Original Article

Formulation and Evaluation of Oral Fast Dissolving Films of Poorly Soluble Drug Ezetimibe Using Transcutol Hp

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ABSTRACT

Introduction: The objective of the present formulation research is to deliver the drugs at a faster rate and to provide immediate onset of action in a shorter period of time with improved bioavailability. **Materials and Methods:** Ezetimibe, a gift sample from Lupin Ltd., Pune, Transcutol HP, a gift sample from Gattefosse India Pvt. Ltd., Goa., HPMC E5, HPMC E6, HPMC E15 are gift samples from Colorcon India Pvt. Ltd. **Results and Discussion:** Among prepared formulations coded E1 to E20, formulation E6 was shown promising results, hence further studies done without transcutol HP and documented clear results saying that, without transcutol HP has shown around 50% of drug even after 90 min of time, whereas within 10 min complete drug release observed with transcutol HP formulation. **Conclusion:** The study clearly indicated the influence of transcutol HP in enhancing the solubility of the poorly soluble drugs as the films made without transcutol HP failed to give the desired release characteristics within 10 min.

Key words: Ezetimibe, Transcutol HP, HPMC E5, HPMC E6, HPMC E15, Pectin.

INTRODUCTION

The objective of the present formulation research is to deliver the drugs at a faster rate and to provide immediate onset of action in a shorter period of time with improved bioavailability. However, poorly soluble drugs pose problems for achieving this goal. The selection of formulation is considered to play an essential role in the development of a successful product of a poorly soluble molecule. Numerous approaches are being followed by the research scientists all over the world to improve the solubility of poorly water soluble molecules with different formulation techniques[1,2,3] like complexation, surfactant co-solvent systems, liquisolid systems, lipid systems etc. Rapid mouth disintegrating drug delivery systems were first developed as substitutes to unit dosage forms like tablets, capsules and syrups or suspensions for paediatric and geriatric patients who are having difficulty in swallowing traditional oral solid dosage forms. In continuation, different range of oral disintegrating tablets were developed and commercialized, which disintegrate at around 60 sec after administering in the mouth without water.[4] Wide range of drugs like neuroleptics, cardiovascular drugs, analgesics, antihistamines, anti-asthmatics, anti-diarrheal and erectile dysfunctions can be considered as candidates for oral fast disintegrating dosage forms.[5] The aim of present work is to know the effect of transcutol HP on increasing the solubility and thereby bioavailability of poorly water soluble drugs. For poorly water soluble drugs the rate limiting step for absorption is the disintegr tion followed by dissolution of the drug, hence the objective of majority of formulation scientists is to improve the disintegration of solid dosage

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forms followed by dissolution of solid dosage form with different approaches of solid dispersions like hot melt extrusion, compression moulding, fusion method and solvent evaporation methods. Oral fast dissolving films contains water soluble polymer which allows the films to quickly hydrate by saliva, adhere to mucosa and disintegrate in seconds followed by releasing of active ingredient for oro-mucosal absorption when administered on the tongue.[6] These films or strips can reportedly incorporate soluble, insoluble or taste masked drug substances. Films are manufactured in large sheet and then divided into individual dosage units by cutting for suitable packaging in a range of pharmaceutically acceptable formats. Orally fast dissolving films (OFDFs) are useful in patients such as bedridden, geriatric, paediatric, developmentally disabled, feeling difficulty in swallowing conventional dosage forms.[7] OFDFs can give quick absorption and immediate bioavailability of drugs due to high blood flow as permeability of oral mucosa is 4 to 1000 times greater than that of skin absorption.[8]

There are four methods for manufacturing of OFDFs available, those are solvent casting, hot melt extrusion, semisolid casting, solid dispersions. However the most common method used in industry are solvent-casting and hot-melt extrusion methods.

Solvent casting method[9]

OFDFs are preferably formulated using the solvent casting method. In this process initially all the water soluble (plasticizers, sweeteners etc.) ingredients including active ingredients are dissolved in solvent to form a clear solution. Then the remaining ingredients are dissolved in smaller amounts in the above aqueous clear solution and filtered. The entrapped air is removed by vacuum and casted as film on appropriate plates or conveyers which are non-stick and allowed to dry. The films are then dried and cut in to pieces with desired size (1 cm^2). Advantages of this method are uniformity in thickness, glossy appearance of film, more flexible and good physical properties. The disadvantages with this process are polymers must be soluble in volatile solvent or purified water to form stable solution with a reasonable minimum solvent.

