ORIGINAL ARTICLE

Design and Evaluation of Ezetimibe Rapidmelts by Direct Compression and Sublimation Methods

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Abstract

Aim: The aim of this study was to formulate and evaluate ezetimibe rapidmelts by sublimation and direct compression techniques. **Materials and Methods:** As ezetimibe comes under Class II drug, the solubility of the drug should be increased before formulation. For that, solid dispersions were prepared with β-CD and pvp k-30 using coevaporation and kneading methods. Among those solid dispersions prepared with β-CD (1:1.5) using coevaparation method has given better drug entrapment values compared to other solid dispersions. Those solid dispersions were formulated as rapidmelts using direct compression. In direct compression method, rapidmelts were prepared using superdisintegrants such as crospovidone, croscaramellose sodium, and starch 1500. Those are evaluated for both pre- and post-compression parameters. Ezetimibe rapidmelts were prepared by sublimation method using subliming agents camphor, urea, and ammonium bicarbonate. Each subliming agent is used in three different concentrations (2.5, 5.0, 7.5%). **Results and Discussion:** Rapidmelts prepared with the two methods were evaluated for weight variation, hardness, friability, % drug content, and disintegration time. The best formulation was subjected to stability testing for 6 months at 25°C/60% RH and 40°C/75% RH. All the prepared formulations compiled with the pharmacopeial limits. **Conclusion:** The results suggest that E12 formulation has given the best disintegration and dissolution results. From the result, it was concluded that rapidmelts prepared using sublimation method had given better result than direct compression method. That final formulation was further evaluated for *in-vivo* studies.

Key words: Coevaporation, direct compression, ezetimibe, kneading, PEG4000, PEG6000, sublimation, subliming agents, superdisintegrants, β-cyclodextrin

INTRODUCTION

The oral route of administration is most convenient for drug administration. Orally disintegrating systems are dosage forms, which when placed in the mouth rapidly disperse and dissolve in the mouth without the need of water. After disintegration, the drug solution can be partially or completely absorbed by the sublingual blood vessels and bypasses first-pass metabolism by the liver or be absorbed from the gastrointestinal tract after swallowing. Prescription orally disintegrating tablet (ODT) products initially were developed to overcome the difficulty in swallowing among pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules.[1]

Today, ODTs will be more widely available as OTC products for the management of many conditions such as lowering cholesterol, heart problems, allergies, and cold. The presence of a highly porous surface in the tablet matrix is the key factor for the rapid disintegration of ODT.[2]

Many methods were reported for solubility and dissolution enhancement of poorly soluble drug such as mechanization, complexation, solid dispersions, and kneading method. Solid dispersions are a technique that depends on melting or dissolution process to disperse one or more active ingredient in a carrier or matrix in the solid state. This ensures increased

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drug wettability and reduction of particle aggregation and hence increased drug dissolution.

Pediatric and geriatric patients may have difficulties in swallowing or chewing pharmaceutical dosage forms for oral administration. Tablets that rapidly dissolve upon contact with buccal cavity could present a solution to those problems, and so there is an increased interest fast dissolving dosage forms for buccal, sublinguial and oral administration. Fast dissolving/disintegrating tablets are perfect fit to those patients as they immediately release the active drug when placed upon the tongue by rapid disintegration.[3] So in the present investigation rapidmelts of ezetimibe were prepared.

Ezetimibe is widely used in the treatment of hyperlipidemia. It acts as a cholesterol absorption inhibitor. Hyperlipidemia drugs are mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Statins generally work *via* nuclear receptors, statins may have benefits other than just lowering cholesterol, they have anti-inflammatory properties, which help stabilize the lining of blood vessels. Ezetimibe is practically insoluble in water and crystalline compound. Dissolution is the rate limiting step that controls oral absorption. Therefore, improvement in solubility and dissolution rate is essential to enhance drug bioavailability.[4]

As ezetimibe comes under BCS Class II drug, solid dispersions of ezetimibe were prepared by using different polymers in different ratios using different techniques to enhance the solubility of the drug. Then, those solid dispersions were formulated as rapimelts using different superdisintegrants using direct compression method. To improve the porosity, volatile substances such as subliming agents can be used in tabletting process, which sublimated from the formed tablet. Ezetimibe rapidmelts were prepared using direct compression and sublimation techniques.

