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Oral Dosage Form Containing Solubility Enhanced Forms of Atorvastatin Calcium and Ezetimibe

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ABSTRACT

The aim of the research work was to increase the solubility of atorvastatin calcium (ATC) and ezetimibe (EZT) by preparing solid dispersion containing tablet. Solvent evaporation method using combination of polymers [PVP K30/HPMC E5, PEG 6000/HPMC E5] involving various drug: polymer ratio was used to prepare solid dispersion. The prepared solid dispersion was evaluated for its solubility. The solubility of pure drugs and optimized batch was found to be 0.029±0.001, 0.012±0.0002 (ATC, EZT) and 0.427±0.003, 0.179±0.002 (ATC, EZT) respectively. The optimized solid dispersion showing increased solubility (14-fold) was selected and formulated into tablets. The tablet was subjected to various quality control tests like content uniformity, thickness, weight variation, hardness, friability, disintegration. *In vitro* drug release profile was also studied. The formulated tablets show higher percentage of drug release in compared with marketed tablets (Storvas®EZ10).

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Hyperlipidemia is characterized by high levels of lipids (fats) in the blood [1]. Atorvastatin calcium (ATC) and ezetimibe (EZT) both are antihyperlipidemic agents, which are co-administered in the treatment of hyperlipidemia [2]. ATC is a HMG-CoA (3-hydroxy 3-methylglutaryl coenzyme A) reductase inhibitor, which catalyses the reduction of HMG-CoA to mevalonate, in the rate limiting step of cholesterol biosynthesis [3, 4]. EZT acts as a cholesterol absorption inhibitor by inhibit sterol transporter protein at brush border and absorption of cholesterol from dietary and biliary sources [5-7]. Combination of these drugs inhibits cholesterol synthesis and absorption as well as significantly improves the lipid parameters in the blood and reduces the side effects [8-10]. Both the drugs come under BCS class II. Due to the poor solubility of both the drugs , the oral bioavailability of ATC and EZT is only 14% and 30-60% respectively [11, 12]. Various processes have been reported to increase the solubility of atorvastatin calcium and ezetimibe which involves solid dispersion techniques [13,14], nanosuspension [15], cocrystallization [16], self-emulsifying drug delivery systems [17], floating microcapsules [18] for ATC and nanosuspension [5], solid dispersion [19, 20], spray dried micro particles [21], self-nanoemulsifying drug delivery system (SNEDDS) [22], liquisolid technique [23], nanocrystals [24] for EZT. Literature review suggests that no method has been reported for formulation of solid dispersion of ATC/EZT using combination of polymers. Solid dispersion is a technique, which involves dispersing one or more active ingredient (hydrophobic) in an inert matrix (hydrophilic) at solid stage by using various methods such as solvent evaporation, fusion methods. The reason behind enhanced solubility and dissolution rate of poorly soluble drugs is due to the release of drug as fine colloidal particles when the inert carrier gets dissolved upon the contact of solid dispersion with the aqueous medium [25-27]. Improved oral bioavailability of several poorly aqueous soluble drugs has been confirmed by using solid dispersion technique. Both ATC/ EZT are crystalline in nature which gets converted into amorphous form upon formulating it as solid dispersion which results in enhanced solubility of both the drugs [2]. Solid dispersion has several benefits such as decrease in the drug crystallinity, increase in the dissolution rate, but also has some disadvantages such as instability, difficulty in handling and scale up during manufacturing process [28, 29]. Both the method of preparation and type of carriers used are important parameters in formulation of solid dispersion. PVP K30 and PEG 6000 are widely used as carriers in the formulation of solid dispersion, due their improved solubility by decreasing particle aggregation, reducing crystallinity, increasing wettability and dispersibility of drug [30]. HPMC in aqueous solution has increased swelling and dissolution properties y formation of soluble complex with the insoluble drug, which is used to control the rate of release of drug from solid dispersion [31]. In pharmaceutical industry wet granulation technique is the most widely used method for granulation process. It is done by the addition of excipients and active pharmaceutical ingredients (API) to form wet mass, which is subsequently dried to yield granules. The dried granules are the sieved to obtain granules of uniform size [32]. The dried granules are then compressed into tablets, which are then evaluated post compression and *in vitro* drug release study. Various methods have been reported for enhancing the solubility of ATC and EZT using different polymers. Hence to enhance the solubility of ATC and EZT combination of carriers [PVP K30/ HPMC E5 and

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PEG 6000/ HPMC E5] was used. The optimized batch was converted into solid dosage form and compared with marketed product.