Hot melt extrusion[10]

Hot melt extrusion is a technique where drug, polymer and excipients are mixed together and extruded under high temperature to form a homogenous liquid mass which is cast on the drying tunnel and finally slitting of mass to form smooth film. The films are punched, pouched and sealed. The major advantages of this technique are solvent free process, few unit operations involved, not required compressibility properties for API selection, uniformity in dosage forms.

Semisolid casting[11]

In this method, water soluble film forming polymers are mixed with the solution of acid insoluble polymer to get homogenous viscous solution (e.g. cellulose acetate phthalate, cellulose acetate butyrate). Plasticizers are added to form gelled mass and smooth cast on non-treated casting film. The ratio between acid insoluble polymer and film forming polymer should be 1:4.

Solid dispersion extrusion[12]

Solid dispersions by extrusion method are prepared by mixing of immiscible components, drug and then this mixture is shaped in to strips by pouring method in dies.

MATERIALS AND METHODS

Ezetimibe, a gift sample from Lupin Ltd., Pune, Transcutol HP, a gift sample from Gattefosse India Pvt. Ltd., Goa., HPMC E5, HPMC E6, HPMC E15 are gift samples from Colorcon India Pvt. Ltd., and other ingredients like pectin, sodium saccharin, orange oil, PEG-400 from India glycols limits, citric acid from R.M. chemicals are utilized from laboratory.

Preparation of oral fast dissolving films (OFDFs)

The OFDFs were prepared by using solvent casting method in petri plate. In the present investigation it was proposed to prepare film containing 10 mg of drug ezetimibe in 1 cm^2 (1 x 1 cm) film. The amount of drug to be incorporated into the film was calculated based on this assumption and the calculations.

Procedure for preparation of ezetimibe OFDFs

Formulae of ezetimibe OFDFs are presented in the Table 1. Solvent casting method was used for preparation of films using polymers (HPMC E5, E6, E15 and pectin). Initially the polymer was weighed accurately and dissolved in half quantity of water and mixed on magnetic stirrer. Ezetimibe was weighed and dissolved in transcutol HP. Citric acid and sodium saccharine were both dissolved in remaining amount of water. This solution was added to the polymeric solution and stirred well using a magnetic stirrer to obtain a homogenous solution, followed by the addition of PEG-400 as plasticizer and flavouring orange oil. This solution was allowed to stand for 30 min for deaeration of the solution. Solution was then casted in to petri dish and kept in hot air oven for 8-10 h at 50°C. After drying, films were removed. Thus the obtained large film was cut into

Table 1: Formulae of ezetimibe OFDFs.

Ingredients (mg)	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13	E14	E15	E16	E17	E18	E19	E20
Ezetimibe	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365	365
HPMC E5	330	355	380	405	430	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
HPMC E6	-	-	-	-	-	330	355	380	405	430	-	-	-	-	-	-	-	-	-	-
HPMC E15	-	-	-	-	-	-	-	-	-	-	330	355	380	405	430	-	-	-	-	-
Pectin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	330	355	380	405	430
Citric acid	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71	71
Sodium saccharine	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Transcutol HP	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
PEG-400	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Orange oil	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
P. water (ml)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

pieces with the area of 1.0 cm^2 (1 cm length x 1 cm breadth).

Evaluation of OFDFs

The oral fast dissolving films were evaluated for their dissolution, organoleptic characteristics and mechanical properties like thickness, dryness, tensile strength and folding endurance, transparency, disintegration time, surface pH, moisture loss, moisture uptake and uniformity of drug content were also evaluated.

Organoleptic properties

The organoleptic characters like colour, odour and appearance were examined physically and reported accordingly.

Thickness

Precise film thickness measurements were carried out using calibrated digital micrometre NIKON Digi-Micro screw gauge and then mean average (n = 3) is calculated subsequently. Uniformity of film weight is calculated in triplicate by cutting the film in 1 x 1 cm for determining the weight of film. Thickness of the film measured at five points i.e. from the centre to all the four corners and mean thickness is calculated. It is necessary to determine the uniformity in thickness as it is directly related to accuracy of dose in the film.