MATERIALS AND METHODS

Materials

Ezetimibe was obtained as a gift sample from Dr. Reddy's Laboratories Ltd. Hyderabad. β-cyclodextrin, polyethylene glycol 6000, polyethylene glycol 4000, crospovidone, croscaramellose sodium, starch 1500, magnesium stearate, aerosil, microcrystalline cellulose, camphor, urea, ammonium bicarbonate, talc, aspartame, mannitol were kindly supplied by BMR pharma and chemicals. All the other solvents used were analytical grade.

Methods

Calibration curve for ezetimibe

For this stock solution of ezetimibe (1 mg/ml) was prepared. For the stock solution ezetimibe 10 mg was taken and dissolved in few ml of methanol. The stock solutions were diluted with methanol to prepare the concentrations 5, 10, 15, 20, and 25 µg/ml of ezetimibe. They were analyzed by ultraviolet-visible spectrophotometer at 233 nm using methanol as blank. A calibration curve was plotted against concentration and absorbance.

Preparation of solid dispersions

Solvent evaporation method

Drug and polymers were mixed in different ratios (1:0.5, 1:1, 1:1.5) in a mortar. Methanol was added in proportion wise with constant and continuous stirring until the mixture was completely dissolved. Ethanol was evaporated under constant stirring and resultant solid dispersions were collected. Preapration of solid dispersions by solvent evoparation method was given in Table 1.

Kneading method

In a mortar, 50% of solvent was taken to that add calculated amount of polymer and is triturated to get slurry-like consistency. Then, the drug was incorporated, remaining solvent was added and trituration is continued for 1 h, air dried at 25°C for 48 h, and the resulting dried product was pulverized and passed through mesh sieve. Preapration of solid dispersions by Kneading method was given in Table 2.

Evaluation of solid dispersions

Drug entrapment efficiency

Percentage yield was determined by weighing the dried solid dispersion and calculated with respect to the weight of the initial components according to the following formula;

%yield = [mass of solid dispersion/(mass of drug + mass of lipidic substances)] ×100.

Table 1: Preparation of solid dispersions using cosolvent evaporation method

Excipients	1:0.5 (EZE1)	1:1 (EZE2)	1:1.5 (EZE3)	1:0.5 (EZE4)	1:1 (EZE5)	1:1.5 (EZE6)
Drug (mg)	500	500	500	500	500	500
Bcyclodextrin (mg)	250	500	750			
PEG 6000 (mg)				250	500	750
Water and ethanol	10 ml and 10 ml for all the preparations					

Table 2: Preparation of solid dispersions using kneading method

Excipients	1:0.5 (EZE1)	1:1 (EZE2)	1:1.5 (EZE3)	1:0.5 (EZE4)	1:1 (EZE5)	1:1.5 (EZE6)
Drug (mg)	500	500	500	500	500	500
Bcyclodextrin (mg)	250	500	750			
PEG 4000 (mg)				250	500	750
Water and ethanol (ml)	Quantity sufficient for paste formation					

About 10 mg of each solid dispersion was weighed in glass stoppard tubes and redispersed in 3 ml distilled water. The dispersion was then lysed with 1 ml chloroform to allow for complete release for entrapped drug. Complete extraction of the drug was facilitated by shaking the tubes for 6 h in water bath shaker at 37°C. The samples were centrifuged at 6000 rpm for 5 min and then allowed to stand for complete separation of the two phases. The collected aqueous solutions were analyzed for determining the drug concentration as previously described. The resuls were given in Table 3. Drug concentration was also used for determining % encapsulation efficiency according to the following formula.