MATERIALS AND METHODS

Atorvastatin Calcium (ATC) and ezetimibe (EZT) both obtained from Sigma Aldrich Chemicals and Medreich Pvt Ltd., Bangalore, India respectively. ATC/EZT tablet (Storvas®EZ10) 10 mg/ 10 mg obtained from the market. Polyvinyl pyrrolidine K30, hydroxy propyl methyl cellulose E5 and polyethylene glycol 6000, methanol, starch, microcrystalline cellulose and talc were obtained from Loba Chemie Pvt Ltd., Mumbai, India. Croscarmellose sodium was obtained from yellow chemical Pvt Ltd, Mumbai. Magnesium stearate was obtained from HiMedia laboratories Pvt Ltd, Mumbai.

Preparation of solid dispersion [2]:

Solid dispersions containing atorvastatin calcium/ ezetimibe, by solvent evaporation method by using different drug: polymer ratios of PVP K30 and HPMC E5. Drug: Polymer (PVP K 30: HPMC E5) in various ratios [1:1:1, 1:2:1, 1:3:1, 1:4:1, 1:2:2, 1:1.5:1.5] were dissolved in methanol and stirred for 15 minutes at room temperature. After complete dissolution, the solvent was removed by heating in an electrical water bath at 70˚C. The residues were pulverized, sieved [mesh size 60] and stored in desiccators for further study. Solid dispersion containing PEG 6000 and HPMC E5 was prepared by using same procedure. The composition of various formulations is shown in Table 1.

Table 1: Composition of Drugs and Carriers

Formulation Code	Drug & carrier ratio	ATV/EZT (1:1 ratio) (mg)	PVP K30 (mg)	PEG 6000 (mg)	HPMC E5 (mg)
F1	1:1:1	400	400	-	400
F2	1:2:1	400	800	-	400
F3	1:3:1	400	1200	-	400
F4	1:4:1	400	1600	-	400
F5	1:2:2	400	800	-	800
F6	1:1.5:1.5	400	600	-	600
F7	1:1:1	400	-	400	400
F8	1:2:1	400	-	800	400
F9	1:3:1	400	-	1200	400
F10	1:4:1	400	-	1600	400
F11	1:2:2	400	-	800	800
F12	1:1.5:1.5	400	-	600	600

ATC: Atorvastatin calcium, EZT: Ezetimibe, PVP K30: Polyvinyl Pyrrolidone, PEG 6000: Polyethylene Glycol, HPMC E5: Hydroxyl Propyl Methyl Cellulose

Preparation of physical mixture [13]:

Different weight ratios of drug: PVP K30: HPMC E5 (1:1:1, 1:2:1, 1:3:1, 1:4:1, 1:2:2, 1:1.5:1.5) were mixed and passed through 60 mesh size. It was stored in a desiccator at ambient temperature. The same procedure was repeated for the preparation of physical mixture using PEG 6000 and HPMC E5.

Solubility study [5, 21]:

Solubility of prepared solid dispersions was determined by saturation solubility method. The known excess of solid dispersion was added to 2ml of water, until solution gets saturated. The samples were centrifuged (Eppendorf 5415 E) at 12,000 rpm for 15 minutes and filtered through 0.45 μm membrane to separate undissolved drugs. After suitable dilution, the absorbance was measured at 246 nm and 233 nm respectively by using UV-Visible spectrophotometer (UV-1650PC, Shimadzu Corporation).The same procedure was followed for pure drugs and physical mixture. Based on the solubility studies, optimized batch of solid dispersion was chosen, and it was subjected for further evaluation.

Fourier-transform infrared (FT IR) spectroscopy study [2, 12]:

Drug excipients compatibility was determined by KBr pellet method using FTIR Spectrophotometer (Shimadzu FT-IR 8400 S, Shimadzu corporation) for pure drugs, excipients, drug excipient mixture and solid dispersion. The samples were prepared as KBr pellets by compressing at 6 ton/ nm2. The wavelength ranges were selected between 4000-400 cm-1.

Differential scanning calorimetry (DSC) study [24, 30, 33]:

Thermogram of optimized solid dispersion and their physical mixture was obtained by differential scanning calorimetry (DSC3 Mettler-Toledo GMbH, Switzerland) at a heating rate of 10°C/minute, from 50°C to 200°C using samples (5-10 mg) contained in aluminium pans and sealed. The thermograms obtained were compared with the thermogram in the reference literatures.