Dryness

The ability to adhere a piece of paper pressed between two strips was studied in dryness test.[13] There were eight stages involved in film drying process as per the literature, which were viz. dry-to touch, dry-to-recoat, dry hard, set-to-touch, dust-free, dry-through, tack-free and dry print-free were observed. These tests are used to evaluate dryness of films in pharmaceutical industry especially for orally disintegrating films.[6] Tack-free is the tenacity with which, the strip adheres to a piece of paper that has been pressed into contact with the other strip, instruments are also available for conducting this study.

Tensile strength

Mechanical properties of the film formers are important for film casting on release liners, punching and packaging. Tensile strength is defined as maximum stress applied at which, the film breaks. A quality control test was adapted using number 5 test specimen. Tensile strength test was performed using stable micro system's film support rig apparatus to assess strength and elasticity of the prepared films. 1 cm^2 film was taken and

kept between two cup holder and tight them with screws and place it on the film support rig instrument. It can be calculated from applied load at rupture divided by the strip cross-sectional area given in the equation below:

$$\text{Tensile strength} = \frac{\text{load at failure}}{\text{strip thickness}} \times 100$$

Folding endurance & Transparency

Folding endurance to determine mechanical properties of film and was measured by repeatedly folding of the film at the same place to the extent where film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value.[14] This parameter was checked simply by visual inspection of films.

Disintegration time

A film was placed onto 2 ml distilled water taken in petri dish. Time taken by the film to dissolve completely is considered as the disintegrating time. The disintegration time is the time when the film starts to break or disintegrates completely, normally disintegration time for oral films s within 2 min.[15]

Dispersion time

For determination of *in vitro* dispersion time, one film with the dimensions 1 x 1 cm was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37 ± 0.5°C and the time required for complete dispersion was determined.[16]

Surface pH

The surface pH of OFDF was determined to investigate the possibility of any side effects in *in vivo* studies. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was ensured to keep the surface pH as close to pH 6.8 (oral cavity pH). The pH of an oral film was usually determined by putting the film in petri dish and film was made wet with distilled water and noting pH by touching the film surface with a pH paper.[15]

Moisture loss, moisture uptake

Moisture loss was determined by weight variation. Initial weight of the film was determined and afterward film was kept in a desiccator containing calcium carbonate for about 72 h. Films were then taken out and weighed. Percentage moisture loss is calculated by using the following formula as below.[16]

$$\%\ \text{Moisture loss} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Moisture uptake of an oral thin film was determined by expose to the environment with a relative humidity 75% at room temperature for 72 h. Percentage moisture uptake is calculated as % weight gain of the films as per below formula.[17]

$$\%\ \text{Moisture loss} = \frac{\text{final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

Uniformity of drug content

Drug Content of oral fast dissolving films were determined by standard assay method taken for 10 individual samples as per the test procedures. The acceptance value of the test is less than 15 in accordance with all pharmacopoeia. A film of size 1 cm^2 was cut and kept in 100 ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and dilutions were measured at 232 nm to get absorbance.[18]

DISSOLUTION

The dissolution studies were carried out using USP dissolution apparatus type V (Paddle over disc, Electro lab, Mumbai, India) at 37 ± 0.5°C and 50 rpm, 900 ml of pH 6.8 phosphate buffer solution served as medium for ezetimibe OFDFs and 5 ml of samples were withdrawn at the time intervals of 5 min and 10 min. Each film having 10 mg of ezetimibe was placed in dissolution apparatus.

Compatibility studies

Drug-polymer compatibility studies were performed by Fourier transform infrared spectroscopy (FTIR) using pressed pellet technique. The pellet was prepared by compression of small pinch of the material with potassium bromide (KBR) and analysed at wave number range 4000-500 cm^{-1}.

Powder X-ray diffractometry

The powder X-ray diffractograms of pure drugs ezetimibe, physical mixtures of optimized formulations, placebo films and optimized film formulations of ezetimibe were recorded on pXRD with copper radiation in the 2θ range of 5-80° at 40 mA and 45 KV to identify the possible interactions.