% encapsulation efficiency = (actual drug loading/theoretical drug loading) ×100.

Drug entrapment for solid dispersions

Among both the methods cosolvent evaporation was found to be entrapped good compared to kneading method.

Preparation of ezetimibe rapidmelts

Ezetimibe rapidmelts were prepared using direct compression and sublimation methods.

Direct compression method

Solid dispersions equivalent to 10 mg were taken. Rapidmelts were prepared using superdisintegrants CCS, CP, starch 1500 (2, 4, 6%). All the ingredients were passed through the mesh. Then, all the ingredients were mixed in geometric order and the tablets were compressed with 12 mm size round Punch. The formulation of rapidmelts by direct compression method was givne in Table 4.

Sublimation method

Different rapid melts of ezetimibe were prepared using subliming agents such as camphor, urea, ammonium bicarbonate in different concentrations (2.5, 5, 7.5%) from the final tablet weight. All of the materials were passed through sieve No. 60 before use, and the accurately weighed amounts of ingredients were thoroughly mixed and compressed into 200 mg tablets using single punch machine of 12 mm round punch and die set. Ezetimibe tablets were then placed in an oven at 40°C till a constant weight is obtained. The formulaion of rapidmelts by sublimation method was given in Table 5.

Table 3: Drug entrapment efficiency values

SD	Cosolvent method	Kneading method
EZE1	65.7	53.5
EZE2	66.46	58.23
EZE3	69.6	60.28
EZE4	52.6	54.98
EZE5	61.8	60.23
EZE6	65.6	62.9

SD: Standard devation

Evaluation of ezetimibe rapid melts

Pre-compression parameters

The various characteristics of blends to be conducted before compression are as follows.

Angle of repose

Angle of repose (θ) was determined using the fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granular cone was measured, and angle of repose was calculated using the following equation:

$\tan \theta = h/r$

Where h and r are the height and radius of the cone.

Bulk density and tapped density

A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduced into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 s intervals. The tapping was continued until no further change in volume was noted.

Bulk density = weight of the powder/bulk volume of the powder.

Tapped density = weight of the powder/tapped volume of the powder.

Table 4: Formulation of ezetimibe rapidmelts by direct compression method

Compound name	E1	E2	E3	E4	E5	E6	E7	E8	E9
Equivalent SD (mg)	50	50	50	50	50	50	50	50	50
CP (mg)	4			8			12		
CCS (mg)		4			8			12	
Starch 1500 (mg)			4			8			12
Mg Stearate (mg)	3	3	3	3	3	3	3	3	3
Aerosil (mg)	2	2	2	2	2	2	2	2	2
MCC (mg)	141	141	141	137	137	137	133	133	133

SD: Standard deviation

Table 5: Formulation of ezetimibe rapidmelts by sublimation method

Compound name	E10	E11	E12	E13	E14	E15	E16	E17	E18
Ezetimibe (mg)	10	10	10	10	10	10	10	10	10
Camphor (mg)	5	10	15						
Urea (mg)				5	10	15			
Ammonium bicarbonate (mg)							5	10	15
Crospovidone (mg)	4	4	4	4	4	4	4	4	4
Aspartame (mg)	2	2	2	2	2	2	2	2	2
Mg stearate (mg)	2	2	2	2	2	2	2	2	2
Talc (mg)	1	1	1	1	1	1	1	1	1
Mannitol (mg)	176	171	166	176	171	166	176	171	166

Carr's index

The compressibility index of the powder blend was determined by the Carr's index. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which its packed down.

Carr's index = (tapped density - bulk density/tapped density) ×100

Hausner's ratio

Hausner's ratio was calculated from the bulk and tapped density of ezetimibe blend powder formulation and it is expressed as:

Hausner's ratio = tapped density/bulk density

Post-compression parameters

Hardness

The average breaking strength of tablets was determined by tablet hardness tester (Monsanto hardness tester). From each formula, 10 tablets were tested for their hardness. The mean hardness (±standard devation [SD]) of each formula was determined.[5] It is expressed in kg/cm^2.