Drug Content of solid dispersion [4, 6]:

The optimized batch F10 (ATC 10 mg / EZT 10 mg) was evaluated for its drug content. Solid dispersion equivalent to 10/10 mg of ATC/ EZT was dissolved in suitable quantity of methanol. The samples were centrifuged after suitable dilution. It was filtered through 0.45 μm membrane and the absorbance was measured at 246 nm and 233 nm respectively.

Preparation of granules [33]:

The optimized solid dispersion (F10) containing ATC/EZT was formulated into tablet by wet granulation method. Accurately weighed solid dispersion containing ATC/EZT was taken. To that specified quantity of diluents and binder solution were added and mixed thoroughly to get wet granules. Granules were then passed through sieve (#10 mesh sieve) and allowed to dry at 60°C for 1 hour using hot air oven. Dried granules were passed through #20 mesh and magnesium stearate and talc were added.

Formulation of Atorvastatin calcium and Ezetimibe tablets [24, 33]:

Dried granules containing ATC/EZT was compressed on RIMEK mini press-I tablet punching machine using 8mmdiameter flat faced beveled edges punches. The average weight of the tablet was fixed as 150 mg to match with the marketed tablet (Storvas®EZ10). Each tablet contains 124 mg of ATC/EZT solid dispersion equivalent to atorvastatin calcium 10.15 mg and 10 mg of ezetimibe pure drug. The compositions of various excipients are shown in the Table 2.

Table 2: Composition of Tablet Containing Solid Dispersion and Excipients

Ingredients	For one tablet (mg)	For 100 tablets (g)
ATC/EZT solid dispersion	124	12.4
Starch	q. s	q.s
Microcrystalline cellulose	15.5	1.55
Croscarmellose sodium	6	0.6
Magnesium stearate	3	0.3
Talc	1.5	0.15

ATC: Atorvastatin calcium, EZT: Ezetimibe, q.s: Quantity sufficient. Each tablet contains 124mg of ATC/EZT solid dispersion equivalent to atorvastatin calcium 10.15mg and 10mg of ezetimibe pure drug

Weight variation test [33, 34]:

Weight variation of ATC/EZT tablet was performed using 20 tablets as per Indian Pharmacopoeia. The tablets were weighed individually using electronic balance (Electronic balance AY220, Shimadzu corporation, Japan). The average weight, % deviation was calculated and compared with individual weight of the tablets. As per Indian pharmacopoeia, ±7.5% deviation from the average weight is acceptable for tablet weighing around 84 mg to 250 mg [34]. The percentage deviation was calculated by,

$$\text{Average weight of the tablet} = \frac{\text{Total weight of the tablets}}{\text{Number of tablets}}$$

$$\text{Percentage deviation} = \frac{\text{Weight of individual tablet} - \text{Average weight of the tablet}}{\text{Average weight of the tablet}} * 100$$

Content uniformity test [20, 34]:

The content uniformity test of ATC/EZT tablet was performed using 20 tablets as per Indian Pharmacopoeia. Randomly selected tablets were crushed individually and from each, powder equivalent to 50 mg of drug was dissolved in methanol. The samples were centrifuged, filtered through 0.45 μm membrane and the absorbance was measured at 246 nm and 233 nm respectively.

Thickness test [33, 34]:

Vernier calipers was used to measure the thickness of the tablets. Randomly selected tablet (6 tablets) was put between jaws of vernier caliper and thickness of the tablet was measured by reading scale. The ±5% variation in thickness was allowed.

Hardness test:

The hardness test was performed using ERWEKA hardness tester (ERWEKA TBH 125, Erweka India Pvt Ltd, Mumbai). Randomly selected (10 tablets) tablets were placed on anvil of tablet hardness tester. When the device was operated, knurled screw moved automatically and breaks the tablet. The reading at breakage point of tablet in Newton (9.807 Newton = 1 kg) was displayed on LED screen.

Friability test [6, 12]:

Tablet friability was determined by friability tester (INWEKA iTAR, Erweka India Pvt Ltd, Mumbai). Randomly selected 6 tablets were weighed and placed in the rotating drum. It was rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were removed after rotations, dusts were wiped and weighed again to calculate percentage friability using following equation,

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} * 100$$

Disintegration time [33]:

Disintegration test was performed by using USP Disintegration apparatus (LABINDIA DT 1000, Lab India analytical Pvt Ltd, Mumbai). Randomly selected 6 tablets were placed in USP disintegration apparatus filled with phosphate buffer pH 6.8 (1000 ml) maintained at 37°C. The time taken for complete disintegration of tablet was noted.