Differential scanning calorimetry (DSC)

Thermal analysis studies were performed to pure APIs ezetimibe and optimized film formulations of ezetimibe. The samples were sealed in aluminium pan and heated at 10ºC /min rate from 20–200ºC with empty aluminium pan kept as reference sample.

Surface texture

Surface texture of ezetimibe was studied by SEM analysis. The surface morphology of pure APIs ezetimibe and optimized films of ezetimibe were observed by scanning electron microscopy.

RESULTS AND DISCUSSION

Drug release of OFDFs

Ezetimibe OFDFs drug release was around 90% for all the formulations within 10 min. The drug release data shown in Table 2 and release profiles in Figure 1. The drug release in the formulations coded E1 – E20 was ranging from 86.4% to 99.4% within 10 min. Thus from the dissolution studies of all the films developed with different grades of HPMC E series and pectin clearly showed that the drug release was high due to enhanced solubility of the ezetimibe, which indicated that the solubility of ezetimibe was increased in oral fast disintegrating films.

Evaluation of oral fast dissolving films

Oral fast dissolving films were evaluated for their organoleptic characteristics and mechanical properties like thickness, dryness, tensile strength, folding endurance, transparency, surface texture, disintegration time, drug content, and surface pH.

Organoleptic characteristics

The organoleptic characteristics such as description, appearance, and odour were observed for films of ezetimibe. They were found to be clear and free from foreign materials and air bubbles without odour.

Thickness

The thickness of the ezetimibe OFDFs formulations E1 – E20, developed with HPMC E5, E6 and E15 and pectin were found ranging from 0.116 mm to 0.358 mm. From the obtained thickness data it was observed that the thickness of the film was increased by increasing in the concentration of the film former. Hence, the thickness of the film was directly proportional to its film former concentration.

Table 2: Evaluation parameters of ezetimibe OFDFs.

Formulation	Thickness (mm)	Folding endurance	Transparency	Surface texture	Disintegration time	Surface pH	Drug content (%)
E1	0.131	50	Transparent	Smooth	24 sec	6.85	101.9
E2	0.141	75	Transparent	Smooth	30 sec	6.80	98.0
E3	0.181	89	Transparent	Smooth	35 sec	6.75	99.0
E4	0.241	96	Transparent	Smooth	49 sec	6.80	101.0
E5	0.278	105	Transparent	Smooth	1 min 5 sec	6.85	98.2
E6	0.116	184	Transparent	Smooth	36 sec	6.80	100.0
E7	0.174	189	Transparent	Smooth	48 sec	6.80	101.3
E8	0.215	193	Transparent	Smooth	59 sec	6.85	99.7
E9	0.310	196	Transparent	Smooth	1 min 2 sec	6.75	98.0
E10	0.358	199	Transparent	Smooth	1 min 30 sec	6.75	99.0
E11	0.119	263	Transparent	Smooth	40 sec	6.80	99.0
E12	0.123	274	Transparent	Smooth	49 sec	6.80	100.6
E13	0.125	291	Transparent	Smooth	54 sec	6.80	98.0
E14	0.214	297	Transparent	Smooth	1 min 20 sec	6.75	97.3
E15	0.258	300	Transparent	Smooth	1 min 50 sec	6.80	99.0
E16	0.124	188	Transparent	Smooth	26 sec	6.80	99.6
E17	0.167	192	Transparent	Smooth	32 sec	6.75	99.7
E18	0.191	200	Transparent	Smooth	41 sec	6.75	98.67
E19	0.212	227	Transparent	Smooth	50 sec	6.75	100.42
E20	0.265	250	Transparent	Smooth	1 min	6.80	99.57

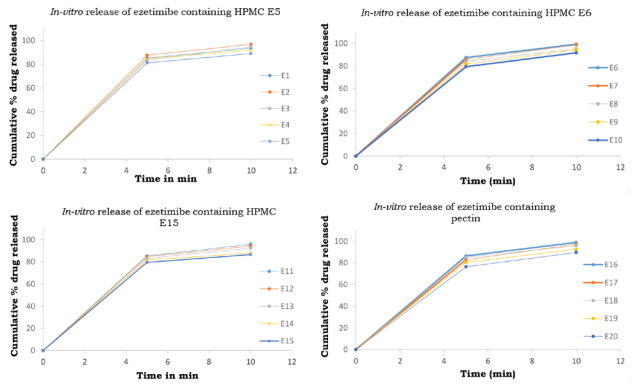

Figure 1: Dissolution profiles of ezetimibe OFDFs.

