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FORMULATION & EVALUATION OF ATORVASTATIN CALCIUM CO-CRYSTAL

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ABSTRACT:

The current study aimed to improve the solubility and dissolving characteristics of the poorly soluble medication atorvastatin calcium (ATC) by producing cocrystals of it. Cinnamic acid (CA) was employed as a conformer, and solvent evaporation was performed in an equimolar ratio. Solubility tests have shown that the ATC cocrystal is more soluble than the standard ATC plain drug. The ATC cocrystal FTIR spectra and DSC thermogram revealed a sharp drop in melting point from 164.27C to 63.80C, which suggests a decrease in cohesive energy and an increase in solubility. New crystalline peaks at 2θ values of 9.10^0, 15.50^0, 22.90^0, 25.80^0, and 29.80^0 were visible in the XRD pattern. When compared to drugs and CCF, SEM examination revealed morphological alterations that suggested a distinct crystalline composition.

KEYWORDS: Atorvastatin calcium, co-crystallization; solvent evaporation technique.

Introduction:-

Solubility and permeability are key elements that impact a drug's oral bioavailability. The solubility of the drug is one of the most important biopharmaceutical parameters for effective drug delivery since it affects the systemic exposure in terms of dissolution, especially when the drug is taken orally. Pharmaceutical companies have significant difficulties when developing

and formulating medications with low solubility while trying to increase the drugs' bioavailability. Many techniques, such as complexation, micellar solubilization, salt formation, nanonization, and micronization, are available to increase the bioavailability of the medications.[1]Amorphous, anhydrous, or polymorphic forms of the Active Pharmaceutical Ingredient (API) have several disadvantages when it comes to maintaining the component's stability, balancing its hygroscopicity, and eliminating the hazardous solvents utilized during the crystallization process. Therefore, it is discovered that the co-crystallization procedure is advantageous for the pharmaceutical sector to fine-tune the API features such solubility, stability, and micromeritics [2]. Cocrystals are homogeneous crystalline materials with a specific stoichiometry that are made up of at least two distinct components integrated into the same crystal lattice[3].Noncovalent interactions between the API and the coformers result in supramolecular synthon production, which is the basis of cocrystal structures[4]. Supramolecular assembly helps to address flow, compressibility, and manufacturability in addition to fine-tuning the physical properties of the API in its crystal structure, such as solubility, hygroscopicity, and stability.

A HMG-CoA reductase inhibitor called atorvastatin calcium (ATC) is used to treat hyperlipidemia. With a reported low oral bioavailability of roughly 12%, [5] AVA is classified as a class II medication in the Biopharmaceutical categorization system (BCS). It is lipophilic in nature. Despite having a high intestinal permeability at a pH that is physiologically relevant, the main problem with this medication is that it is not very therapeutically effective. This is a result of its varied bioavailability due to its poor solubility under physiological circumstances.

One method used to enhance the physical and chemical characteristics of active pharmaceutical ingredients (APIs) without compromising their structural integrity is co-crystallization. These features include solubility, dissolution, stability, hygroscopicity, compressibility, and more. A cocrystal is a multicomponent complex made up of an API and a cocrystal former (CA) that is bonded to the substrate in a specific stoichiometric ratio by strong superamolecular synthons and remains solid in ambient settings [6]. The functional groups found in API and CCF as well as other non-covalent linkages between them, such as hydrogen bonds, aromatic-aromatic interactions, and van der Waals bonds, determine the formation of cocrystals [7]. ATC propensity to generate amide, hydroxyl, and carbonyl groups suggests that it is a suitable material for cocrystal formation. While hydroxyl groups can readily participate in hydrogen bonding and act as donors, carbonyl and amide groups can act as acceptors of hydrogen bonds. ATC cocrystals with three distinct CA were described by the research group Wicaksono et al., but other than that, not much has been done with the cocrystallization strategy [8,9,10].Several

other CA that have not yet been published were investigated in the current work in accordance with ATC cocrystallization.

Materials and Method:

Ajanta Pharma Pvt.Ltd. is offering a gift sample of Atorvastain calcium. The analytical grade chemicals and coformers were procured from Research Lab Fine Chem Industries.

