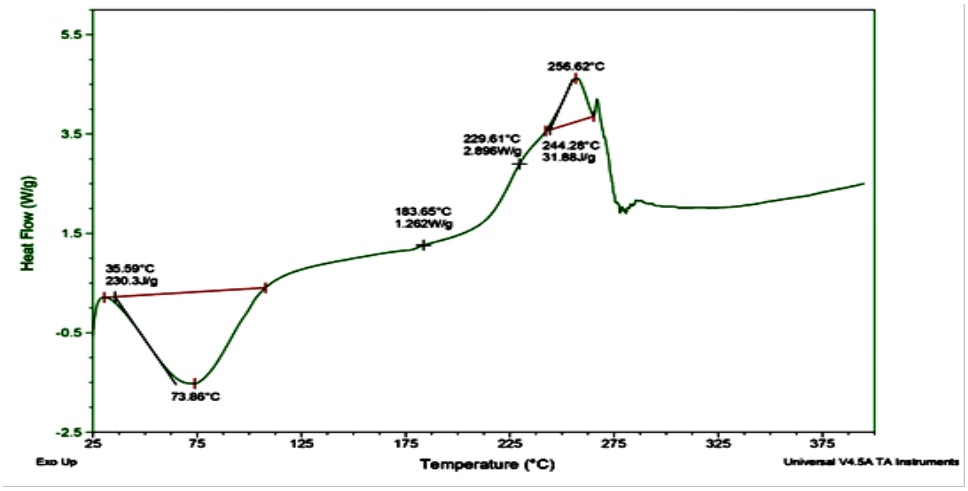

Fig. 14: DSC spectrum of polyvinyl pyrrolidone

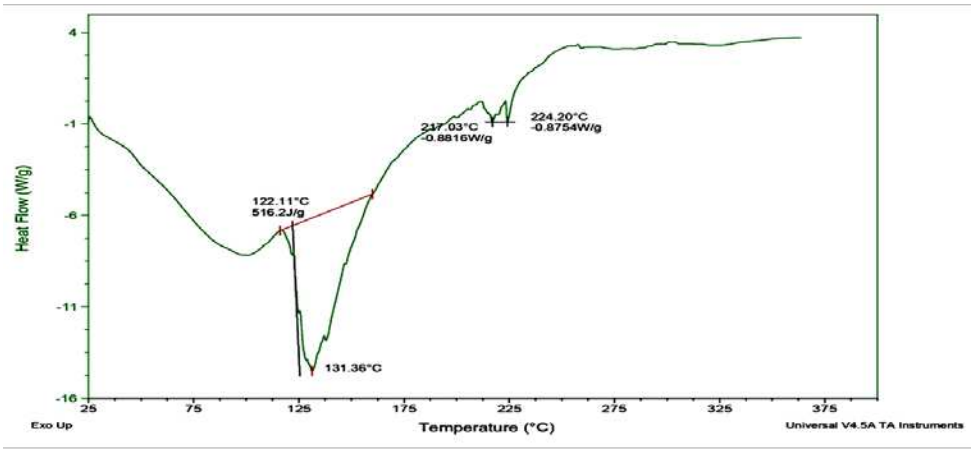

Fig. 15: DSC spectrum of optimized formulation E11

Table 5: DSC thermogram interpretations

Ezetimibe	NaCMC	HPMC E5	PVA	PVP K30	Optimized formulation (E11)
164.12 °C Sharp endothermic peak	271.33 °C Sharp endothermic peak	220.13 °C Broad endothermic peak	183.31 °C Sharp endothermic peak	103.66 °C Broad endothermic peak	128.99 °C, 219.33 °C, 234.60 °C Broad Endothermic Peak, Sharp Endothermic Peak, Sharp Endothermic Peak