***In vitro* drug release study [2, 13, 20]:**

In vitro drug release studies of solid dispersion, formulated tablet containing solid dispersion and marketed tablet (Storvas®EZ10) were carried out using USP type II (paddle) dissolution apparatus (LABINDIA DS8000, Lab India analytical Pvt Ltd, Mumbai). The phosphate buffer pH 6.8 (900 ml) maintained at 37 ± 0.5°C was used as the dissolution medium. The tablets were directly placed in the medium and the apparatus was operated at 50 rpm. The sample (5 ml) was withdrawn at intervals of 10, 20, 30, 40, 60 minutes and sink condition was maintained by replacing with fresh dissolution medium. The filtered samples were analysed using UV-Visible spectrophotometer at 246 nm and 233 nm respectively. The percentage drug release was calculated.

***In vitro* release kinetics [35, 36]:**

In vitro dissolution data of formulated tablet was fitted to various kinetic models using DD solver to find the drug release pattern from optimized formulation F10.

$$M_0 - M_t = K_0 t \quad \text{.....Zero order}$$

$$\ln\left(\frac{M_0}{M_t}\right) = K_t t \quad \text{.....First order}$$

$$M_t = K_H \sqrt{t} \quad \text{.....Higuchi}$$

$$(w_0)^{\frac{1}{3}} - (w_t)^{\frac{1}{3}} = K_{HC} t \quad \text{.....Hixson Crowell}$$

$$\frac{M_t}{M_\infty} = K_{KP} t^n \quad \text{.....Korsemeyer-Peppas}$$

Where M_t, M_0 and M_∞ are amount of ATC/EZT dissolved at time t, at zero time and at infinite time respectively. The term Wt and W0 are weight of the drug at time t, and initially respectively. The terms K_0, K_t, K_H, K_{HC} and K_{KP} are release kinetic constants of zero order, first order, Higuchi model, Hixson Crowell and Korsemeyer-Peppas model respectively. Inference of Koresmeyer-Peppas 'n' value was shown in the Table 3.

Table 3: Inference Of Koresmeyer-Peppas 'n' Value

'n' value	Drug transport mechanism	Rate as a function of time	Drug release mechanism
0.5	Fickian transport	$t^{-0.5}$	Diffusion controlled
0.5 <n<1.0	Non-Fickian transport	t^{n-1}	For both diffusion and erosion
1	Case II transport	Time-independent	Zero order release
≥1	Super caser II transport	t^{n-1}	(relaxation/ erosion)

n: Release exponent, t: Time

***In vitro* release profiles comparison [37, 38]:**

The similarity factor (f_2) and difference factor (f_1) for solid dispersion, optimized formulation containing solid dispersion (F10) and marketed formulation (Storvas®EZ10) was compared by using DD solver. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and the reference products. The difference factor (f_1) calculates the % error between the two curves over all time point. The dissolution profiles are considered to be similar when f_2 is higher than 50 (50-100) and f_1 is lower than 15. The f_2 and f_1 are calculated from the following equations,

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\} \quad \text{...Difference factor}$$

$$f_1 = \frac{\sum_{t=1}^{n}|R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \quad \text{.....Similarity factor}$$

Where, n is the number of dissolution time points, R_t and T_t are dissolution value of the reference and test drug product at time t, respectively.

Statistical analysis [33]:

Statistical analysis of the all parameters was done by using Graph Pad prism 8.4.3.686 software. The results (n=3) are expressed as mean and standard deviation (mean±SD). Significance level was fixed at P< 0.05. Comparative statistical study was carried out by using the One-way analysis of variance (ANOVA).

RESULTS AND DISCUSSION:

The current research work was performed to enhance the solubility of ATC and EZT by preparing it as solid dispersion. Solvent evaporation method was used to prepare solid dispersion which is one of the most commonly used methods. The selection of polymer plays an important role in the preparation of solid dispersion. When compared to single polymer, combination of polymers always helps in improving solubility [39]. Various ratios of polymers such as PVP K30/HPMC E5 and PEG 6000/ HPMC E5 were used in this study.