Method of Preparation of Atorvasatin Calcium Co-crystal :

Atorvastatin calcium were prepared using of cinnamic acid as a conformer. ATC was co-crystallized with different coformers in stoichiometric ratio of 1:1 i.e. ATC (1 mmol). We were used solvent evaporation method. The both mixture mix together in a beaker add 10ml methanol stired or sonication and then pour in petri plate cover with foil paper and placed in cool and dry placed for 24hr. The solution was allowed to evaporate slowly. The products obtained via all these methods were stored at ambient conditions till further evaluation [11].

Comaparative dissoulation rate of plane drug , ATC-CA co-crystal :

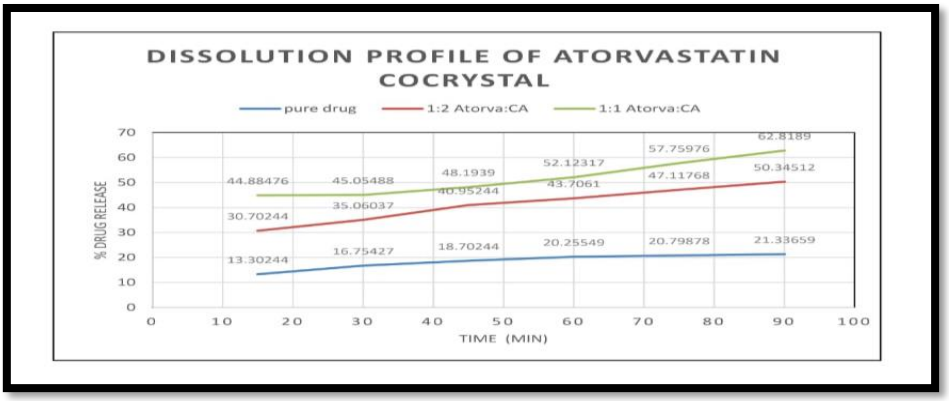

Fig. No.1 :In-vitro drug release of pure drug and ATC CA co-crystal

Table.No1 : Dissolution Profile in 0.1N HCL

Time	Pure Drug	ATC-CA (1:2 CC)	ATC-CA (1:1 CC)	ATC-CA (1:2 CC)	ATC-CA (1:1 CC)
15min	13.30244	30.70244	44.05488	34.41951	37.12378
30min	16.75427	35.06037	45.88476	34.76524	38.14024
45min	18.70244	40.95244	48.1939	36.3622	39.5122
60min	20.25549	43.7061	52.12317	37.58598	40.04451

75min	20.79878	47.11768	57.75976	38.46951	40.61524
90min	21.33659	50.34512	62.8189	39.66037	43.73232

From above in-vitro study data it can conclude that cocrystal formulation 1:1 and 1:2 ratio batch. The 1:1 ratio cocrystal formulation shows significant drug release i.e 62.81. From comparative in-vitro study data it is concluded that ,in-vitro study comparison done between pure drug, ATC-CA co-crystal formulation, its shown in fig. no. 1.

CHARACTERIZATION OF ATC CO-CRYSTAL:

Solubility determination :

The shake-flask method was used to assess the solubility of ATC co-crystals generated using various techniques in phosphate buffer at pH 6.8. Glass jars with caps were used to hold a sample of 10 mg of drug equivalent each preparation, along with 10 ml of buffer. The vials were incubated for twenty-four hours at 37± 0.5 °C on a glass shaker incubator. After passing the material through whatman filter paper, the filtrate was examined at a preset analytical wavelength with a UV spectrophotometer [12].

Melting point determination:

Using the Thiele tube method, the melting points of plain ATC and ATC cocrystals with selected coformer. A tiny mound of the dry material, weighing around 25 mg, was produced on a glass slide. The capillary tube's closed end was tapped after the open end was inserted into the powder and shook down the tube. The filled capillary was placed into the Thiele apparatus's main tube and fastened to the thermometer's lower end. Using a small flame, it was heated quickly at first, and then steadily and gently at a rate of 2 °C per minute. The measured melting point range was defined as the temperature at which the solid started to liquefy and at which it vanished [13].