Weight variation

To ensure the uniformity of tablets, weight variation test was carried out. 20 tablets were randomly selected from each formulation and separately weighed. Their average weight and (±SD) were calculated.[5]

Friability

To evaluate the friability, 10 tablets from each batch were collected and weighed. The tablets were placed in the roche friabilator and subjected to 25 rpm for a period of 4 min. Afterward the tablets were dusted and once again reweighed. The percentage loss in weights was calculated and taken as a measure of friability.[5]

In vitro disintegration time

The *in vitro* disintegration studies were carried out using a digital tablet disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket assembly, and then disk was added to each tube. This assembly was then suspended in a 1 L beaker containing water with its temperature being maintained at 37°C ± 2°C. The basket was then moved up and down through a distance of 5-6 cm, at the frequency of 28-32 cycles/min. The time required for the complete disintegration of the tablet was recorded. It is expressed in seconds.

In vitro dissolution studies

The dissolution profiles of ezetimibe from rapidmelts were determined in a dissolution tester, Apparatus II. All tests were conducted in 900 ml phosphate buffer pH7.0 containing 0.5% SLS at a temperature of 37°C ± 0.5°C with a paddle rotation speed at 50 rpm. At specified time intervals 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 min; 5 ml of dissolution medium was withdrawn and replaced with an equal volume of medium to maintain a constant total volume. Samples were filtered through a 0.45 µm milliporefilter and assayed for drug content spectrophotometrically at 235 nm.

Characterization

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum was obtained on a Perkin Elmer 2000 FTIR. System (Perkin-Elmer, Norwalk, CT) using the KBr press pellet method. The scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential scanning calorimetry (DSC)

Drug - excipients compatibility was evaluated using differential scanning calorimeter. The endotherms of pure drug and optimized formulation were recorded separately. The DSC thermograms are obtained by a differential scanning calorimeter (DSC 220C, Seiko, Japan) at a heating rate of 10°C/min from 10°C to 200°C in the nitrogen atmosphere.

Stability studies

To study the stability of the rapidmelts, representative samples of the were packed in amber colored air tight glass containers, and they were stored in stability chambers maintained at 25°C/60% RH and 40°C/75% RH. The physicochemical properties of these samples were analyzed at 0, 3 and 6 months. At each time point, one container was taken out from the respective storage conditions and subjected to content uniformity and dissolution rate studies.

RESULTS AND DISCUSSION

Pre-compression parameters

The values of angle of repose were found to be within the range of 25-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.30-0.70 (g/cm^2). Carr's index was found to be in the range of

Table 6: Preformulation parameters for rapidmelts by direct compression method

Formulation code	Angle of repose (°)	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index (%)	Hausner's ratio
E1	24.53±0.01	0.61±0.01	0.71±0.01	16±0.01	1.2±0.01
E2	25.26±0.12	0.61±0.11	0.71±0.11	14.0±0.15	1.15±0.25
E3	29.13±0.21	0.59±0.02	0.73±0.25	24.01±0.1	1.83±0.11
E4	28.58±0.11	0.61±0.2	0.71±0.03	14.10±0.10	1.17±0.13
E5	27.78±0.05	0.6±0.01	0.74±0.15	18.32±0.10	1.2±0.21
E6	24.3±0.17	0.58±0.11	0.71±0.05	22.13±0.02	1.6±0.05
E7	26.83±0.10	0.6±0.15	0.75±0.24	19.32±0.05	1.23±0.04
E8	29±0.03	0.59±0.14	0.73±0.06	18.18±0.15	1.2±0.06
E9	28.15±0.05	0.62±0.04	0.74±0.11	16.26±0.20	1.18±0.05

