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NOVEL MULTICOMPONENT FORMS OF ETODOLAC WITH ANTIOXIDANTS BASED COFORMERS: PROMISING STRATEGIES FOR OSTEOARTHRITIS

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Abstract
The current research focuses on enhancing the biopharmaceutical characteristics of the anti-osteoarthritic drug etodolac (ET) through the creation of a new solid form. This was achieved by using mechanochemical synthesis to combine ET with coformers that possess antioxidant properties (syringic acid, ascorbic acid, and nicotinic acid), resulting in the formation of three eutectic mixtures (EMs). Differential scanning calorimetry confirmed the formation of these eutectic mixtures, while the exact 50/50% w/w stoichiometry was determined through phase diagrams and Tamman's triangle. The interaction between the components and steric hindrances played a crucial role in eutectic formation. The EMs exhibited significantly increased apparent solubility (between five- to nine-fold) and a notable improvement in intrinsic dissolution rate (two- to three-fold) compared to the original drug. As a result, these solid forms of ET hold promise as viable multicomponent alternatives for further development as therapeutically effective products in the treatment of osteoarthritis.

Keywords: Anti-osteoarthritis; Solubility; Dissolution: Eutectics; Coformers

INTRODUCTION

Eutectic mixtures have garnered significant attention within the realm of pharmaceuticals due to their intriguing properties and potential applications. These mixtures, composed of two or more crystalline solids, exhibit a distinctive behavior wherein they are immiscible in their solid state but become miscible when in a liquid state (1)(2). The formation of eutectic mixtures is governed by a complex interplay of intermolecular forces, including hydrogen bonding, ionic interactions, van der Waals forces, and aromatic interactions. This unique behavior has led to their exploration as a means of addressing various pharmaceutical challenges. One of the key areas where eutectic mixtures have shown promise is in enhancing the solubility and dissolution characteristics of poorly water-soluble drugs. The low aqueous solubility of many active pharmaceutical ingredients (APIs) can severely

limit their bioavailability and therapeutic efficacy. Eutectic formulations offer a solution by creating novel composite materials that can dramatically improve the dissolution rates of these APIs, ultimately leading to more efficient drug absorption and enhanced therapeutic outcomes. Furthermore, eutectic mixtures can serve as a platform for tailoring drug delivery systems with improved performance(3,4). By manipulating the composition and properties of eutectic blends, optimization of drug release profiles, stability, and bioavailability can be done. This versatility makes eutectic formulations a promising avenue for developing innovative pharmaceutical products, ranging from conventional oral dosage forms to advanced delivery systems like nanoparticles and solid dispersions. Osteoarthritis is a progressive condition of the joints that impacts a significant number of individuals worldwide. It emerges when the protective cushioning cartilage covering the ends of bones deteriorates gradually over time. This process leads to discomfort, inflexibility, and restricted movement in the impacted joint (5–7). Additionally, osteoarthritis places a considerable strain on healthcare systems and economies. It contributes to escalated healthcare expenses, involving expenditures on medical consultations, medications, and surgical procedures like joint replacements(8). Furthermore, it has the potential to result in absenteeism from work and decreased efficiency, affecting both individuals and society on the whole.

Etodolac is categorized as a class II drug with low solubility, according to the Biopharmaceutics Classification System (BCS). Additionally, ET was observed to fulfill the criteria for low solubility as defined by the BCS classification. Several tactics, such as combining substituted cyclodextrins (9), bile acids, and chitosan, forming salts with alkali (10), drug-drug cocrystallization, and producing solid dispersions of ET with a water-soluble carrier, have been employed to tackle this concern. Nevertheless, while amorphous systems are prone to losing their structure and crystallinity through solid dispersion, which may lead to stability issues, salt formation increases solubility and dissolution rate with some limitations. Consequently, it is imperative to devise an innovative alternative strategy to overcome these constraints.

The current investigation centers on the mechanical synthesis of composite solid structures involving ET alongside specific coformers. These coformers, namely Syringic Acid (SYR), Ascorbic acid (ASC), and nicotinic acid (NICA), possess complementary functional components. Notably, they exhibit notable solubility and have documented antioxidant attributes that provide protection against oxidative stress and display anti-inflammatory effects in the context of osteoarthritis(11). Initial findings suggest that the co-milling of the drug with these coformers yields eutectic blends. These blends have been subjected to analysis and assessment regarding their apparent solubility and intrinsic dissolution rate.

EXPERIMENTAL

Materials

The current investigation involved the selection of the anti-osteoarthritic drug Etodolac for the study. A gift of Etodolac was provided by Sun Pharma Private Ltd., India, with a purity level exceeding 98%. Syringic acid (in an anhydrate form) and Ascorbic acid (also in an anhydrate form) were procured from Himedia Labs, India. Additionally, Nicotinic acid (in an anhydrate form) was sourced from Loba Chemie Pvt. Ltd., Mumbai. The solvents Ethanol, acetonitrile, and methanol were acquired from E. Merck (India) Ltd., Mumbai.

Preparation of Eutectics

Drop-wise solid state assisted grinding technique was used for the synthesis of the eutectics. Etodolac and the respective coformers were triturated in a pestle mortar assisted by the addition of catalytic amounts of Ethanol (2ml) for 40 min. Etodolac and selected coformers (SYR, ASC, and NIC) were individually weighed in different compositions (90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, and 10:90 % w/w). The eutectics were formed with syringic acid (ETSYR), ascorbic acid

(ETASC), and nicotinic acid (ETNIC) which were stored under dry and airtight conditions in desiccators till further analysis.

