

Methods

Calibration curve for ezetimibe

For the preparation of ezetimibe stock solution. For the stock solution, ezetimibe 10 mg was taken and dissolved in few ml of methanol. The stock solutions were diluted with methanol to organize the concentrations 5, 10, 15, 20, and 25 µg/ml of ezetimibe. They were analyzed by UV-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

For the preparation of solid dispersions, drug and polymers were mixed in a mortar with ratios (1:0.5, 1:1, and 1:1.5). Ethanol 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 (Table 1).

Kneading method

In a mortar, 50% of solvent was taken there to add calculated amount of polymer and is triturated to urge slurry-like consistency. Then, the drug was incorporated, remaining solvent was added, and trituration is sustained for 1 h, air-dried at 25°C for 48 h, and therefore, the resulting dried product was pulverized and skilled mesh sieve (Table 2).

Evaluation of solid dispersions

Drug entrapment efficiency

Each solid dispersion about 10 mg was weighed and placed in glass Stoppard tubes and redispersed in 3 ml water. The dispersion was then lysed with 1 ml chloroform to permit for complete release for entrapped drug. Complete extraction of the drug was done by shaking the tubes for 6 h in water bath shaker at 37°C. The centrifugation of the samples was done at 6000 rpm for 5 min and then allowed to face for complete separation of the two phases. The collected aqueous solutions were analyzed for determining the drug concentration as previously described (Table 3). Drug concentration was also used for determining % encapsulation efficiency consistent with the subsequent formula.

$$\% \text{ Encapsulation efficiency} = (\text{Actual drug loading} / \text{Theoretical drug loading}) \times 100.$$

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

In direct compression method supported entrapment values 69.6 mg of solid dispersions which was taken equivalent to 10 mg

of drug ezetimibe. Formulation of rapidmelts was done using superdisintegrants croscarmellose sodium, crospovidone, and starch 1500 in concentrations of 2, 4, and 6%. All the ingredients were skilled through the mesh. Then, all the ingredients were mixed in geometric order, and therefore, the tablets were compressed with 8 mm size round punch (Table 4).

Sublimation method

Rapidmelts of ezetimibe were prepared using subliming agents such as camphor, urea, and ammonium bicarbonate in concentrations of 2.5, 5, and 7.5% from the ultimate tablet weight. Accurately weighed amounts of ingredients were thoroughly mixed and compressed into 200 mg tablets using single punch machine of 8 mm round punch and die set. Ezetimibe tablets were then placed in an oven at 40°C till a continuing weight is obtained (Table 5).

Evaluation of ezetimibe rapidmelts

Pre-compression parameters

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

Angle of repose

The fixed funnel method was used to decide the angle of repose. The funnel height was adjusted in such how that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow onto the funnel freely onto the surface. The peak and diameter of the granular cone was measured and angle of repose was calculated.

Bulk density and tapped density

An appropriate amount of powder from each formulation was taken and was introduced into the 10 ml measuring cylinder. After measuring initial volume, the cylinder was allowed to fall into its own weight onto a tough surface from a height of 2.5 cm at 2 s intervals. The tapping of the measuring cylinder was continued until there is no further change in volume which was noted.

$$\text{Bulk density} = \text{Weight of the powder} / \text{Bulk volume of the powder}$$

$$\text{Tapped density} = \text{Weight of the powder} / \text{Tapped volume of the powder}$$

Carr's index: The Carr's index was used to measure the compressibility index of the powder blend.

$$\text{Carr's index} = (\text{Tapped density} - \text{Bulk density} / \text{Tapped density}) \times 100$$

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

$$\text{Hausner's ratio} = \text{Tapped density} / \text{bulk density}.$$

Table 1: Preparation of ezetimibe solid dispersions using solvent 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
β-cyclodextrin (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 ezetimibe solid dispersions using kneading method

Excipients	1:0.5 (EZE7)	1:1 (EZE8)	1:1.5 (EZE9)	1:0.5 (EZE10)	1:1 (EZE11)	1:1.5 (EZE12)
Drug (mg)	500	500	500	500	500	500
β-cyclodextrin (mg)	250	500	750			
PEG 4000 (mg)				250	500	750
Water and ethanol (ml)	Quantity sufficient for paste formation					

Post-compression parameters*Hardness*

The typical breaking strength of tablets was decided by tablet hardness tester (Monsanto hardness tester). Ten tablets from each formula were tested for its hardness. The mean hardness (\pm SD) of every formula was determined.