Table 7: Post-compression parameters for rapidmelts by direct compression method

Formulation code	Hardness (kg/cm^2)	Wt variation (mg)	Drug content (%)	Friability (%)	Disintegration time (s)
E1	6.1±0.01	198±0.01	99.98±0.01	0.7±0.01	160±0.01
E2	7.5±0.01	196.5±0.21	101.32±0.11	0.82±0.10	168±0.05
E3	7.1±0.23	199.3±015	100.01±0.10	0.65±0.05	152±0.10
E4	7.3±0.15	197.8±0.05	102.32±0.20	0.74±0.11	163±0.12
E5	6.5±0.22	198.5±0.25	101±0.10	0.56±0.05	165±0.24
E6	6.3±0.34	200.6±0.12	102.4±0.05	0.58±0.02	159±0.10
E7	6.2±0.01	200.2±0.01	100.4±0.02	0.7±0.06	150±0.15
E8	6.9±0.24	196.4±0.01	101±0.01	0.5±0.11	172±0.06
E9	7±0.04	195.5±0.11	100.5±0.05	0.45±0.12	150±0.08

14-25%. The Hausner's ratio was within the range of 1.15-1.35. From the result, it was concluded that powder blends have good flow properties. The pre compression parameters were given Tables 6 and 7.

Post-compression parameters

Hardness of all the formulations was in the range of 6-7.5 kg/cm^2. It indicated that all the formulations possess

Table 8: Pre-compression parameters for ezetimibe rapidmelts using sublimation method

Formulation code	Angle of repose (°)	Bulk density (mg/ml)	Tapped density (mg/ml)	Carr's index (%)	Hausner's ratio
E10	25.3±0.01	0.33±0.21	0.42±0.11	21.38±0.01	1.20±0.01
E11	26. 5±0.12	0.36±0.02	0.41±0.01	22.12±0.21	1.35±0.12
E12	24.2±0.25	0.31±0.06	0.46±0.21	17.53±0.32	1.28±0.05
E13	27.13±0.12	0.35±0.05	0.52±0.04	20.41±0.11	1.19±0.22
E14	26.4±0.11	0.32±0.15	0.46±0.03	25.18±0.15	1.26±0.14
E15	28.33±0.32	0.39±0.12	0.43±0.01	19.25±0.21	1.34±0.22
E16	25.65±0.15	0.41±0.22	0.49±0.11	16.93±0.24	1.20±0.21
E17	29.5±0.14	0.37±0.08	0.51±0.21	18.85±0.32	1.30±0.13
E18	26.25±0.01	0.34±0.10	0.45±0.25	24.58±0.11	1.34±0.11

Table 9: Post-compression parameters for ezetimibe rapidmelts using sublimation method

Formulation code	Hardness (kg/cm^2)	Wt variation (mg)	Drug content (%)	Friability (%)	Disintegration time (s)
E10	6.08±0.05	200.1±0.01	100.1±0.05	0.49±0.05	120±0.01
E11	6.15±0.02	199.8±0.12	98.39±0.12	0.45±0.06	135±0.12
E12	7.09±0.12	198.12±0.03	100.25±0.01	0.53±0.01	115±0.01
E13	5.80±0.11	201.50±0.05	101±0.05	0.62±0.12	125±0.15
E14	6.9±0.14	200±0.06	100±0.21	0.65±0.13	129±0.21
E15	6.10±0.10	197.5±0.15	99.93±0.11	0.59±0.24	149±0.10
E16	6.18±0.21	199±0.21	97.85±0.23	0.35±0.15	143±0.04
E17	6.3±0.05	200±0.15	100.30±0.10	0.42±0.11	127±0.02
E18	7±0.04	199±0.10	98.3±0.11	0.52±0.10	146±0.12

Table 10: Cumulative percentage drug release for formulations prepared using direct compression method