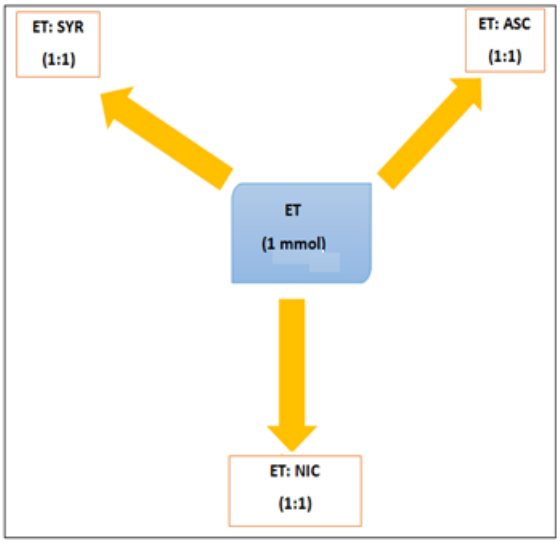

Figure: 1 Schematic representation of the preparation of eutectics of ET

Differential Scanning Calorimetry (DSC)

The DSC thermograms were acquired using a Q20 instrument (manufactured by TA Instruments Waters LLC, USA), equipped with a cooling assembly. The instrument's temperature and heat flow accuracy were calibrated using the melting point of pure indium (156.6 °C) and its heat of fusion (25.45 Jg-1). A precisely measured quantity (5-7 mg) of the specimen was carefully placed in a sealed aluminum pan. The pan was then subjected to scanning with a heating rate of 10 °C per minute while being purged with nitrogen at a flow rate of 50 mL per minute. The temperature range for the sample's heating was set from 40°C to 350°C. To manage the data, the TA Q series Advantage software (Universal Analysis 2000, USA) was employed.

Hot Stage Microscopy

For obtaining microscopic images of the prepared Eutectic Mixture under controlled temperature conditions, a NIKON ECLIPSE-LV100NPOL microscope with an integrated hot stage and TMS 94 temperature controller from Linkam Scientific Instruments Ltd. was utilized. The hot stage was employed to mount the eutectic mixture. The samples underwent a controlled heating process, beginning from 50°C and rising to 100°C at a rate of 10°C per minute. Subsequently, the temperature was increased to 125°C at a rate of 5°C per minute while observing under a microscope at 10X magnification. Upon reaching 125°C, the heating rate was raised to 10°C per minute, then to 150°C per minute, and finally reduced to 5°C per minute as the temperature reached 200°C.

Powder X-ray diffraction (PXRD)

Powder X-ray diffraction (PXRD) measurements were conducted using an X-ray diffractometer (XPERT-PRO, PANalytical, Netherlands) equipped with a Cu tube anode, which emitted CuKα radiation at a wavelength of 1.54060 Å. The sample was illuminated under the following conditions: a tube voltage of 45 kV and a current of 40 mA, with the divergence slit and anti-scattering slit both set to 0.48°. Approximately 200 mg of the sample was carefully placed in an aluminum sample holder and subjected to scanning within a 2θ range spanning from 2° to 50°. The scanning process involved a step size of 0.017° and a dwell time of 10 seconds. The resulting PXRD patterns were analyzed using the X'PERT High Score software.

Fourier transform infrared (FTIR) spectroscopy

The FT-IR spectra of the drug and coformers were contrasted with those of the prepared samples. An FTIR spectrometer, specifically the Spectrum RX II model from Perkin Elmer, England, was

employed in the diffuse reflectance mode to capture the infrared vibrations exhibited by the samples. An anhydrous powdered sample, weighing approximately 2-4 mg, was evenly distributed within dry KBR, amounting to around 20 mg. This mixture was then carefully ground using a pestle and mortar before being compressed manually into a thin pellet using a press. Subsequently, the data collected was subjected to analysis utilizing Spectrum software.

High-Performance Liquid Chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) analysis was conducted to determine the concentration of ET. The measurement utilized a Waters HPLC system with an autosampler and an LC-10 AT pump. Detection was performed using a PDA detector (Waters 2996) in conjunction with a C18 Hypersil Gold column (Thermofisher, USA) measuring 4.6 mm × 250 mm with a particle size of 5 µm, which facilitated analyte separation. Empower 2 software was employed for data acquisition and analysis. To create the calibration curve, various dilutions of ET were prepared. The quantitative analysis of etodolac in all the eutectics was carried out using the mobile phase acetonitrile and orthophosphoric buffer in70:30 ratio. This solvent mixture was pumped through the column at a flow rate of 1.0 mL/min. Before use, the mobile phase was filtered through a 0.45 µ Millipore filter and degassed. The detector was set to measure wavelengths at 206 nm.

Scanning Electron Microscopy

The morphology of individual particles within the pure components and eutectic mixtures (EMs) was investigated through the utilization of a scanning electron microscope (JSM-6100; Jeol, Peabody, MA, USA). To prepare the samples for imaging, they were affixed onto a metal stub using adhesive tape. Subsequently, a thin layer of gold was applied under vacuum conditions using an ion splitter (JFC-1100) for coating purposes.

Apparent solubility studies

The assessment of the solubility of Etodolac (ET) and its prepared eutectic mixtures was carried out using the shake flask technique as outlined by Higuchi and Connors in 1965 (Higuchi and Connors, 1965). In this approach, an excessive quantity of ET (approximately 50 mg) and its eutectic mixtures was combined within a vial containing 5 mL of phosphate buffer with a pH of 6.8(12). The mixture underwent agitation for 24 hours utilizing a water bath shaker operating at 200 RPM and kept at a temperature of 37 °C. After agitation, 0.2 mL of the resulting slurry was filtered through a 0.45 µm membrane filter. The filtrate was then diluted by a factor of 10, and the quantification of OXN was performed through high-performance liquid chromatography (HPLC). The outcomes of the solubility analysis were expressed as mean ± standard deviation (SD) values.

Intrinsic Dissolution Studies

The intrinsic dissolution assessments for ET, and its eutectics were conducted utilizing a rotating disk dissolution test apparatus within a phosphate buffer environment at pH 6.8 for ET, maintained at 37°C and 150 rpm for a duration of 24 hours. Initially, an HPLC-based standard curve for the drugs was established. To ensure consistent particle size, all samples were homogenized by passing through a Gilson mesh sieve no. 80. Subsequently, 100 mg of the sample pellets were placed in a die cavity, and a benchtop carver press was employed for 1-2 minutes under 2000 psi pressure to achieve uniformity. The base plate was detached from the die, generating a densely compacted pellet exhibiting a surface area of 0.5 cm2. A neoprene gasket was fitted around the threaded portion of the die, which was then affixed to the shaft holder. This assembly was connected to the stirring drive mechanism of the dissolution apparatus. Before installation, the dies were immersed into the dissolution vessel containing 500 mL of phosphate buffer. At predetermined intervals (5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, and 1440 minutes), aliquot samples (5 mL) were withdrawn from the solution (with subsequent replacement), then subjected to filtration through a 0.45µm membrane filter, and eventually subjected to analysis using high-performance liquid chromatography(12,13).