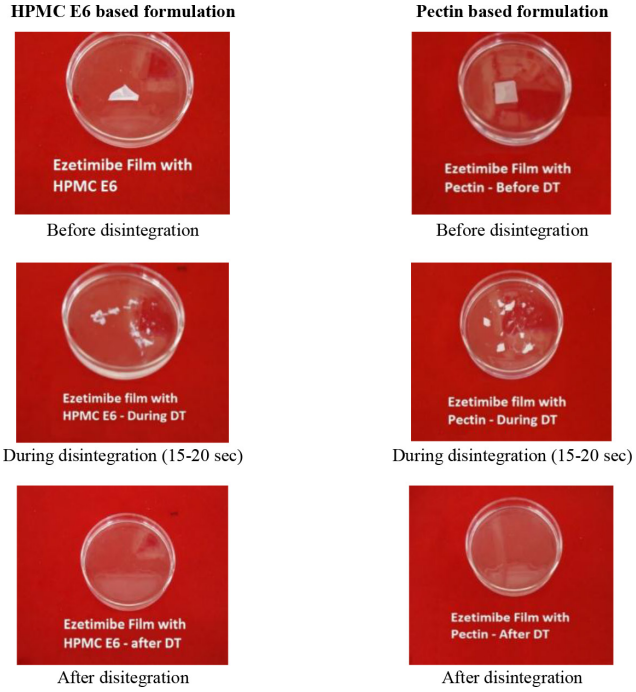

Figure 2: Ezetimibe OFDFs disintegrating pattern of E6 and E16 formulations.

Dryness

The dryness of ezetimibe OFDFs formulations E1 – E20 was shown by their non-sticky nature to the papers on either side of the film.

Folding endurance

Formulations E1-E5 folding endurance was in the range of 50-105, E6-E10 was in the range of 184-199, E11-E15 was in the range of 263-300 and E16-E20 was in the range of 188-250. The observed folding endurance data of the films developed with various viscosities and concentrations of film formers indicated that the increase in viscosities and concentrations of the film lead to increase in the folding endurance of the films.

Transparency

The transparency of ezetimibe OFDFs was observed by placing the films before black background and found that all the films were transparent.

Disintegrating time

The formulations E1 – E5 developed with different concentrations of HPMC E5, disintegration time were found in the range of 24 sec to 1 min 5 sec, formulation E6 to E10 developed with varied concentration of HPMC E6 were in the range from 30 sec to 1 min 30 sec. Formulations E11 – E15 taken with HPMC E15 having altered concentrations were in the range of 40 sec to 1 min 50 sec. The formulations E16 – E20 prepared with pectin having different concentrations were ranging from 26 sec to 1 min. The data of disintegration time indicates that increasing the concentrations of polymer along with different viscosities tends to increase the disintegration time. The films disintegration pattern shown as below in Figure 2 for ezetimibe OFDFs at initial, around 15 – 20 sec and final completion time snaps were represented.

Surface pH

The surface pH of the film should be similar to that of saliva i.e. 6.8 as it is being kept in the oral cavity for dissolution for avoiding the irritation. The pH of ezetimibe was measured in triplicate for each sample and found in the range from 6.75 – 6.85 with an average of around pH 6.80 which, indicated that pH range was well within the targeted pH and suitable in oral cavity.

Moisture loss and moisture uptake

The formulated OFDFs were evaluated and the %moisture loss was calculated. A reduced % moisture loss was observed with increase in polymer concentration varying from 6.5% to 4.50% w/w for ezetimibe films. The moisture uptake studies indicated an increase in uptake of moisture with increase in concentration of polymer and found to be in the range of 6.5% to 9.5% w/w which, may be due to increased hydrophilic nature of polymer with increase in viscosity of the polymer.

Drug Content

The Content uniformity was worked out on individual films of 10 samples. A film of size 1 cm^2 was cut and kept in 100 ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and measured at 232 nm. For E1 – E20

Table 3: Cumulative % drug released vs. time from ezetimibe OFDFs.