Fourier Transform Infrared(FT-IR) Spectroscopy:

Using the KBR pellet technique, FT-IR spectra of ATC cocrystal and coformer were acquired on an FT-IR spectrometer (FTIR-Brucker OPUS 75,UK). KBr powder was used to gently triturate the drug sample at a weight ratio of one to one hundred. After that, the disc was put in the sample holder and scanned between 4000 and 500 cm-1. Next, the cocrystal's spectra was contrasted with that of ordinary ATC [14].

Differential Scanning Calorimetry:

Using the DSC Mettler 10.00 Star system, Mettler-Toledo, Switzerland (DSC-1 Mettler Toledo,USA), DSC thermograms for ATC cocrystals and coformer was obtained. In aluminum pans with nitrogen environment, a precisely weighted sample was run at a scanning rate of 20 °C/min over a temperature range of 100 to 300 °C, respectively [15].

X-ray Diffraction Study:

Using X-ray diffractometry, the crystalline behavior of ATC, Coformer and cocrystals was assessed. (PW 1728 Philips, Netherland) was used to obtain diffraction patterns. 35 mA of tube current and 40 kV of tube voltage were used to run the X-ray generator. In the step scan mode, the scanning angle varied between 3 and 60°, with a step time of 39.8 seconds [16].

Scanning electron microscopy:

A scanning electron microscope (Nova NanoSem NPEP303) was used to image the surface of ATC, Coformer, and cocrystals using an electron beam [17].

Drug content:

In a volumetric flask, 10 mL of methanol was poured to 10 mg of the cocrystal sample, which had been weighed beforehand. After that, the flask was sonicated for thirty minutes. After passing the solution through Whatman filter paper, appropriate dilutions were prepared and the solution was subjected to spectrophotometric analysis using a UV-Visible double beam spectrophotometer at the selected analytical wavelength [18].

RESULT AND DISCUSSION

Drug Content:-

The content of Atorvastain Calcium from ATC-CA cocrystal had been found . The drug content in every case was found to be within standard assay limit of Atorvasatin Calcium.The drug content is 97.12± 0.13.

Stability Study of co-crystal:

Physical Appearance :

The co-crystal's physical characteristics remained unchanged at the stability point. ATC-CA co-crystals were non-hygroscopic, white, and crystalline.

Drug Stability :

It was discovered from the drug content analysis at the anticipated stability time point that the drug content for the entire 30-day stability period was within the standard test limit of atorvastatin calcium. 96.38 ±0.43 is the stability determination.

Fourier Transform Infrared(FT-IR) Spectroscopy:

The FT-IR spectrum of ATC exhibited a showed C-H (alkyl), C=O (carbonyl), N-H (amide), and O-H (hydroxyl) group at 3057.17 cm-1(stretch), 1651.07 cm-1 (stretch) , 3363.86 cm-1(stretch) and 2360 cm-1 (stretch) shows fig. in 1 respectively.

The FT-IR absorption peaks of cinnamic acid C=O (carbonyl), C=C (alkene), C-H (alkyl) group at 1685.79 cm-1 (stretch),1627.92 cm-1(stretch), 3064.89 cm-1 (stretch) shows fig. in 2 respectively.

ATC were observed in ATC cinnamic acid cocrystal spectrums is N-H(amide), O-H (hydroxyl), C=O (carbonyl) group at 3402.43 cm-1 (stretch), 2358.94 cm-1 (stretch), 1681.93 cm-1 (stretch) shows fig. in 3 respectively.

These findings show that functional groups are present in the spectra of cinnamic acid and ATC. ATC-cinnamic acid cocrystal shifts and the existence of distinctive peaks, like those for N-H and O-H groups, indicating the creation of hydrogen bond synthons. [19].