RESULT AND DISCUSSION

Designing and preparation of eutectics of etodolac

The presence of carboxylic group in the ET (Figure 2 a) make it a potential candidate for the formation of multicomponent solid forms due to its propensity to generate new networks with the coformers as given the previous literature studies. It is well established that antioxidants also play an essential role in reducing pain, inflammation and immune function which occur due to the arthritis. Furthermore, they also provide protection against cartilage damage and reduction in tumor necrosis factor-α (TNF-α) associated with osteoarthritis rheumatoid arthritis(14). Therefore, it was planned to use some of the molecule having antioxidant potential as coformers to create non covalent bonds of the ET that may fulfils desired goals like improving biopharmaceutical performance along with healing the inflammation in joints(15). In this regard syringic acid, nictonic acid and ascorbic acid (Figure 2 b) was subjected to thermo analytical techniques. The ground product of drug with coformers revealed all of them to be eutectics. All of these prepared eutectics ETSYR (etodolac: syringic acid), ETNIC (etodolac: nicotinic acid) and ETASC (etodolac: ascorbic acid) were further characterized by other thermal methods.

The eutectics were primarily distinguished by a lower melting endotherm in DSC. Eutectics also had a distinctive V-shaped binary phase diagram and no apparent alterations in the FT-IR and PXRD.

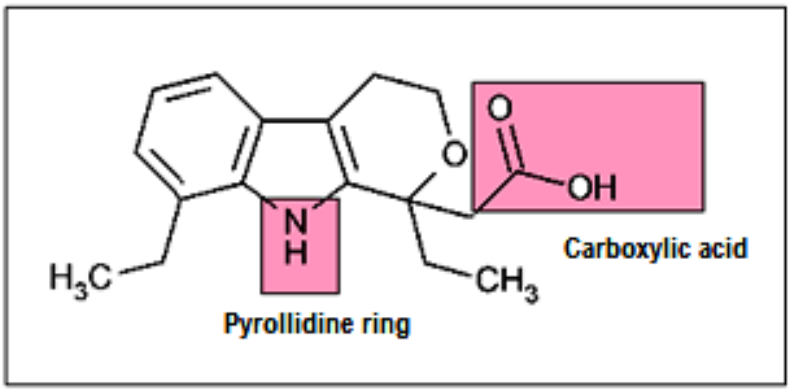

Figure 2 (a) Chemical structure of ET with potential functional group.

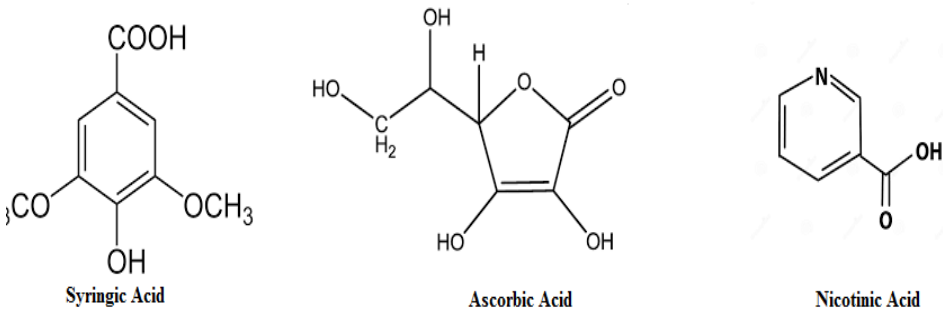

Figure 2 (b) Chemical structure of coformers which produced eutectics with ET

Thermal characterization

Differential Scanning Calorimetry

DSC is the utmost essential thermal tool for characterization and confirmation of existence of eutectic mixtures. All the DSC thermograms for etodolac, the conformers and eutectics (ETSYR, ETASC and ETNIC) are shown in Figure 3 (a-c).

In case of ETSYR, Figure 4(a) represents the melting endotherm for pure etodolac and syringic acid at151°C and 207.09°C, respectively. However, in the different binary compositions consisting of ET

and SYR, as the ET concentration is gradually enhanced from 10% molar composition, another endotherm appeared at 118.76°C Figure 4(a). As the composition of ET was further increased, this lower melting endotherm in composition containing etodolac: syringic acid emerged at 118.76°C (10:90), 120.01°C (20:80), 122.68°C (30:70) and 124.21°C (40:60) [Figure 4(a-j)]. Melting endotherm corresponding to pure SYR also shifted from 207°C to 192.03°C, 178.08°C, 159.22°C and 143.73 as the compositions of etodolac: syringic acid varies from 10:90, 20:80, 30:70 and 40:60 molar ratios. After this point, with the rise in concentration of etodolac to 50%, a single endothermic peak appeared at 120.65°C Figure 4(d) which indicate the formation of eutectic.

With the further increase the percentage of ET in the binary mixture up to 60% and beyond, the melting endothermic peaks kept on appearing at temperatures i.e., 129.76 °C, 138.38°C, 142.42°C, 146.08°C and 184.01°C corresponding to (60:40) [Figure 4(e)], (70:30), (80:20) and (90:10) molar compositions of etodolac.