Time (min)	E1	E2	E3	E4	E5	E6	E7	E8	E9
0	0	0	0	0	0	0	0	0	0
5	31.02±0.02	20.13±0.11	9.39±0.10	17.3±0.10	18.12±0.02	15.26±0.010.21	40.12±0.05	18.12±0.10	16.09±0.01
10	48.5±0.25	31.52±0.20	22.83±0.05	40.12±0.05	49.05±0.10	50.12±0.05	69.88±0.10	40.6±0.15	32.69±0.05
15	65.83±0.01	48.92±0.10	30.12±0.02	55.8±0.01	65.23±0.10	61.68±0.06	85.32±0.11	56.12±0.20	61.83±0.20
20	79.12±0.11	60.64±0.01	36.39±0.01	63.35±0.20	73.42±0.05	68.39±0.10	100±0.11	65.85±0.14	86.25±0.10
25	87±0.05	74.24±0.02	51.02±0.21	76.21±0.11	80.78±0.11	76.41±0.12		80.5±0.20	100.1±0.11
30	91.22±0.21	85.13±0.06	67.58±0.20	88.01±0.01	88.24±0.12	88.89±0.15		99.89±0.05	
35		91.43±0.21	75.93±0.10	99.59±0.11	92.59±0.21	99.55±0.01			
40		101±0.10	82.63±0.01		101.65±0.25				
45			90.99±0.20						
50			100±0.25						

Table 11: Cumulative percentage drug release for formulations prepared using sublimation method

Time (min)	E10	E11	E12	E13	E14	E15	E16	E17	E18
0	0	0	0	0	0	0	0	0	0
1	20.11±0.01	18.02±0.01	25.03±0.11	4.12±0.01	5.01±0.01	9.01±0.05	3.02±0.01	5.02±0.05	5.02±0.05
2	31.12±0.25	29.01±0.11	45.05±0.21	8.03±0.10	7.02±0.10	18.02±0.10	8.04±0.05	9.03±0.10	10.01±0.20
3	45.21±0.11	43.52±0.10	72.12±0.15	10.15±0.12	9.04±0.05	25.05±0.20	10.02±0.02	11.05±0.20	15.01±0.25
4	75.12±015	73.11±0.15	89.01±0.14	15.09±0.20	14.09±0.10	32.15±0.22	13.05±0.10	16.09±0.11	22.12±0.10
5	98.73±0.21	96.3±0.21	99.89±0.20	19.12±0.25	18.12±0.11	50.12±0.10	16.09±0.15	22.83±0.05	30.12±0.06
10				60.12±0.10	45.05±0.02	75.15±0.15	40.06±0.20	51.02±0.20	67.58±0.05
15				88.02±0.15	69.12±0.21	98.15±0.12	69.88±0.20	82.63±0.03	85.13±0.10
20				95.32±0.10	85.13±0.22		88.80±0.21	98.73±0.05	99.59±0.10
25					97.16±0.25		96.32±0.11		

Table 12: Stability studies

Time (min)	Percentage dissolution rate	25°C/60% RH (dissolution rate after storage) (%)		40°C/75% RH (dissolution rate after storage) (%)	
		3 months	6 months	3 months	6 months
0	0	0	0	0	0
1	25.03±0.11	25.05±0.15	25.07±0.01	25.01±0.06	25.05±0.05
2	45.05±0.21	46.01±0.07	45.10±0.05	45.01±0.20	45.05±0.04
3	72.12±0.15	72.15±0.08	72.10±0.10	72.10±0.13	72.11±0.14
4	89.01±0.14	89.05±0.11	89.00±0.10	89.05±0.11	89.04±0.13
5	99.89±0.20	99.87±0.16	99.85±0.08	99.88±0.21	99.89±0.16