Saturation solubility studies were performed for all the prepared formulation and results are shown in table 4. The solid dispersions prepared using PVP K 30/HPMC E5 shows increase in solubility but it was less significant when compared to PEG6000: HPMC E5.

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Table 4: Solubility Study of Prepared Solid Dispersion

Formulation	ATC Solubility in water (mg/ml) (mean±SD)	EZT Solubility in water (mg/ml) (mean±SD)
Pure ATC	0.029±0.001	-
Pure EZT	-	0.012±0.0002
PM	0.177±0.002	0.049±0.001
F1	0.248±0.003	0.080±0.001
F2	0.288±0.003	0.090±0.001
F3	0.289±0.003	0.104±0.003
F4	0.298±0.003	0.117±0.002
F5	0.288±0.003	0.095±0.002
F6	0.268±0.003	0.086±0.001
F7	0.354±0.005	0.128±0.002
F8	0.375±0.004	0.145±0.003
F9	0.394±0.004	0.158±0.002
F10	0.427±0.003	0.179±0.002
F11	0.379±0.001	0.146±0.001
F12	0.374±0.002	0.135±0.001

(mean±SD, n=3), PM: Physical mixture of solid dispersion F10, ATC: Atorvastatin calcium, EZT: Ezetimibe, PM: Physical mixture

The solubility studies indicate that formulation F 10 [1:4:1 of ATC/EZT: PEG 6000: HPMC E5] shows 14-fold increased solubility upon comparison with pure drug. This may be due to the increased concentration of PEG 6000 and the surfactant and wetting property of HPMC E5 [40]. By combining PEG 6000 with HPMC E5, the drug polymer miscibility during preparation of solid dispersion was increased.

The FTIR study was performed to determine possible interactions between ATC/EZT and carriers used in the formulations were tested using infrared spectroscopy and results are shown in Figure 1. ATC showed characteristic peak at 1652.09 cm^{-1} (acidic carboxylic C=O stretch), 2968.55 cm^{-1} (C-H stretch), between 3255.95 cm^{-1} and 3403.51 cm^{-1} (Inter molecular hydrogen bond, O-H stretch), Three peaks between 1436.05 cm^{-1} and 1510.31 cm^{-1} (Aromatic C=C stretch), 1436.05 cm^{-1} (C-N stretch),as well as 3364.93 cm^{-1}(N-H stretch). EZT showed characteristic peak at 3265.84 cm^{-1} (O-H stretch), 1719.73 cm^{-1} (C=O stretch), 1509.39 cm^{-1} (C=C stretching band of aromatic ring), 1221.69 cm^{-1} (C-F stretch), 1401.28 cm^{-1} (C-O stretch). Physical mixture showed no substantial shifting in the position of absorption peak between drugs and carriers. This confirms that there is no physical interaction between drug and carriers. Solid dispersion (formulation F10) shows significance decrease in the intensity at N-H stretch also the broad peak was observed between 3300 cm^{-1} and 3500 cm^{-1}. This is due to the presence of oxygen from hydroxyl groups of PEG6000 chain and suggesting possible hydrogen bond between drug and carrier thereby increasing the solubility leading to enhanced dissolution [41].

DSC thermogram of solid dispersion F10 and its physical mixture (PEG 6000, HPMC E5, pure ATC, and pure EZT) are shown in Figure 2. Physical mixture shows less intensity endothermic peaks at 62°C and at 80-100°C indicating the melting point of PEG 6000 and HPMC E5 respectively. This correlates well with the data reported in the literature [42, 43]. The sharp endothermic peak was observed at 168°C and less intensity endothermic peak at 170°C corresponding to melting point of ATC [18] and EZT [2] respectively. This may be due to the combined effect of the closeness of ATC and EZT melting points [2]. The DSC thermogram of solid dispersion shows the absence of drug peak suggesting that drug has interacted with carrier and converted in to amorphous form [14, 43].

The % drug content was determined for the optimized formulation (F10) and it was found to be 98.3±0.02%, 96.8±0.01% for ATC and EZT respectively. It helps in standardizing the dose to be incorporated in the tablet which should be equivalent to the marketed formulation.

The ATC/EZT tablet containing solid dispersion was formulated by wet granulation technique and its post compression parameters were also evaluated as per Indian Pharmacopoeia. Weight variation test was conducted with a rationale to confirm that required amount of powder to fill the die uniformly [33], since changes in the weight of tablet will change the amount of drug present in the tablet. Thus, it is important for all tablets to have a uniform weight. Weight variation results (Table 5) indicates that individual tablet deviates within ±7.5% (as per IP limits) from the average weight of the tablets.