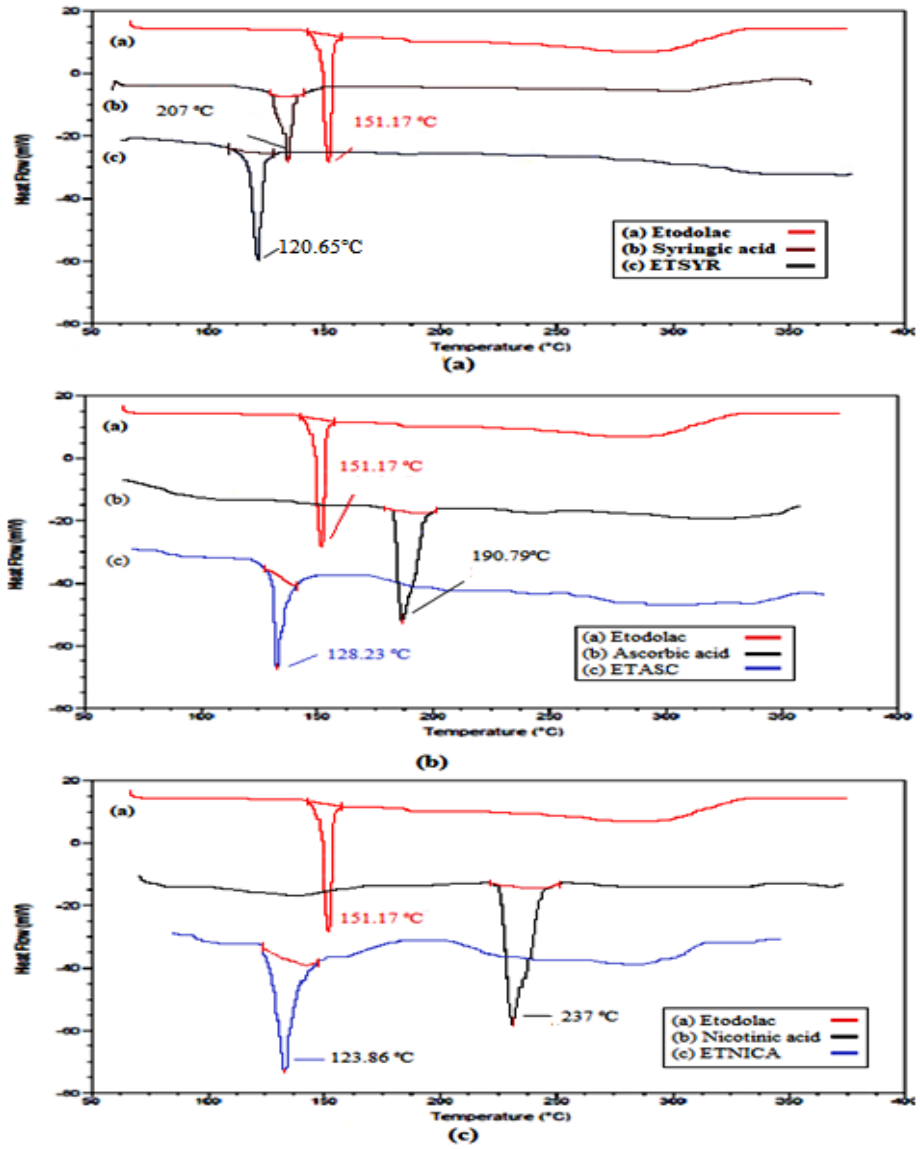

Figure 3: DSC thermograms of (a) ETSYR (b) ETASC (c) ETNICA

These melting endotherms, however, were accompanied by a new endotherms appearing at 123.87°C, 124.57°C, 125.43°C and 126.98°C corresponding to, 60:40, 70:30, 80:20 and 90:10 compositions of ET and SYR respectively are due to excess of unreacted ET.

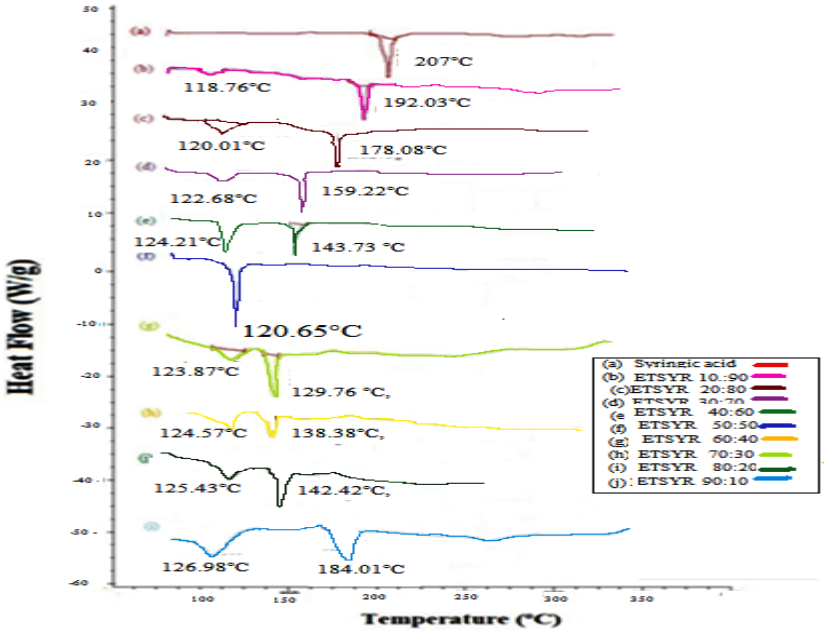

Figure 4: DSC thermograms of syringic acid and all compositions of ETSYR

The various endothermic peaks are explained in Figure 4(a-i) and there is a clear comparison with those of pure ET (Figure 4 a) and SYR (Figure 4j) The position of low melting endotherm is constant in all the compositions and is known as the solidus. The 50:50 composition of etodolac: syringic acid representing a single eutectic endothermic peak is the true stoichiometry at which this eutectic ETSYR is produced. Thus, the existence of low melting endotherm in DSC, the lack of the new peaks and reappearance of constituent's peaks in FT-IR and PXRD spectrum of the eutectics is a further confirmation for the formation of eutectic phase.

Similarly, the eutectic ETASC, (Figure 5) the low melting melting endotherm appeared at 121.13°C, 120.48°C, 119.25°C, 117.08°C as the ratio of ET and ASC varies from (10:90,20:80,30:70,40:60 and 50:50). One single melting endothermic peak corresponding to 60:40 appeared at 128.23°C which is recognized as the invariant solidus point of ETASC and lower than both the etodolac (m.p= 151.71°C) and ascorbic acid (m.p=190.79°C).The enthalpy of eutectic is highest in this composition. After that the peak corresponding to ASC appeared at 118.23°C, 120.15°C, 120.85°C and 121.81°C.