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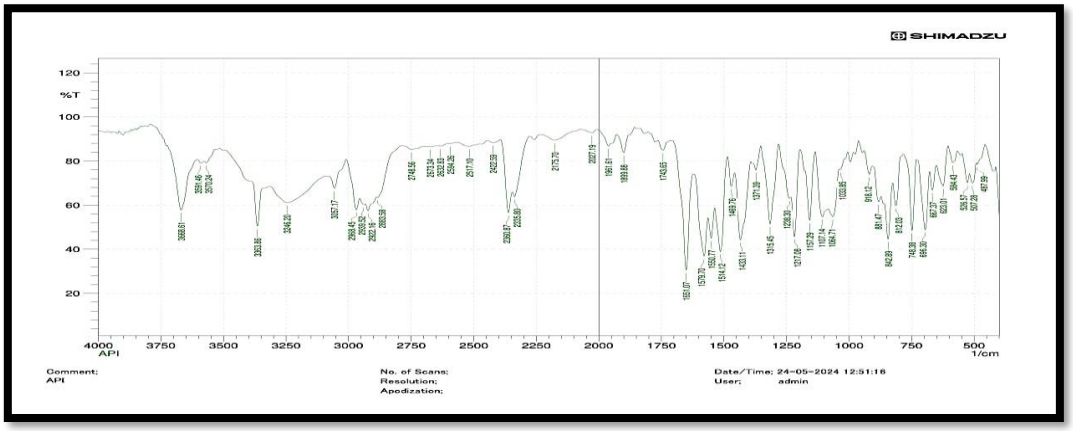

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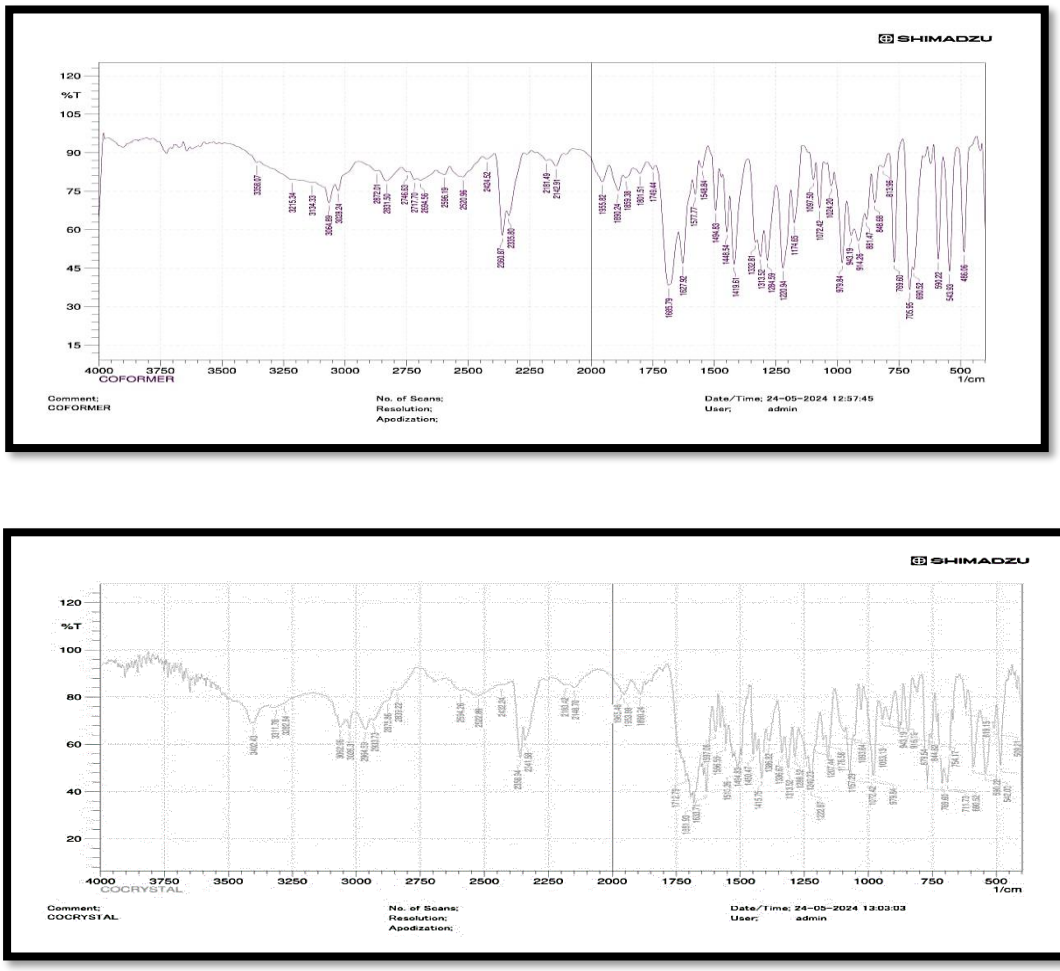