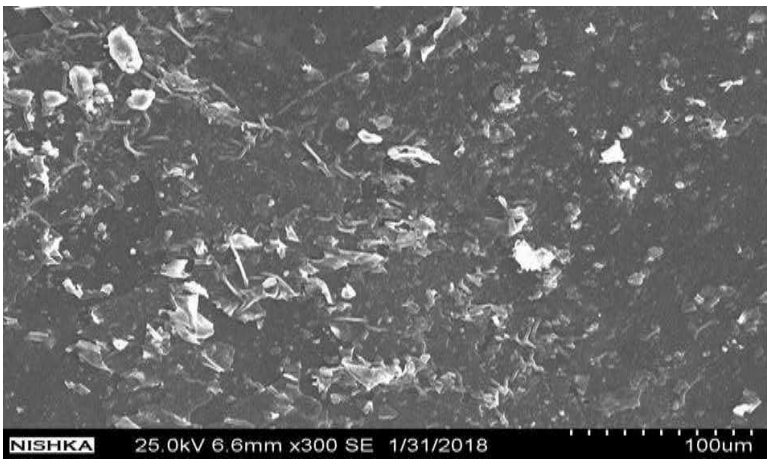

Fig. 16: SEM photograph of ezetimibe pure drug

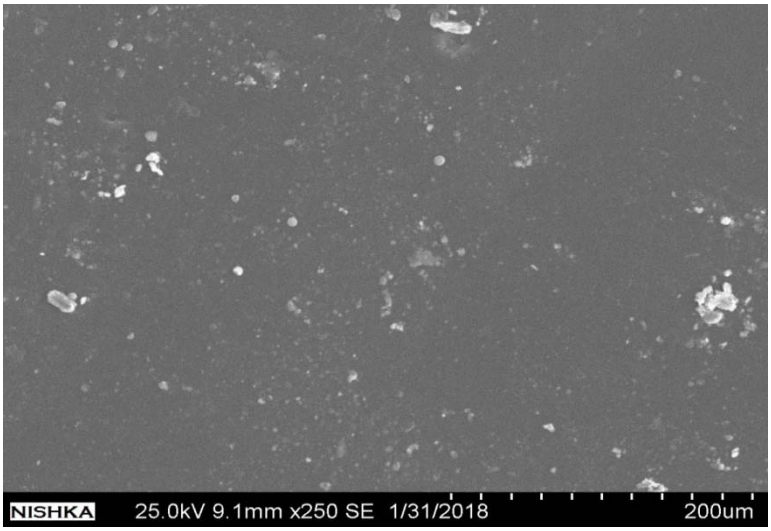

Fig. 17: SEM photograph of optimized formulation (E11)

Scanning electron microscopy analysis

SEM photographs were taken for the E9 optimized film and the pure Ezetimibe drug. The SEM photographs were shown in fig. 16, 17. The E9 demonstrated an even, smooth surface and uniform without any cracks [22, 23].

***In vivo* pharmacokinetic studies of ezetimibe fast dissolving films**

The orally administered Ezetimibe (oral solution) reached the maximum concentration (C_{max}) of 6.9 ng/ml, time of peak plasma concentration (t_{max}) achieved at 15 min with a half-life of 0.2 h. The $AUMC_{(0-t)}$ values obtained for Ezetimibe oral solution were 26.7 ng-h/ml. The mean residence time for the pure drug solution was 2.9 hr. The optimized formulation E11 administered as fast dissolving film achieved a maximum concentration (C_{max}) of 10.1 ng/ml, with time of peak plasma concentration (t_{max}) at 15 min with a half-life of 3.3 h respectively. The $AUC_{(0-t)}$ values obtained for optimized E11 formulation was 50.2 ng-min/ml. The mean residence time for the optimized formulation E11 was up to 24.1 h, respectively. These results thus indicated that optimized formulation E11 exhibited improved Ezetimibe plasma concentrations by extending the mean residence time with increased AUC values resulted in improved dissolution rate, faster onset of action with enhanced bioavailability. The plasma concentration of Ezetimibe and its formulations were shown in table 6 and fig. 18 [24].

Table 6*: In vivo* drug release parameters from optimized formulation E11

Parameters	Optimized formulation E11 (mg/ml)					Ezetimibe (Oral solution)				
	1	2	3	Mean (N=3)	SD	1	2	3	Mean (N=3)	SD
C_{max} (mg/ml)	10.2	10.1	10.05	10.1	0.1	6.7	6.9	6.99	6.9	0.1
T_{max} (min)	15	15	15	15	0.1	15	15	15	15	0.1
$T_{1/2}$ (h)	3.8	3.00	2.97	3.3	0.5	0.137924	0.237047	0.109361	0.2	0.1
$AUC_{(0-t)}$ (ng. h/ml)	50.375	50.225	49.85	50.2	0.3	26.25	26.5	27.225	26.7	0.5
$AUMC_{(0-t)}$ (ng-h* h/ml)	124.25	124.2	123.075	123.8	0.7	48.25	50.25	48.475	49.0	1.1
MRT (h)	28.02161	22.17477	22.04764	24.1	3.4	2.658188	3.818165	2.365337	2.9	0.8

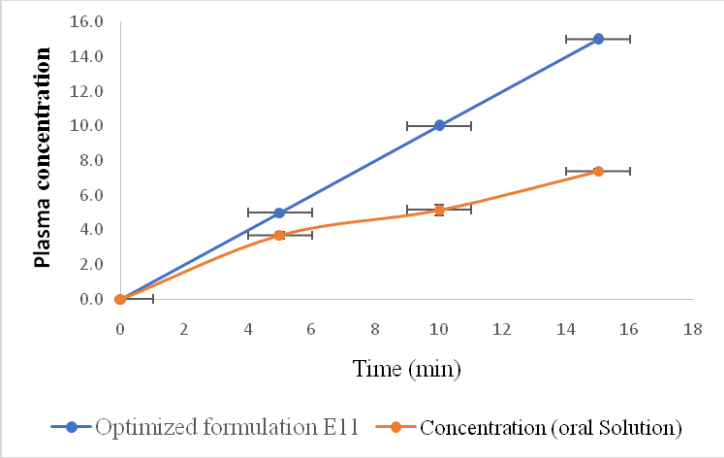

Fig. 18: Drug release profiles for optimized formulation E11. (n=3)

CONCLUSION

Ezetimibe oral fast dissolving films prepared by solvent casting method showed good flexibility and film characteristic properties with good bioavailability. Among all the fast-dissolving film formulations E10-E12 which were prepared by using polyvinyl pyrrolidone, showed an average drug release of 92.36-99.87% within 15 min. when compared to all the film formulations, the optimized formulation E11 prepared by utilizing polyvinyl pyrrolidone showed the average drug release of 99.87% within 5 min, which was desirable for faster dissolution and absorption. The drug content on average was found to be 9.47±0.5, and showed good folding endurance and found that no interactions between the drug and the polymers in FT-IR and DSC studies where as it exhibited the smooth surface in SEM analysis. Ezetimibe fast-dissolving films prepared by solvent casting technique were found to be suitable for the treatment of hyperlipidemia. *In vivo* studies showed that Ezetimibe plasma concentrations by extending the mean residence time with increased AUC values, resulted in improved dissolution rate faster onset of action with enhanced bioavailability.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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