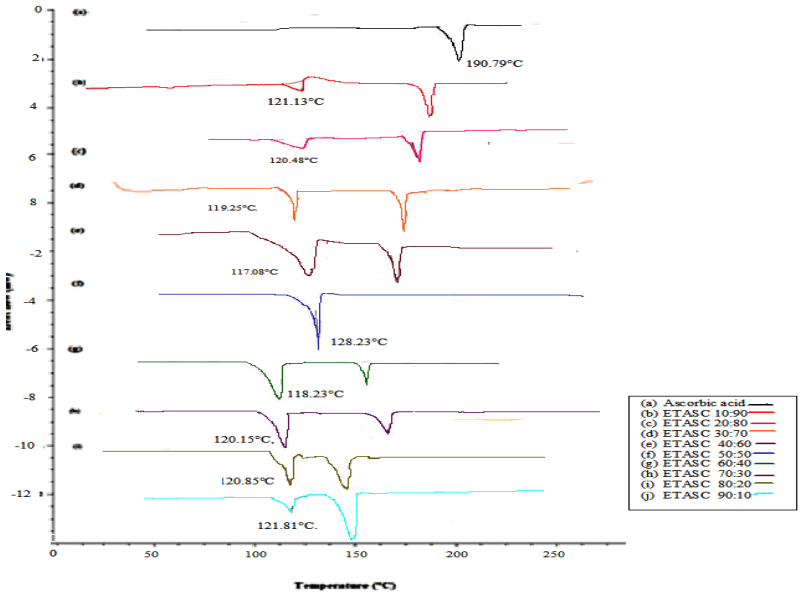

Figure 5: DSC thermograms of ascorbic acid and all compositions of ETASC

Likewise in eutectic ETNIC (Figure 6) the lower melting endothermic peaks emerged at 121.13°C, 120.49°C, 119.25°C and 117.08°C corresponding to (10:90, 20:80,30:70,40:60) composition of etodolac and nicotinic acid. The 50:50 composition of etodolac: nicotinic acid exhibit one single eutectic endotherm at 123.86 °C which is identified as the solidus point of ETNIC and found to be lower as compare to both the constituents. This composition also acquires the maximum enthalpy of fusion of the eutectic phase.

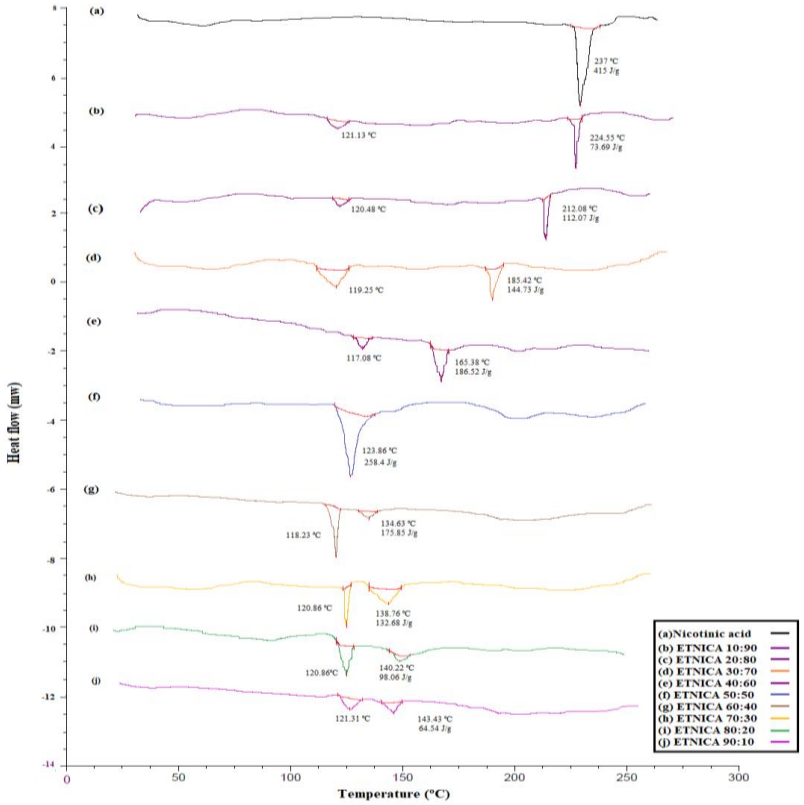

Figure 6: DSC thermograms of nicotinic acid and all compositions of ETNICA Binary phase diagrams.

Binary phase diagram are plotted mainly to find out the point at which the two lines due to variable liquidus temperature unite at a point, on the line formed by the solidus temperature or eutectic melting points. The actual composition of this eutectic is the one with only one melting eutectic endotherm matching to the solidus point(16). This point of convergence is known as the eutectic's true stoichiometry. So, for all the three eutectics binary phase diagrams were created by plotting temperature vs. mole fraction of etodolac, to obtain a distinctive V shaped binary phase diagrams for the eutectics.

Solidus is the invariant single common melting point that emerges in nearly all compositions at around the same temperatures(17). These other compositions, on the other hand, have an additional melting endotherm corresponding to unreacted and surplus reactants, which has a variable temperature and is referred to as the liquidus point for all compositions(18).

The binary phase diagrams were created after utilizing all the compositions which are represented in Figure 7, Figure 8 and Figure 9. Two of the eutectics under study were ideal in nature and showed melting point depression for 50:50 molar ratiosat 120.65°Cfor ETSYR, 123.86°C for ETNICA and 128.23°C for ETASC in 60:40 molar ratios respectively.