Fig No.2 FTIR of (1) Atorvastain Calcium (2) Cinnamic Acid (3.) Atorvastain Calcium Cinnamic acid cocrystal

Powder X-ray Diffraction:

At diffraction angles of 15.5, 17.7, 17.8, and 22.5, ATC displayed numerous powerful, sharp diffraction peaks of crystallinity, suggesting the presence of AVA as a crystalline material shows in fig 1 [20]. Sharp, powerful peaks demonstrating the crystalline nature of cinnamic acid were observed at 2θ values of 9.0, 16.3, 18.1, 22.5, and 28.4 shows in fig 2. While ATC cocrystal of cinnamic acid displayed peaks at 9.1, 15.5, 18.8, 22.9, 25.8, and 29.8, indicating a distinct crystalline nature from ATC, as seen in Fig 3.

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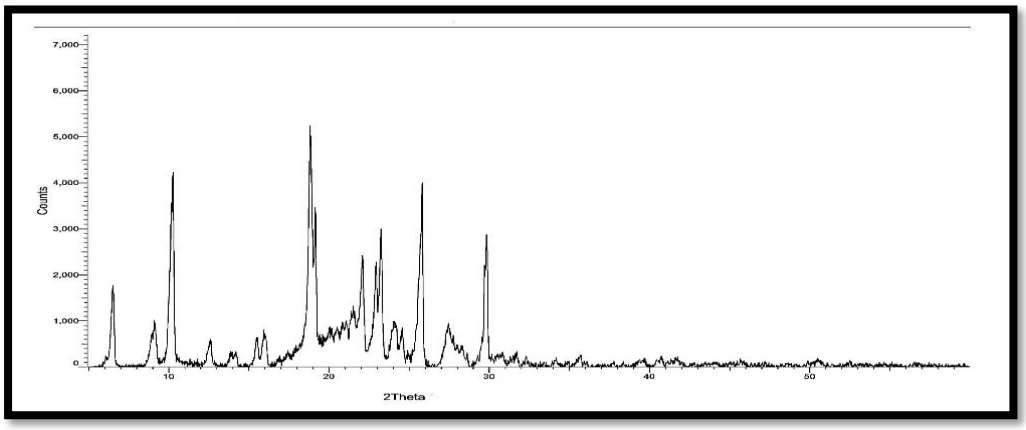

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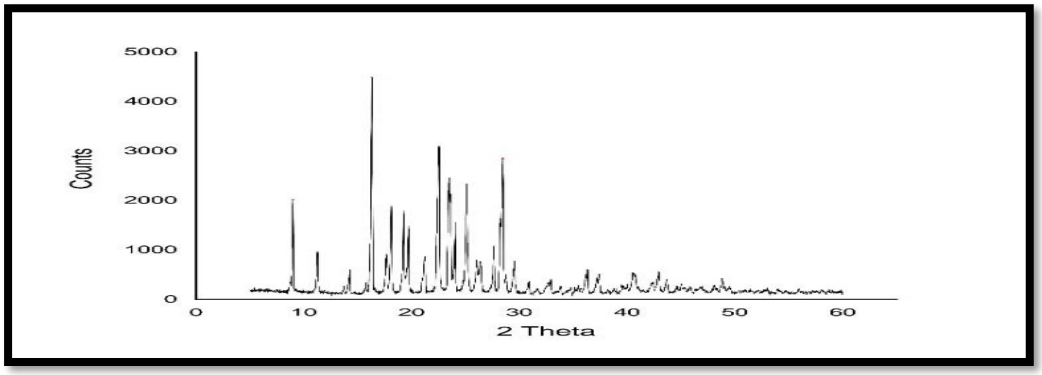