Drug content of the formulated tablets (Table 6) was found to be in the range of 97.8±0.3% to 102.2±0.5% for ATC and 97.3±0.6% to 100.8±0.1% for EZT, thus comply with IP limits. The thickness of the tablet was measured by using Vernier caliper and it was found to be in

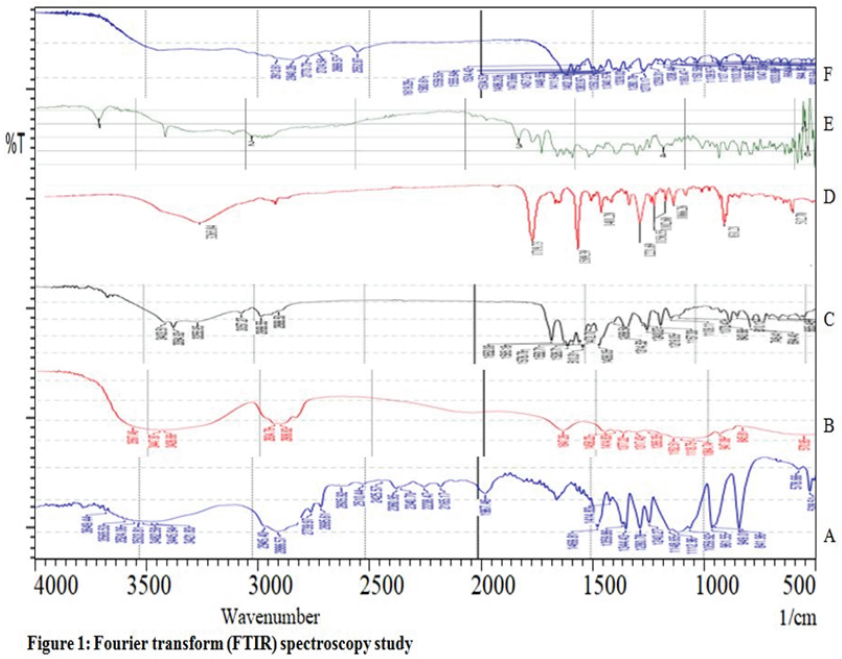

Figure 1: Fourier transform (FTIR) spectroscopy study

Infrared spectrum of A: Polyethylene Glycol 6000, B: Hydroxy Propyl Methyl Cellulose E5, C: Atorvastatin calcium, D: Ezetimibe, E: Physical mixture of solid dispersion F10, F: Solid dispersion (F10)

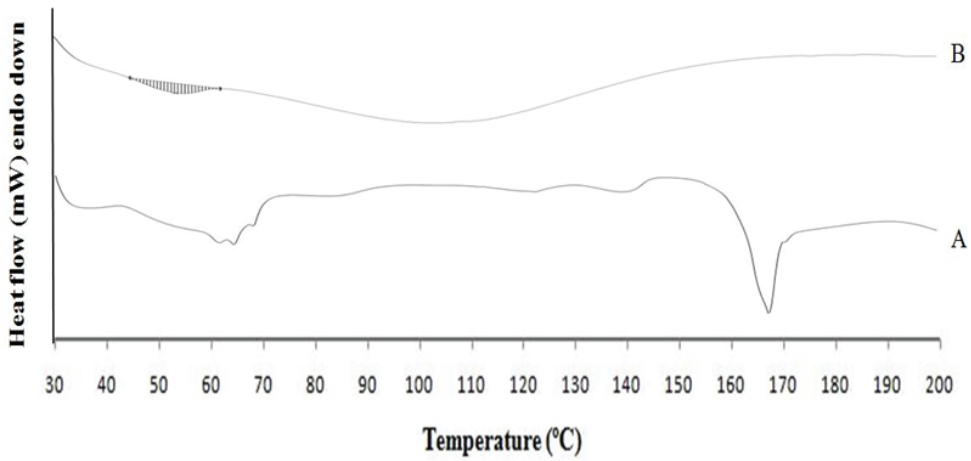

Figure 2: Differential scanning calorimetry (DSC) study

DSC thermogram of A: Physical mixture (PEG 6000, HPMC E5, Pure ATC, Pure EZT), B: Solid dispersion (F10)

the optimum range (Table 7). The hardness of the tablet indicates its ability to withstand the shock of handling, packaging and shipping. The results (Table 8) show that hardness of the tablets was found to be in the range of 4.5±0.55 to 5.1±0.21 kg/cm^2, thus comply with IP limits. The friability test (0.56±0.01%) indicated that the formulated tablets can withstand the physical abrasion and mechanical stress. The results (Table 9) show disintegration time of all the tablets was found to be in the range of 7.6±0.57 to 9.6±2.12 minutes (≤15 minutes), which shows prepared tablets passes disintegration test.