Formulation code		Time (min)	
		5	10
E1	% Drug released (mean ± s.d., n=6)	85.20±0.88	93.60±0.67
E2		87.63±0.58	96.87±0.79
E3		83.26±0.88	94.70±0.47
E4		84.87±0.87	91.89±0.46
E5		81.20±0.16	89.16±0.97
E6		87.46±0.33	99.40±0.49
E7		85.80±0.89	98.80±0.67
E8		84.10±0.15	95.20±0.67
E9		81.70±0.48	94.40±0.97
E10		79.40±0.57	91.70±0.59
E11		85.20±0.39	95.80±0.24
E12		84.70±0.28	94.26±0.19
E13		82.92±0.64	92.30±0.99
E14		81.50±0.64	87.80±0.28
E15		79.40±0.97	86.45±0.89
E16		86.40±0.39	98.80±0.46
E17		82.90±0.64	97.16±0.33
E18		85.20±0.33	95.80±0.26
E19		80.50±0.26	92.46±0.13
E20		76.40±0.34	89.59±0.22

formulations developed with HPMC E5, E6, E15 and pectin with different concentrations the drug content was found in the range of 97.3-101.9%. Even though all the formulations drug content within the specification range, 100% and 99.6% of ezetimibe in each formulation developed with HPMC E6 and pectin polymers respectively. The ezetimibe OFDF's evaluation parameters were shown in Table 3.

Compatibility study by FTIR

The FTIR spectrum of the ezetimibe and ezetimibe optimized formulation E6 analysed and the broad peak at the band range of 3285.95 – 3408.33 cm^{-1} represents the OH group, a sharp peak obtained at 2914.54 cm^{-1} represents CH=CH group, C=O (lactum ring) group was present in the drug ezetimibe and confirmed by the peak obtained at the band width 1722.49 cm^{-1}, a sharp peak obtained at 1491.02 cm^{-1} due to CN bending, and a peak obtained at 1222.91 cm^{-1} was due to C-F bending. The same characteristic bands were observed in the ezetimibe optimized formulation E6 indicating that there was no physical incompatibility in between the ingredients used to develop films.

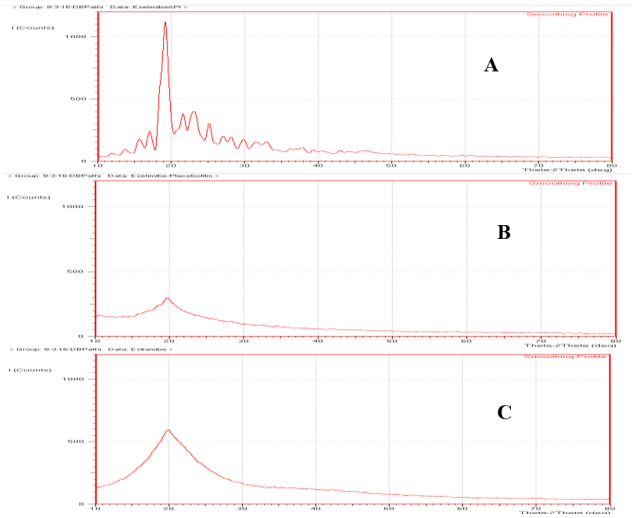

Figure 3: X-ray diffractograms of A) ezetimibe B) placebo film C) ezetimibe OFDF formulation E6.

Powder X-ray diffractometry

Powder X-ray diffractograms of ezetimibe, physical mixture, placebo film and ezetimibe optimized formulation E6 are shown in Figure 3. The powder X-ray diffractograms of ezetimibe showed distinct sharp peaks obtained at diffraction angles from 13.74° to 37.8° indicating the crystalline state of the ezetimibe. The intensity of peaks was reduced within the range of diffraction angle of 13.47° to 27.06° in the optimized ezetimibe film. However, the peak intensity was completely reduced in ezetimibe formulation E6 indicating that the nature of the drug ezetimibe was converted to amorphous form after formulating as film by using transcutol HP. The pXRD data of physical mixture and placebo film does not shown any sharp peaks.