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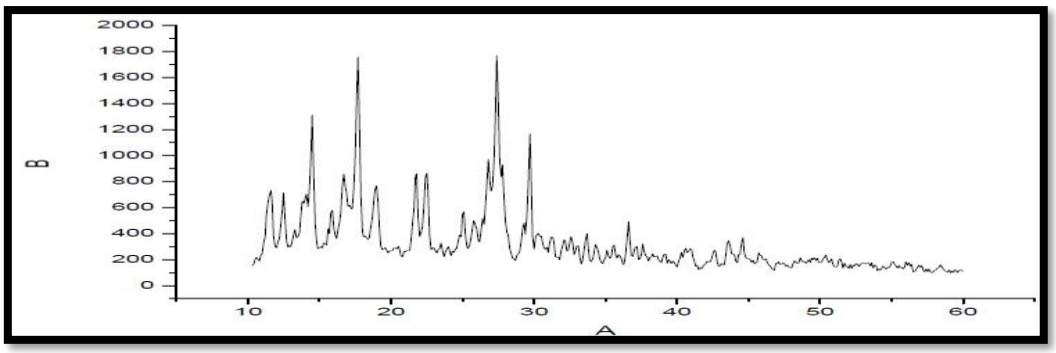

Fig No.3 PXRD of (1) Atorvastain Calcium (2) Cinnamic Acid (3) Atorvastain Calcium Cinnamic acid cocrystal

Differential Scanning Calorimetry:

The thermogram of cinnamic acid showed a strong endothermic peak at 136.8°C, while the AVA showed a diffused endothermic peak at 164.27°C. ATC thermogram of the cocrystallized cinnamic acid revealed an endothermic peak at 63.80°C, which verified the creation of the cocrystal by exhibiting a distinctive alteration in the melting behavior. This sharp drop in melting point implies that the ATC cinnamic acid cocrystal's cohesive energy has dropped relative to that of the plain ATC, suggesting the cocrystal's increased solubility

when compared to the plain drug ATC [21], hence validating the cocrystal's production as shown in Figure 4.

The ATC-cinnamic acid cocrystal's melting point was found to have dropped sharply, which suggests a noticeable change in thermal behavior. This decrease in cohesive energy, which results in a lower melting point, indicating that the cocrystal is more soluble than pure ATC. This action suggests that the cocrystal may become more soluble and confirms that it formed successfully.

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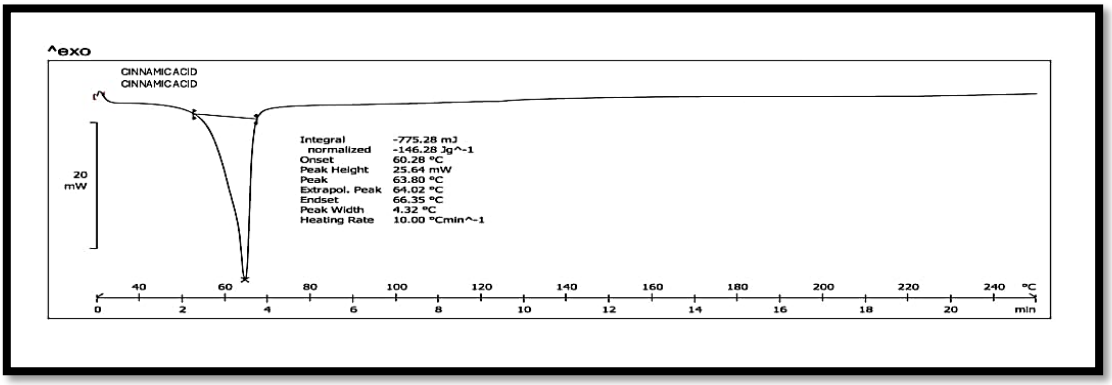