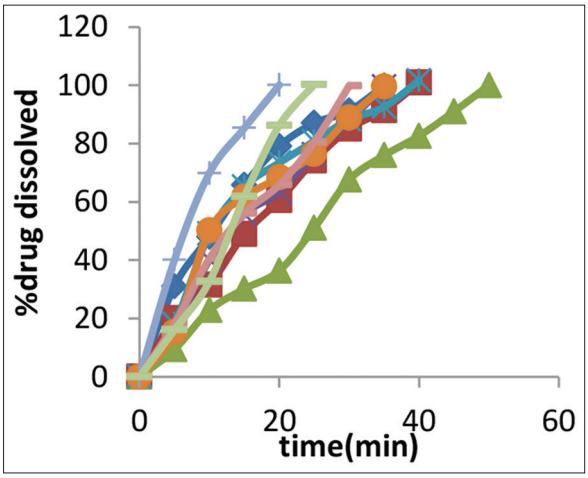

Figure 1: Dissolution profile for ezetimibe rapidmelts by direct compression method in pH 7.0 phosphate buffer containing 0.5% SLS

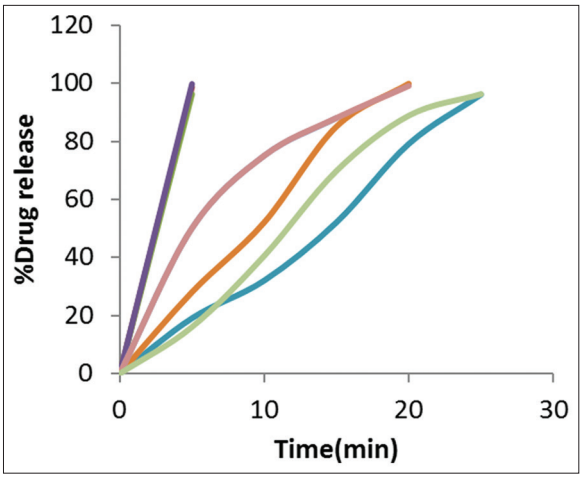

Figure 2: Dissolution profile for ezetimibe rapidmelts by sublimation method in pH7.0 phosphate buffer containing 0.5% SLS

sufficient mechanical strength. Weight variation was found to be in the range of IP limits. Friability values were found to be within IP limits. *In vitro* disintegration time of all the formulations were found to be in the range of 110-180 s. Among all the formulations (E10-E18) prepared with subliming agents have given better disintegration compared to formulations (E1-E9) prepared with superdisintegrants using direct compression method. The post compression parameters were given in Tables 8 and 9. *In vitro* drug release studies were shown in Tables 10 and 11. Among all the formulations E12 has given better dissolution compared to all the formulations. Hence, E12 formulation was selected

Table 13: Drug release kinetics

Formulation code	Zero order	First order
E1	0.925	0.994
E2	0.983	0.955
E3	0.992	0.921
E4	0.979	0.958
E5	0.908	0.992
E6	0.938	0.962
E7	0.950	0.94
E8	0.99	0.977
E9	0.989	0.878
E10	0.975	0.692
E11	0.973	0.753
E12	0.984	0.721
E13	0.970	0.958
E14	0.986	0.928
E15	0.971	0.903
E16	0.985	0.936
E17	0.992	0.854
E18	0.975	0.852

as optimized as 100% drug release in 5 min. Dissolution profiles were given in Figures 1 and 2.

Stability studies

Stability studies: The stability studies revealed that there is no significant changes were observed throughout the study. Hence, we can say that formulation has good stability. Stability studies were given in Table 12.

Drug release kinetics

The results obtained from *in vitro* dissolution studies were fitted to zero and first order kinetics. Drug release kinetic values were given in Table 13.

Characterization

DSC analysis

DSC thermograms for pure drug and optimized formulation were given in the Figure 3. Peaks indicating that there were no interactions between drug and excipients.