Differential scanning calorimetry (DSC)

Figure 4 showed the DSC thermograms of both ezetimibe pure API and ezetimibe optimized film formulation E6. The sharp peak obtained at the range of 160-170°C represents the melting point of pure ezetimibe and it matches the literature values. The sharpness of the peak represents the crystalline nature of the pure ezetimibe. Where in, the ezetimibe optimized film formulation E6 DSC thermogram does not contains sharp peak and a broad peak obtained and it represents the ezetimibe was converted into amorphous form and it results in the enhancement of the drug release rate, it was due to the effect of transcutol HP.

Surface texture

Surface texture of films were found to be smooth in nature irrespective of the films developed. Figure 5 and

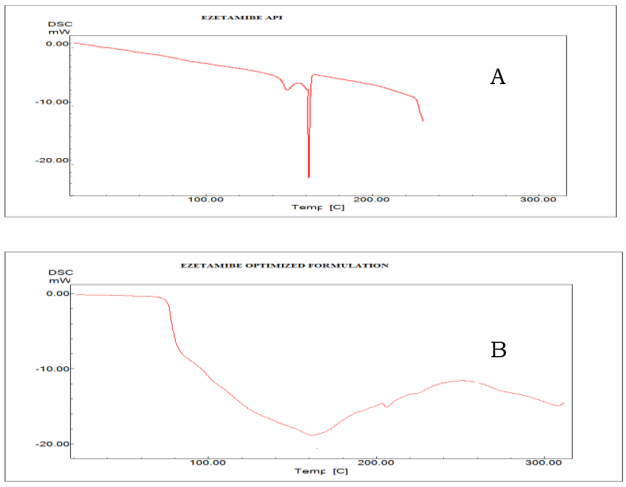

Figure 4: DSC thermograms of A) ezetimibe B) ezetimibe OFDF formulation E6.

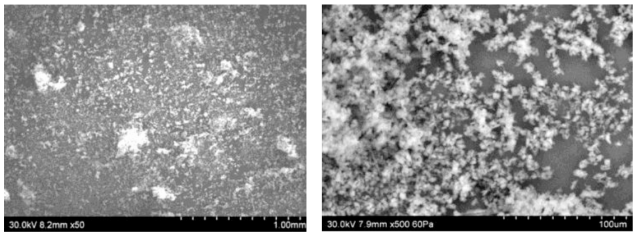

Figure 5: SEM images of ezetimibe pure API at different scales.

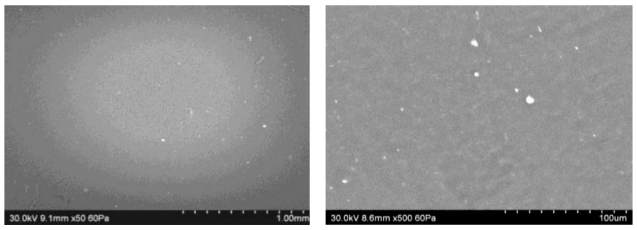

Figure 6: SEM images of ezetimibe OFDF formulation E6 at different scales.

6 showed the Scanning electron microscopy images of both ezetimibe pure API and ezetimibe film optimized formulation E6 at different scales. The crystals obtained at Figure 5 represents the pure ezetimibe API. Where in the ezetimibe OFDF formulation E6 Scanning electron microscopy images contained smooth surface represents the ezetimibe was in amorphous form and it results in the enhancement of the drug release rate, it was due to the effect of transcutol HP shown in Figure 6.

Preparation of OFDFs without transcutol HP for the selected drugs

From the above results it was concluded that the oral fast dissolving films of E6 of ezetimibe gave good results with respect to qualitative and drug release characteristics. Hence, to assess the effect of transcutol HP in increasing the solubility of poorly soluble drug, films of ezetimibe was prepared with the same composition omitting transcutol HP under similar conditions and are coded as BE6. The prepared ezetimibe film without transcutol HP was evaluated for their folding endurance, drug content estimation, disintegration time and dissolution. The prepared films were able to give the satisfactory results with respect to drug content as 99.8% and folding endurance as 175 for BE6 formulation and the disintegration time was 90 sec for BE6 formulation. The drug release studies were performed and the results are shown in Table 4 and Figure 7 in comparison with the films containing transcutol HP.

Table 4: Comparative dissolution studies of ezetimibe optimized films and without transcutol HP films in pH 6.8.