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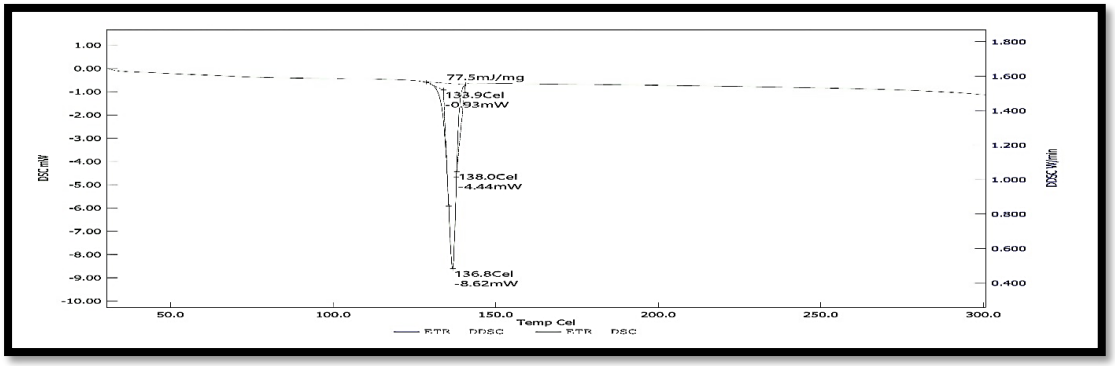

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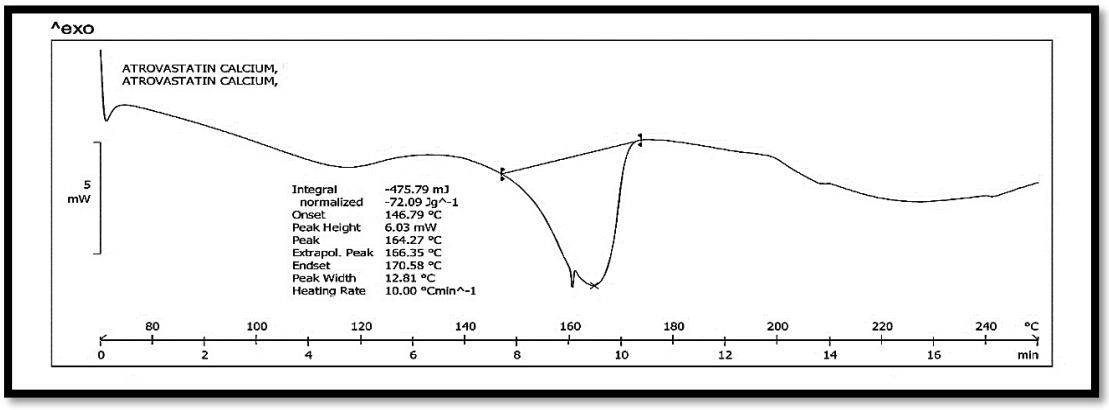

Fig No.4 DSC of (1) Atorvastain Calcium (2) Cinnamic Acid (3) Atorvastain Calcium Cinnamic acid cocrystal

Scanning Electron Microscopy:

ATC, cinnamic acid, and the ATC cinnamic acid co-crystal were all subjected to SEM investigation (Figure 5). Cinnamic acid displayed regular-shaped crystals with a sharp surface, while plain ATC displayed irregularly shaped crystals [20]. In comparison to plain ATC and cinnamic acid, the co-crystals of AVA and cinnamic acid showed irregularly shaped crystals and sharp, indicating a distinct crystalline nature in connection with the drug and coformer.