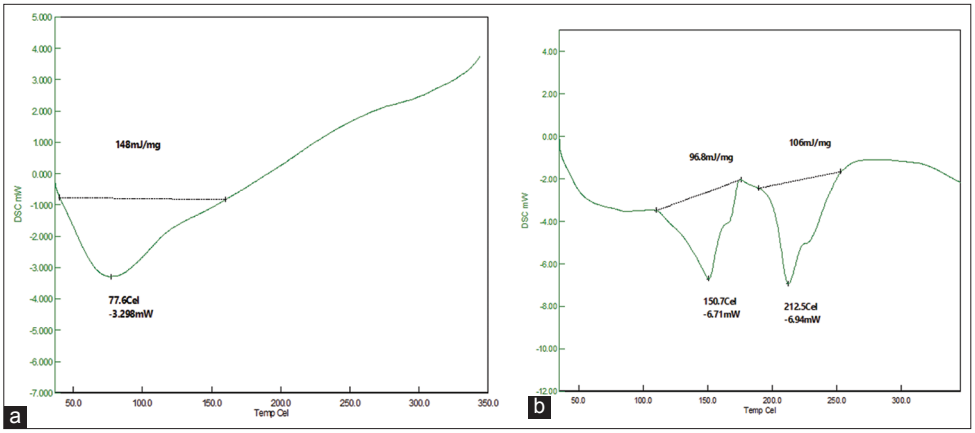

Figure 3: (a and b) Differential scanning calorimetry thermograms for pure drug and formulation

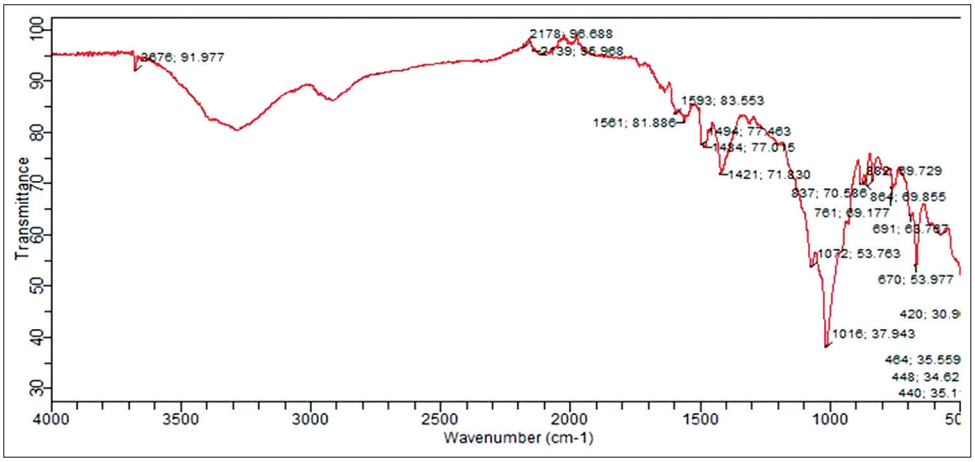

Figure 4: Fourier transform infrared spectroscopy for ezetimibe formulation

FTIR studies

The results obtained with FTIR studies showed that there was no interaction between the drug and other excipients used in the formulation. FTIR spectroscopy analysis was performed to pure drug and optimized formulation and presented in Figure 4.

CONCLUSION

This study was done on rapidmelts of ezetimibe using direct compression and sublimation methods. As ezetimibe comes under BCS Class II solubility of Ezetimibe was enhanced by preparing solid dispersions. The prepared solid dispersions were formulated as rapidmelts using direct compression method. In the sublimation method, rapidmelts were prepared using subliming agents. The prepared blends were evaluated for pre-compression studies such as bulk density, tapped density, Carr's index, haussner's ratio, angle of repose. They were found to be within limits. After completion of pre-compression studies required powder blend was weighed and compressed using tablet compression machine. They were kept for post-compression studies such as weight variation, hardness, friability, *in vitro* disintegration and dissolution studies. From dissolution studies, rapidmelts prepared using camphor (7.5%) has given maximum drug release within 5 min. Hence, it was concluded that rapidmelts prepared using sublimation method has given better result than direct compression method. Hence, sublimation method would be an effective method for the preparation of rapidmelts.

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