Weight variation

Weight variation test was administered to ensure the uniformity of tablets. From each formulation, 20 tablets were randomly selected and separately weighed. Their average weight was calculated.

Friability

Ten tablets from each batch were collected to the gauge evaluate the friability. The tablets were placed in the Roche friabilator and subjected to 25 rpm for a period of 4 min. Then, the tablets were dusted and once more reweighed. The percentage loss in weights was calculated and taken as a measure of friability.

Wetting time

Five circular tissue papers of 10 cm diameter were placed during Petri dish with a 10 cm diameter. A tablet was placed on the surface of tissue. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The wetting time of the formulations was measured in seconds.

In vitro disintegration time

Disintegration test apparatus was used to measure the *in vitro* disintegration time. One tablet was placed in each of the six tubes of

the basket assembly of the disintegration apparatus and then disk was placed on to each tube. This assembly was then suspended during a 1 L beaker containing water with its temperature being maintained at $37\pm 2^\circ\text{C}$. 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 noted.

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 pH 7.0 containing 0.5% SLS at a temperature of $37\pm 0.5^\circ\text{C}$ with a paddle rotation speed at 50 rpm. Samples were collected at specified time intervals 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 50 min. A 5 ml of dissolution medium was replaced with an equal volume of medium to take care of a constant total volume. Samples were filtered through a 0.45 μm Millipore filter and assayed for drug content spectrophotometrically at 233 nm.

Characterization*Fourier transform infrared (FT-IR) studies*

The concentration of the sample in KBr should be within the range of 0.2–1%. The pellet is far thicker than a liquid film, hence, a lower concentration within the sample is required (Beer's law). The infrared IR beam is absorbed completely or scattered from the sample which ends up in very noisy spectra.

Differential scanning calorimetry (DSC)

DSC was used to evaluate drug-excipient compatibility. The endotherms of pure drug and optimized formulation were recorded separately. The DSC thermograms are obtained by a DSC (DSC 220C, Seiko, Japan) at a heating rate of $10^\circ\text{C}/\text{min}$ from 10 to 200°C with in the nitrogen atmosphere.

Stability studies

To review the steadiness of the rapidmelts, representative samples of the were packed in amber colored airtight glass containers and that they were stored in stability chambers maintained at $25^\circ\text{C}/60\% \text{RH}$ and $40^\circ\text{C}/75\% \text{RH}$. The physicochemical properties of those samples were analyzed at 0, 3, and 6 months. From the respective storage conditions at each time point, one formulation was taken out and subjected to content uniformity and dissolution rate studies.

Table 3: Drug entrapment efficiency values of ezetimibe solid dispersions

SD	Solvent evaporation method	SD	Kneading method
EZE1	65.7	EZE7	53.5
EZE2	66.46	EZE8	58.23
EZE3	69.6	EZE9	60.28
EZE4	52.6	EZE10	54.98
EZE5	61.8	EZE11	60.23
EZE6	65.6	EZE12	62.9

Table 4: Composition of ezetimibe rapidmelts by direct compression method

Compound name	E1	E2	E3	E4	E5	E6	E7	E8	E9
Equivalent solid dispersion (mg)	69.6	69.6	69.6	69.6	69.6	69.6	69.6	69.6	69.6
CP (mg)	4			8			12		
CCS (mg)		4			8			12	
Starch 1500 (mg)			4			8			12
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
Aerosil (mg)	2	2	2	2	2	2	2	2	2
MCC (mg)	121.4	121.4	121.4	117.4	117.4	117.4	113.4	113.4	113.4
Total weight (mg)	200	200	200	200	200	200	200	200	200

Table 5: Composition 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
Magnesium 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
Total weight (mg)	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

Pre-compression parameters

The values of angle of repose were found to be within the range of 25–30°C bulk densities and tapped densities of varied formulations were found to be within the range of 0.30–0.70 (g/cm³). Carr's index was found to be within the range of 14–25%. The Hausner's ratio was within the range of 1.15–1.35. From the result, it had been concluded that powder blends have good flow properties.