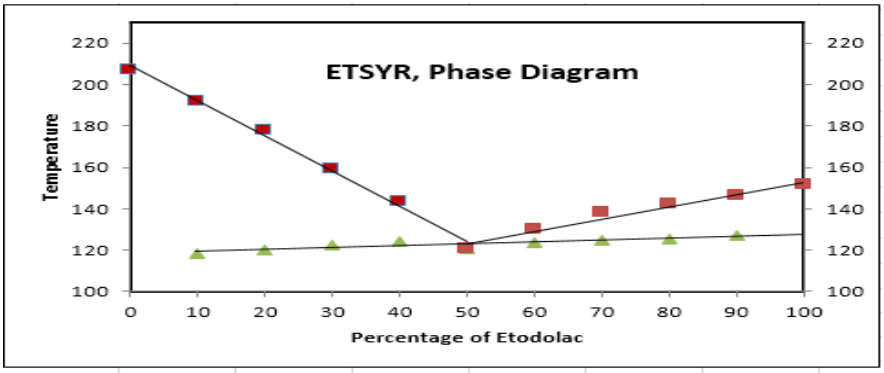

Figure 7: Binary phase diagram of EYSYR

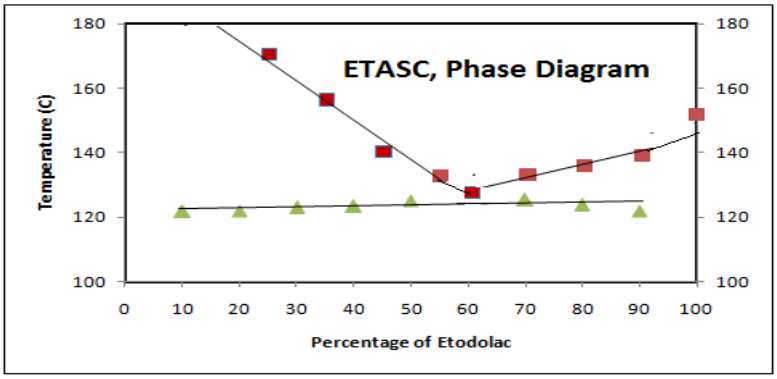

Figure 8: Binary phase diagram of ETASC

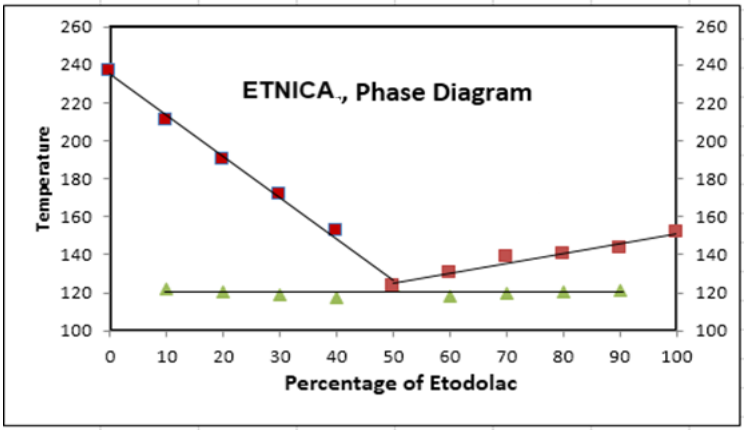

Figure 9: Binary phase diagram of ETNICA

Tammam's triangle

The composition of the pure eutectic as well asshowing a single endotherm in DSC with no additional aberrations owing to any residual mixture, has the maximum enthalpy of fusion of eutectic(19). The binary phase diagram, as previously stated, first identifies this point of maximum enthalpy as the solidus point with no liquidus temperature. So there is no excess or unused reactant.The enthalpy of fusion of eutectics phaseΔH_{fusion} (KJ mol^{-1}) found for all eutectics in entire compositions is plotted against the percentage of etodolac on the X axis to create a particular graph known as Tammam's triangle. Furthermore, it gives rise to an inverted v shaped graph with the tip showing the maximum enthalpy of fusion [$\Delta H_{fusion\ (eutectic)}$] for the true pure eutectic.

In eutectic ETSYR, the Tammam's triangle (Figure 10) supports the result of binary phase diagram by representing that the composition with 50:50 etodolacsyringic acid at the apex, having maximum enthalpy of fusion of eutectics [$\Delta H_{fusion(eutectic)}$] at 334.05J/g,.

In the eutectic ETASC Tammam's triangle (Figure 11) depicts the stoichiometry of 50:50 of etodolac: ascorbic acid, as the one with maximum enthalpy of fusion eutectic ([$\Delta H_{fusion(eutectic)}$] at 362.85 J/g, among all the compositions.

In the eutectic ETNICA Tammam's triangle (Figure 12) illustrates the stoichiometry of 60:40 of etodolac: nicotinic acid, to possess maximum enthalpy of fusion of eutectic [$\Delta H_{fusion(eutectic)}$] of 258.4 J/g, among all the compositions.