Table 5: Weight Variation Test

Tablet number	Weight (mg, mean±SD)	Tablet number	Weight (mg, mean±SD)
1	150.5±0.4	11	150.3±0.9
2	149.3±1.1	12	150.0±1.5
3	150.7±2.0	13	150.7±1.6
4	150.7±1.0	14	150.0±1.4
5	150.4±2.0	15	149.3±1.6
6	149.5±1.1	16	150.2±0.2
7	149.9±0.2	17	150.9±1.4
8	149.3±0.7	18	149.4±0.9
9	149.4±0.1	19	149.3±0.9
10	149.0±1.0	20	150.2±0.9

(mean±SD, n=3) and values within the IP limit of ±7.5 % deviation

Table 6: Content Uniformity Test for Formulated Tablet

Tablet number	Drug content (%, mean±SD)	
	ATC	EZT
1	97.8±0.3	98.1±0.5
2	98.5±0.5	99.4±0.7
3	99.2±0.4	99.2±0.9
4	98.3±0.9	97.3±0.6
5	101±0.6	100.8±0.1
6	98.6±0.6	98.8±0.4
7	101.9±0.8	97.7±0.3
8	102.2±0.5	99.6±0.8
9	99.8±0.3	99.8±0.2
10	97.9±0.4	98.4±0.1

(mean±SD, n=3), ATC: Atorvastatin calcium, EZT: Ezetimibe

Table 7: Thickness Test

Tablets	Thickness (mm, mean±SD)
1	2.4±0.025
2	2.4±0.016
3	2.3±0.011
4	2.4±0.013
5	2.3±0.31
6	2.4±0.023

(mean±SD, n=3) and values within the IP limit of ±5% deviation

Table 8: Hardness Test

Tablets	Hardness (kg/cm^2, mean±SD)
1	4.2±0.36
2	4.5±0.45
3	4.6±0.36
4	4.7±0.17
5	4.9±0.20
6	4.7±0.23
7	4.8±0.25
8	4.1±0.21
9	4.5±0.55
10	4.9±0.21

(mean±SD, n=3) and values within the IP limit of 4-6 kg/cm^2

Table 9: Disintegration Time

Tablets	Disintegration time (minutes, mean±SD)
1	9.6±2.12
2	8.0±2.64
3	9.6±1.53
4	8.3±1.53
5	7.6±1.57
6	9.3±2.51

(mean±SD, n=3) and values within the IP limit of 15 minutes

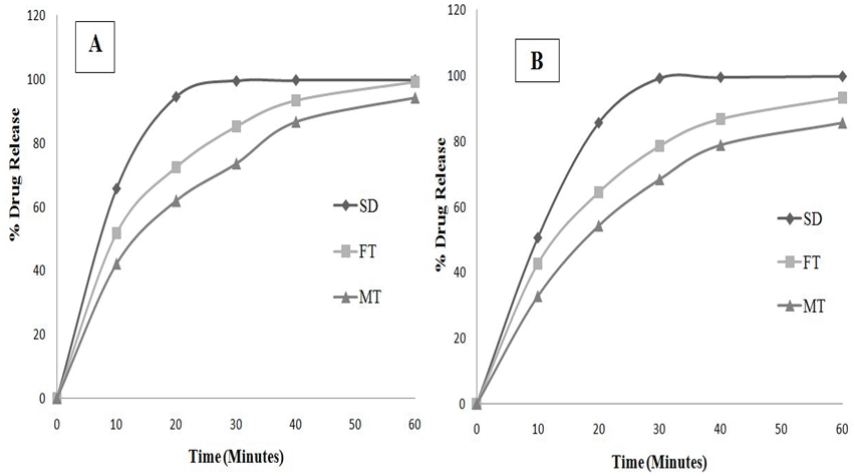

Figure 3: ***In vitro*** **drug release study**

A : % drug release of Atorvastatin calcium from (-♦-) Solid dispersion, (-■-) Formulated tablet and (-▲-) Marketed tablet

B : % drug release of Ezetimibe from (-♦-) Solid dispersion, (-■-) Formulated tablet and (-▲-) Marketed tablet

In vitro drug release study was performed for solid dispersion (F10), formulated tablet and marketed tablet (Storvas®EZ10). The results (table 10) show percentage drug release at 60 minutes was found to be 94.2±0.25 % of ATC and 85.7±0.28% of EZT for marketed tablet and 99.1±0.10% of ATC and 93.3±0.30 of EZT for formulated tablet.