Post-compression parameters

Hardness of all the formulations was found to be within the range of 3–4.5 kg/cm². It indicated that each one of the formulations possesses sufficient mechanical strength. Weight variation was found to be in the range of IP limits. Rapid melts were evaluated for their % friability using

Roche friabilator. The average % friability values were found to be <1%. It indicates good mechanical strength of the tablets. *In vitro* disintegration time of all the formulations was found to be in the range of 110–180 s. The results indicate that increasing concentration of superdisintegrants disintegration time of tablet was decreased. Disintegration time of the tablets was decreased with more concentration of subliming agents (camphor 7.5%). All the formulations have shown disintegration time <3 min. Hence, these formulations are suitable for formulating rapidmelts. Drug content values for the all formulations were found to be within the IP standards (not <95% and not more than 105%) (Tables 6–11).

In vitro drug release studies

The values are shown in Tables 10 and 11. Formulations from E1 to E9 were prepared using superdisintegrants (CCS, CP, and SSG) by direct

Table 6: Pre-formulation parameters for ezetimibe 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 ezetimibe rapidmelts by direct compression method

Formulation code	Hardness (kg/cm ²)	Average weight (mg)	Drug content (%)	Friability (%)	Disintegration time (s)	Wetting time (s)
E1	4.1±0.01	198±0.01	99.98±0.01	0.7±0.01	160±0.01	44.2±2
E2	3.5±0.01	196.5±0.21	101.32±0.11	0.82±0.10	168±0.05	52.8±2
E3	3.1±0.23	199.3±0.15	100.01±0.10	0.65±0.05	152±0.10	58.4±6
E4	4.3±0.15	197.8±0.05	102.32±0.20	0.74±0.11	163±0.12	42.6±5
E5	3.5±0.22	198.5±0.25	101±0.10	0.56±0.05	165±0.24	40.6±1
E6	3.3±0.34	200.6±0.12	102.4±0.05	0.58±0.02	159±0.10	40.8±8
E7	3.9±0.01	200.2±0.01	100.4±0.02	0.7±0.06	150±0.15	29.4±2
E8	3.9±0.24	196.4±0.01	101±0.01	0.5±0.11	172±0.06	30.8±3
E9	4.0±0.04	195.5±0.11	100.5±0.05	0.45±0.12	150±0.08	32.4±1

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

Formulation code	Angle of repose (°)	Bulk density (mg/ml)	TD (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)	Average weight (mg)	Drug content (%)	Friability (%)	<i>In vitro</i> disintegration time (s)	Wetting time (s)
E10	4.08±0.05	200.1±0.01	100.1±0.05	0.49±0.05	120±0.01	36.2±2
E11	3.15±0.02	199.8±0.12	98.39±0.12	0.45±0.06	135±0.12	34.8±4
E12	3.8±0.12	198.12±0.03	100.25±0.01	0.53±0.01	115±0.01	26.4±1
E13	3.80±0.11	201.50±0.05	101±0.05	0.62±0.12	125±0.15	36.8±5
E14	3.9±0.14	200±0.06	100±0.21	0.65±0.13	129±0.21	40.2±7
E15	4.10±0.10	197.5±0.15	99.93±0.11	0.59±0.24	149±0.10	40.8±6
E16	4.02±0.21	199±0.21	97.85±0.23	0.35±0.15	143±0.04	42.8±2
E17	3.4±0.05	200±0.15	100.30±0.10	0.42±0.11	127±0.02	36.4±3
E18	4±0.04	199±0.10	98.3±0.11	0.52±0.10	146±0.12	34.8±1