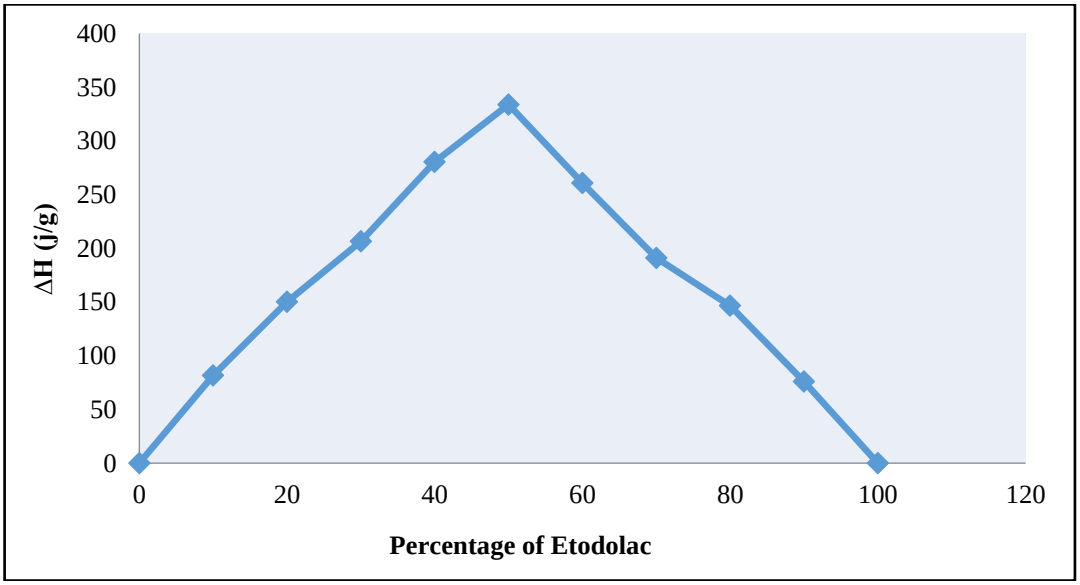

Figure 10: Tammam's triangle of ETSYR

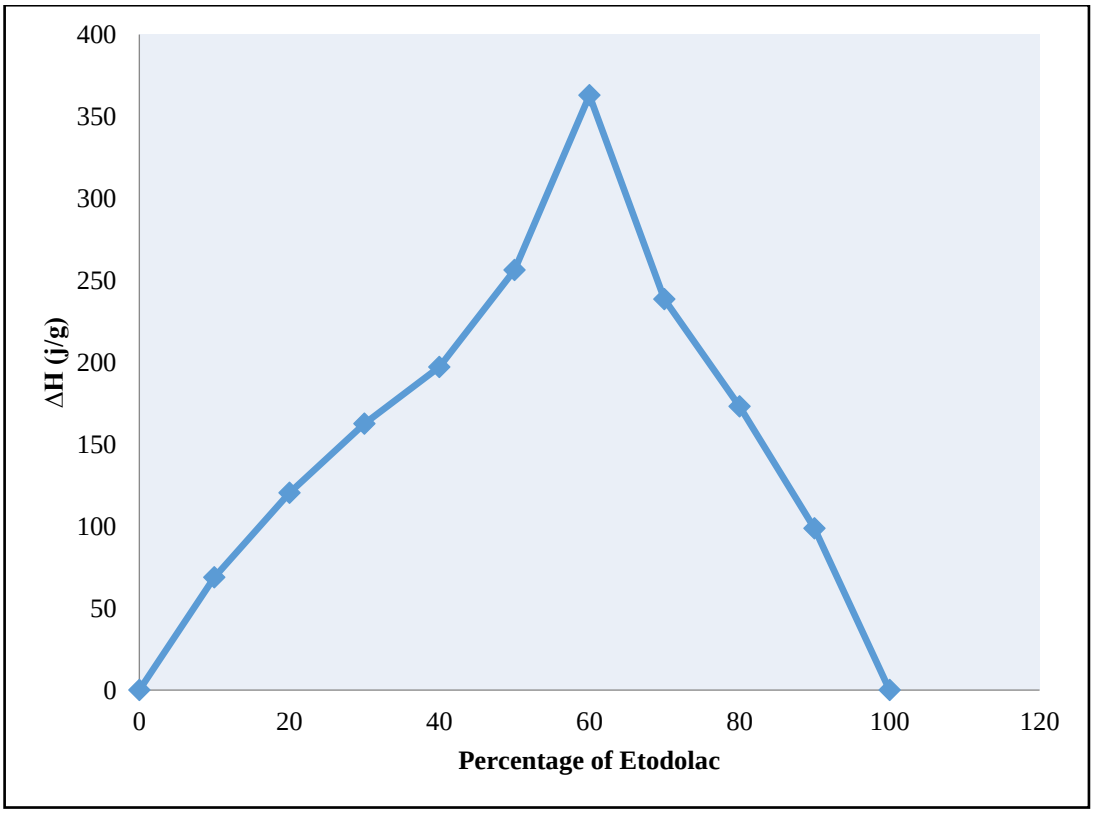

Figure 11: Tammam's triangle of ETASC

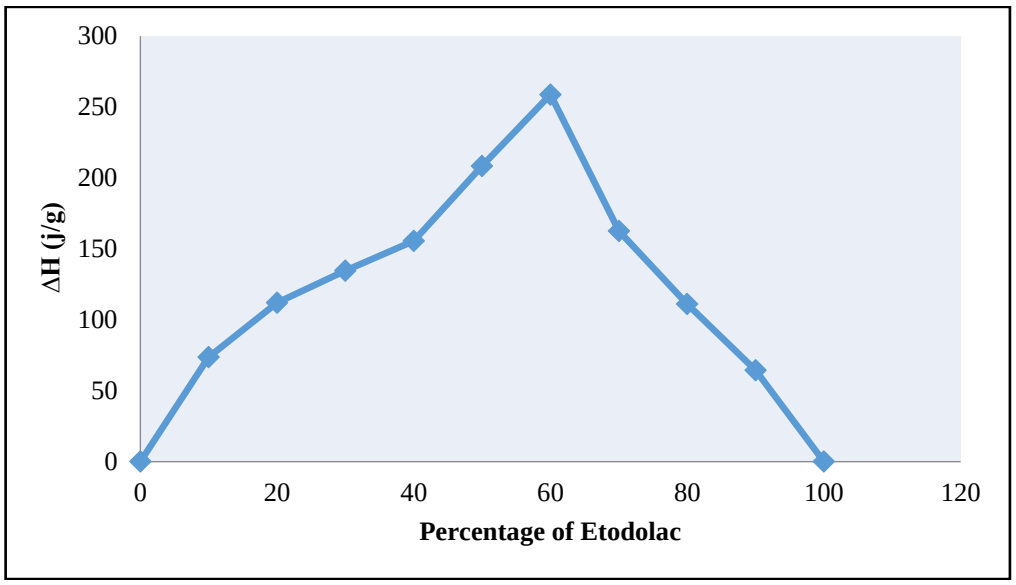

Figure 12: Tammam's triangle of ETNICA

Hot stage microscopy

This technique is based on the commonly held maxim of converting solids to liquids via an endothermic fusion process which fuelled by the absorption of latent heat of melting at their melting point temperature in the eutectic system, this transformation is quite complicated because these seemingly single crystalline entities have two distinctly dissimilar crystalline molecules in their microenvironment, each one with their own intact lattice arrangement, lies in close proximity which are stabilized mutually by weak non covalent forces. The extensive, complete melting endotherm is indication of a pure single entity whereas variable melting temperature pointing towards the partial conversion to eutectic with residual surplus preliminary substance.