The drug release data of formulated tablet was subjected to various kinetic models. The correlation coefficient value (r^2) and Korsemeyer Peppas model with 'n' values are shown in table 11. The model with highest correlation co-efficient (r^2) i.e. close to 1 was chosen as kinetic model for the drug release pattern. According to the correlation coefficient, the release data fitted well to first order kinetics. The exponent value (n) derived from Korsemeyer Peppas model indicates that drug release follows Fickian diffusion controlled mechanism.

Dissolution profile of solid dispersion, formulated tablet and marketed tablet was compared using similarity factor (f2) and dissolution factor (f1) and results are shown in table 12. Two dissolution profiles were considered to be similar when f1 value lies between 0-15, whereas f2 value should be between 50-100. These values (Table 6) indicate that there is a greater dissimilarity in drug release between solid dispersion and marketed product. This is because of the particle size reduction and decreases in the crystallinity of the drug during the solid dispersion process are the possible mechanism for enhancement of dissolution rate [2].

The f1 and f2 value between formulated tablet and marketed tablet was found to be similar (Table 12). When the solid dispersion was converted in to tablet, excipients and compression force involved in the manufacturing process may contribute to the reduction release rate. But this needs to be evaluated in future.

Overall results obtained during these work shows that solid dispersion could improve the dissolution rate of ATC and EZT, when

Table 10: *In Vitro* Drug Release of ATC/EZT Solid Dispersion, Formulated Tablet and Marketed Tablet

Time (minutes)	Percentage drug release (%,mean±SD)					
	ATC/EZT Solid dispersion (F10)		ATC/EZT Formulated tablet		Marketed tablet	
	ATC	EZT	ATC	EZT	ATC	EZT
10	65.6±0.68	50.7±0.51	51.7±0.55	42.7±0.50	42.1±0.35	32.7±0.45
20	94.5±0.35	85.6±0.50	72.5±0.35	64.5±0.83	61.8±0.26	54.3±0.37
30	99.5±0.30	99.2±0.20	85.2±0.51	78.5±0.35	73.5±0.65	68.4±0.95
40	99.6±0.26	99.4±0.15	93.3±0.21	86.8±0.60	86.5±0.41	78.8±0.16
60	99.7±0.15	99.7±0.15	99.1±0.10	93.3±0.30	94.2±0.25	85.7±0.28

ATC: Atorvastatin calcium, EZT: Ezetimibe

Table 11: Inference of Kinetic Modelling

Parameters	Formulated tablet	
	Atorvastatin calcium	Ezetimibe
Zero order (r^2)	-1.2158	-0.3656
First order (r^2)	0.9912	0.9935
Higuchi model (r^2)	0.7874	0.9019
Hixson Crowell (r^2)	0.9338	0.9331
Koresmeyer-Peppas (r^2)	0.9555	0.9504
Koresmeyer-Peppas 'n'value	0.342	0.400
Release order & Main transport mechanism	First order, Fickian	First order, Fickian

r^2: Correlation coefficient, n: Release exponent

Table 12: Inference of Similarity Factor (f_2) and Difference Factor (f_1)

Parameters	Obtained value				Range
	SD vs MT		FT vs MT		
	ATC	EZT	ATC	EZT	
f_1	28.15	35.85	12.20	14.35	0 to ≤15
f_2	32.51	31.00	51.92	51.57	≥50 to 100

f_2: Similarity factor, f_1: Difference factor, SD: Solid dispersion, MT: Marketed tablet, FT: Formulated tablet, ATC: Atorvastatin calcium, EZT: Ezetimibe

using optimized carriers. It can be considered as a better choice for the treatment of hypercholesterolemia when converted into a suitable dosage form. Further in vivo studies and stability studies are required to confirm the feasibility of this method in increasing solubility.

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Conflict of interest:

The authors do not report any conflict of interest pertaining to this work.

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