Time (min)	% Drug released (mean±s.d., n=6)	
	E6	BE6
5	87.5±0.33	15.5±6.15
10	99.4±0.49	22.2±7.27
15	99.6±0.14	25.4±3.15
30	99.1±0.71	30.2±2.44
45	98.6±0.18	35.6±3.42
60	98.5±0.26	40.5±1.28
90	98.7±0.57	45.8±0.77

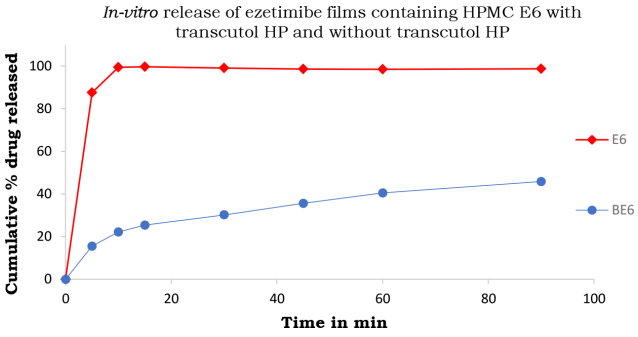

Figure 7: Comparative dissolution profiles of ezetimibe optimized films and without transcutol HP films.

CONCLUSION

In the present study the solubility of selected drug ezetimibe was studied in different solubilizing agents and it was observed that, transcutol HP increased the solubility of the selected drug by 3 to 4 times. Based on the enhancement of solubility when compared with water solubility, it was proposed to prepare the oral fast dissolving film of ezetimibe using transcutol HP as solubilizing agent. The films were prepared by using

HPMC E series with different viscosity grades and pectin using different drug-polymer concentrations. The prepared films were found to be good quality in nature with respect to the dissolution, thickness, disintegrating time, folding endurance, drug content etc. Based on the characteristics of the film formulations E6 for ezetimibe prepared with HPMC E6 gave good results with complete release of drug within 10 mins. Thus it can be concluded that transcutol HP can be used as solubilizing agent for poorly soluble drug like ezetimibe.

The study clearly indicated the influence of transcutol HP in enhancing the solubility of the poorly soluble drugs as the films made without transcutol HP failed to give the desired release characteristics within 10 min.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HPMC: Hydroxypropyl Methyl Cellulose, **OFDF:** Oral Fast Dissolving Films; **API:** Active Pharmaceutical Ingredient; **SEM:** Scanning Electron Microscope; **FTIR:** Fourier Transmission Infrared; **DSC:** Differential Scanning Calorimetry.

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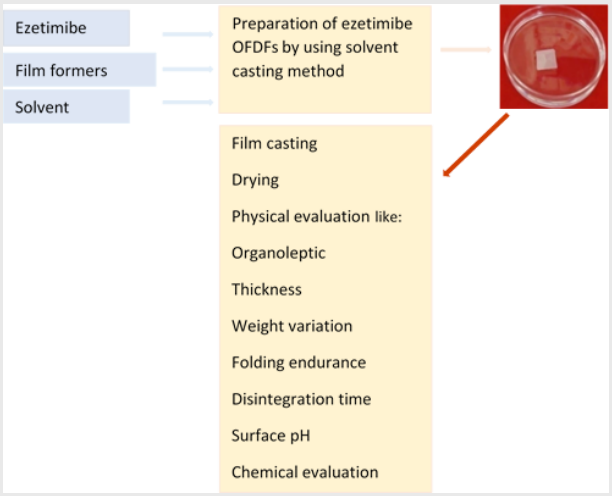
SUMMARY

- BCS class II drugs need the enhancement of the solubility thereby bioavailability, hence different techniques have been explored for the enhancement of the oral bioavailability. In the present study, it was studied the effect of transcutol HP and observed that, improved the solubility of ezetimibe by formulating the OFDFs having different concentrations of film formers indicated that all the prepared formulations were having the physical and chemical properties. Based on the results of all the formulations, optimized formulations have confirmed the improvement in the solubility and also blank formulations were prepared by using similar formula with omitting transcutol HP in the formulation. The results clearly indicated that, the influence of transcutol HP in optimized formulations shown complete drug release within 10 min, whereas only 50% of drug release observed after 90 min in the formulation without transcutol HP. Hence the effect of transcutol HP was clearly established.

PICTORIAL ABSTRACT



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