Table 10: Cumulative % 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±0.01	10.21	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							

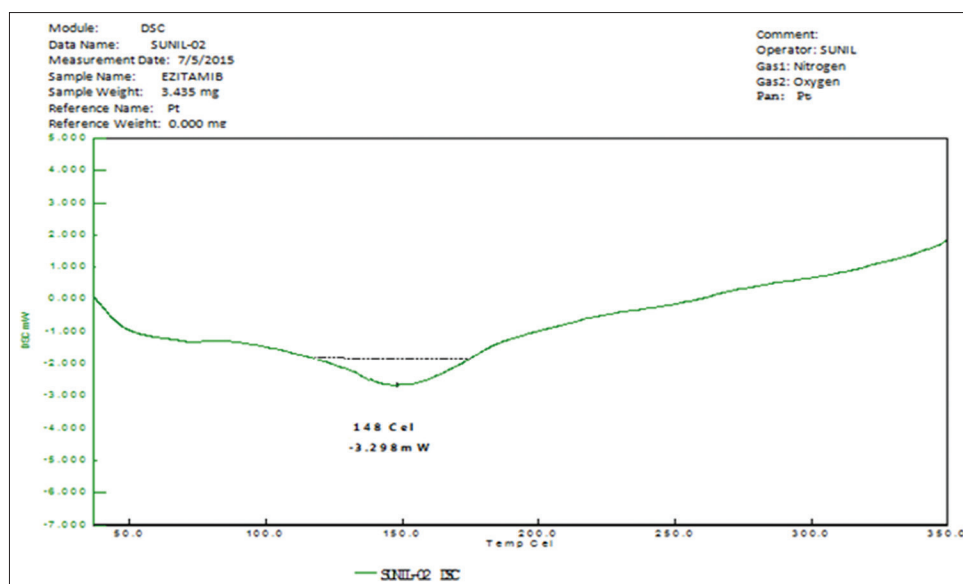


Fig. 1: Differential scanning calorimetry thermogram for ezetimibe pure drug

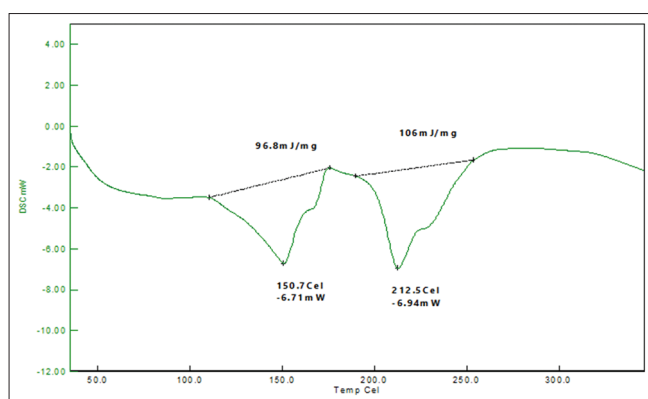


Fig. 2: Differential scanning calorimetry thermogram for ezetimibe optimized formulation

compression method. E10-E18 were prepared using subliming agents (camphor, urea, and ammonium bicarbonate). In direct compression method, superdisintegrants will act by swelling of the drug and it leads to faster disintegration and dissolution. In sublimation method, subliming agents will act by increasing the porosity of drug results in faster wetting and dissolution and bioavailability. Among all the formulations, E12 (camphor 7.5%) has given better dissolution compared to all the formulations. Hence, E12 formulation was selected as optimized as 100% drug release in 5 min.

Stability studies

Hence, based on evaluation parameters and drug release profiles, E12 was selected as optimized and subjected to stability studies and stored at 25°C/60% RH and 40°C/75% RH. The samples were withdrawn at 0, 3, and 6 months, and therefore, the ezetimibe rapidmelts were found to be stable. The amounts of ezetimibe (%) in the rapidmelts stirred under conditions consistent with ICH guidelines are given in Table 12. The steadiness of the tablets indicated that there are no significant changes observed throughout the study. From the stability studies result, we can say that formulation has good stability.