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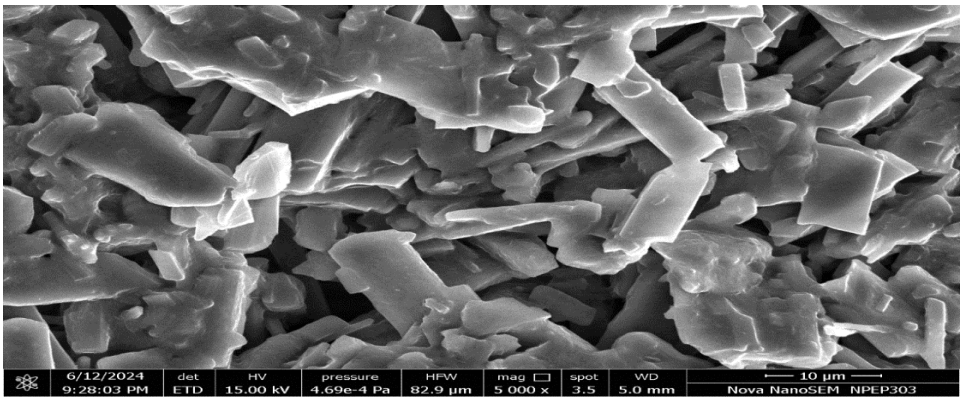

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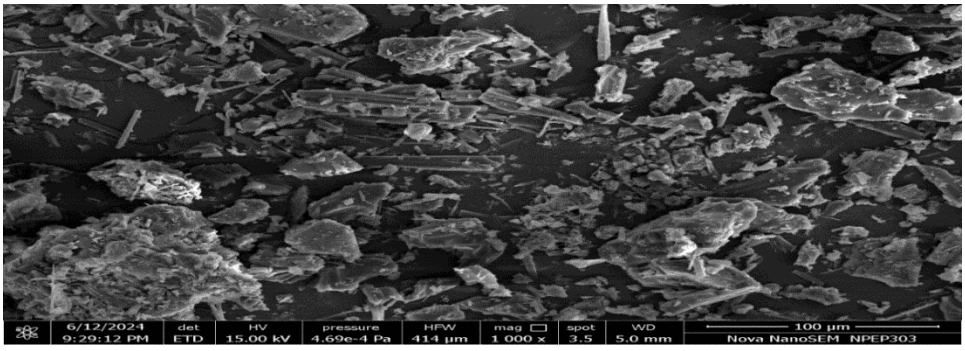

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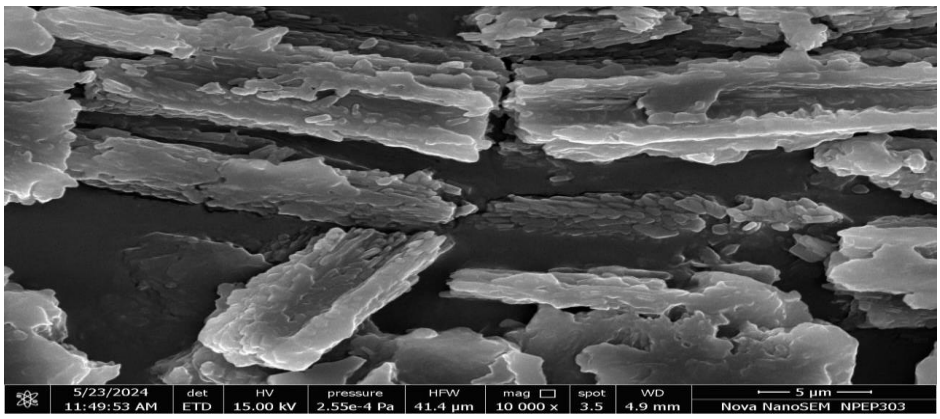

Fig No.5 SEM of (1) Atorvastain Calcium (2) Cinnamic Acid (3) Atorvastain Calcium Cinnamic acid cocrystal

Conclusion:

To get around a number of issues with an API, atorvastatine calcium co-crystals were made using several co-crystal formers. Solvent evaporation was used to create co-crystals of cinamic acid and atorvastatine calcium. By using melting point, ATR-IR, DSC, XRD, and SEM, co-crystals were verified. Co-crystals have demonstrated improved flow characteristics and solubility. Co-crystal formulations exhibit a better dissolving profile than typical pure medication formulations of atorvastatine calcium. The co-crystal form of the poorly soluble medication Atorvastatine Calcium was effectively developed in the above study by employing cinnamic acid as a co-former. Lastly, a larger percentage of drug release was reported for the cocrystal made with cocrystals ATC-CA 1:1 ratio, respectively.

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