Characterization

DSC analysis

DSC thermograms for pure drug and optimized formulation are got within the Figs. 1 and 2. The DSC thermogram of ezetimibe rapidmelts exhibiting a pointy endothermic peak at 150°C corresponding to the melting point of the drug ezetimibe, indicating that there was no change in its characteristics, this means that the drug polymer compatibility. DSC thermograms indicate that there were no interactions between drug and excipients.

FTIR studies

FTIR spectrum of ezetimibe exhibited peaks at 3676 cm^{-1} for alcohol O-H stretch, 1593 cm^{-1} for alcohol C=O stretching, and 756 cm^{-1} for aromatic C-H bending. The same peaks of the drug were observed within the FTIR spectra of the rapidmelts, thereby ruling the absence of drug-polymer interaction from the obtained results. Hence, further

Table 11: Cumulative % 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±0.15	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)	% 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 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

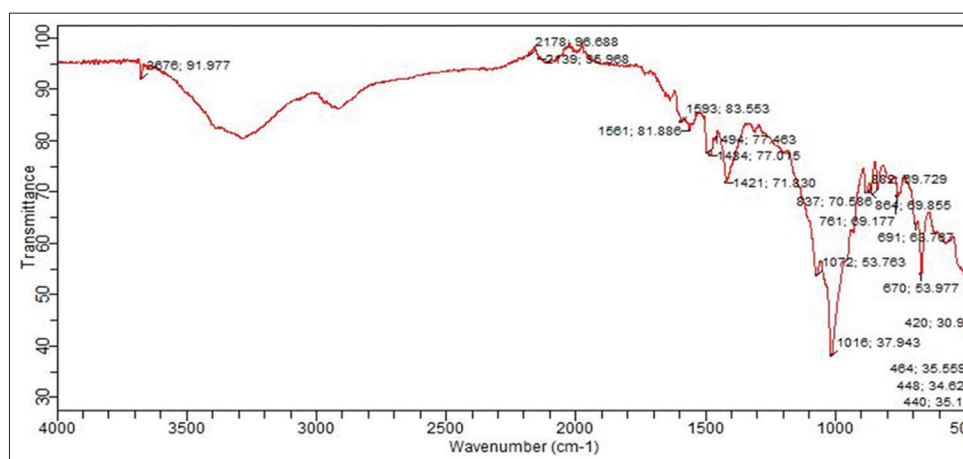


Fig. 3: Fourier transform infrared spectrum for ezetimibe optimum formulation

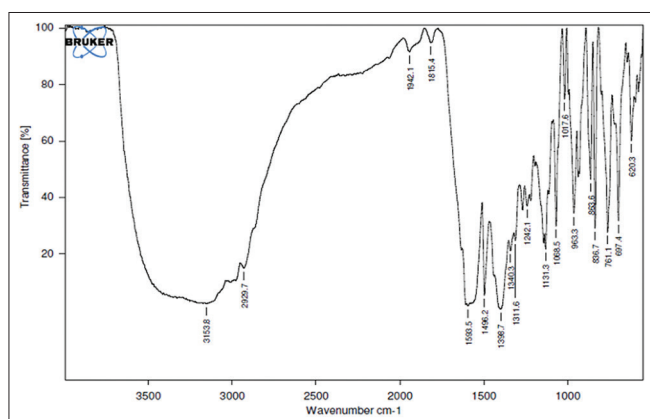


Fig. 4: Fourier transform infrared spectrum for ezetimibe pure drug

studies were performed based on these results. FTIR spectroscopy analysis was performed to pure drug and optimized formulation and presented in Figs. 3 and 4.

CONCLUSION

Rapidmelts are also known as oral disintegrating tablets (or) fast-dissolving tablets. These are mainly intended to be placed in the oral cavity where they dispersed before being swallowed. This is the promising dosage form for the use in pediatrics and geriatrics. The rapidmelts will provide accurate dosing and show good chemical and physical stability with lower doses. The present 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