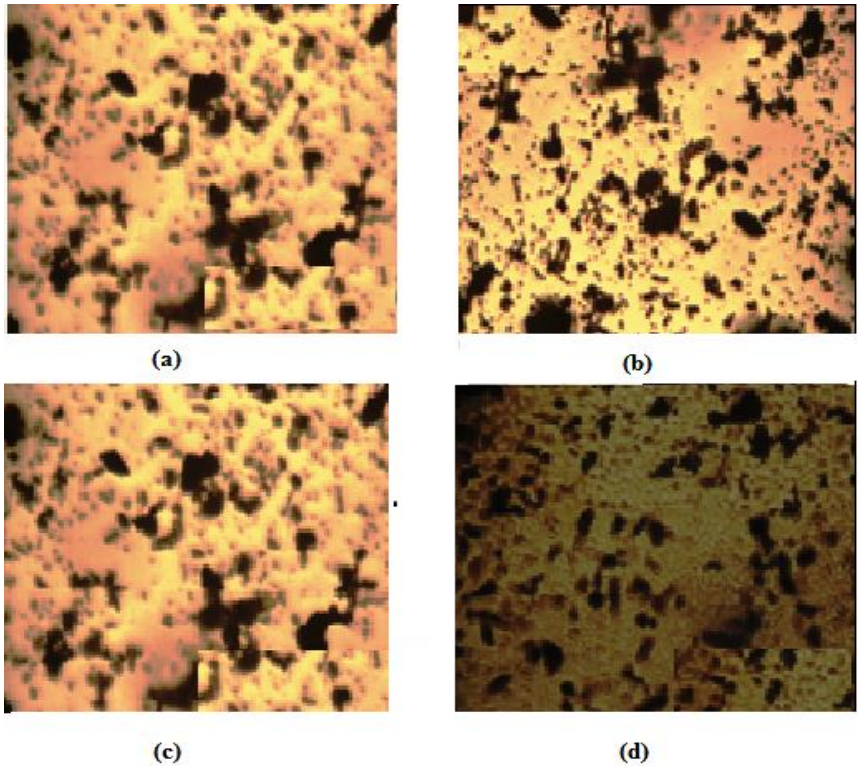

Figure 13: ETSYR before melting, (b) ETSYR starting to melt, (c) ETSYR melting at 120.65°C and (d) ETSYR fully melted

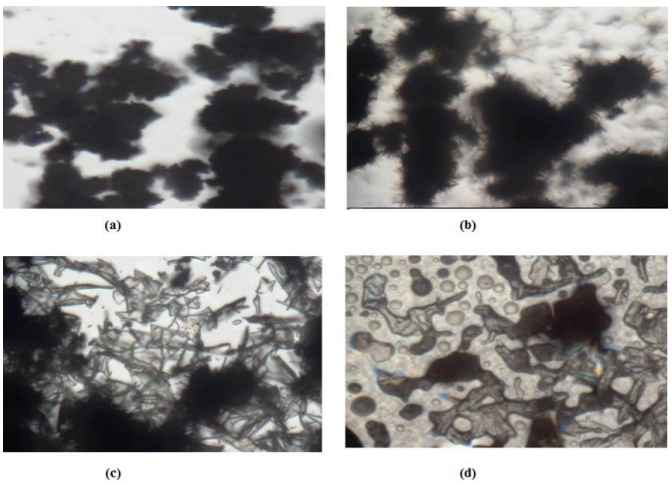

Figure 14: ETASC before melting, (b) ETASC starting to melt, (c) ETASC melting at 123.86°C and (d) ETASC fully melted

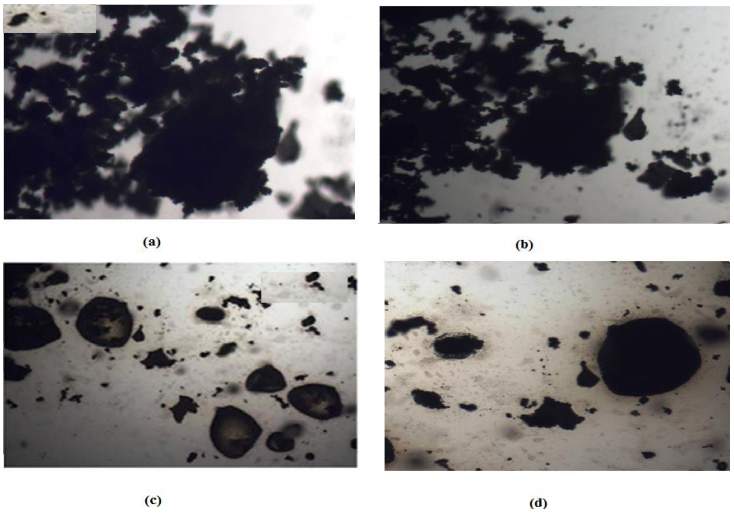

Figure 15: ETNICA before melting (b) ETNICA starting to melt (c) ETNICA melting at 128.23°C (d) ETNICA fully melted

Figure (13), Figure (14), and Figure (15) represent the melting of ETSYR, and ETASC with complete and uniform melting around 120.65°C, 123.86°C and 128.23 °C respectively.

PXRD and FTIR analysis

The vibrational spectroscopic method like FT-IR along with the X-ray diffraction technique are essential analytical means to successfully analyze and characterize the solid-state microstructure of any substance. Each spectroscopic method has a specific threshold or the minimum value of detection below which it is not capable to enlist the deviations in the strength of interactions or the changes in the structures for chemical interpretation(20).

The FT-IR evaluation of eutectics, ETSYR, ETASC, and ETNICA showed vibrational frequencies without any significant changes (Figure 16). Even if there is a shift in any of the frequencies, they are ignorable and are not to be associated with any considerable structure change. Likewise, the X-ray diffraction techniques were also ineffective and inconclusive as the existence of the minor component in the matrix of the major component either interstitially or substitutionally, without any bonding did not result in any significant changes in the characteristics 2θ values concerning the parent molecules (Figure 17). Therefore, powder X-ray diffraction data was of not much support as no new peaks appeared in all eutectic mixtures and none of the peaks were missing. The production of a single crystal of eutectic mixtures was quite impossible through the solution crystallization method, most

likely due to the dissimilar or contrasting solubility of the two components in the solvent which caused them to crystallize out at different points. Besides this, the eutectics also had weak interactions and unfulfilled bonds that inhibited it from crystallizing out as a single crystal.

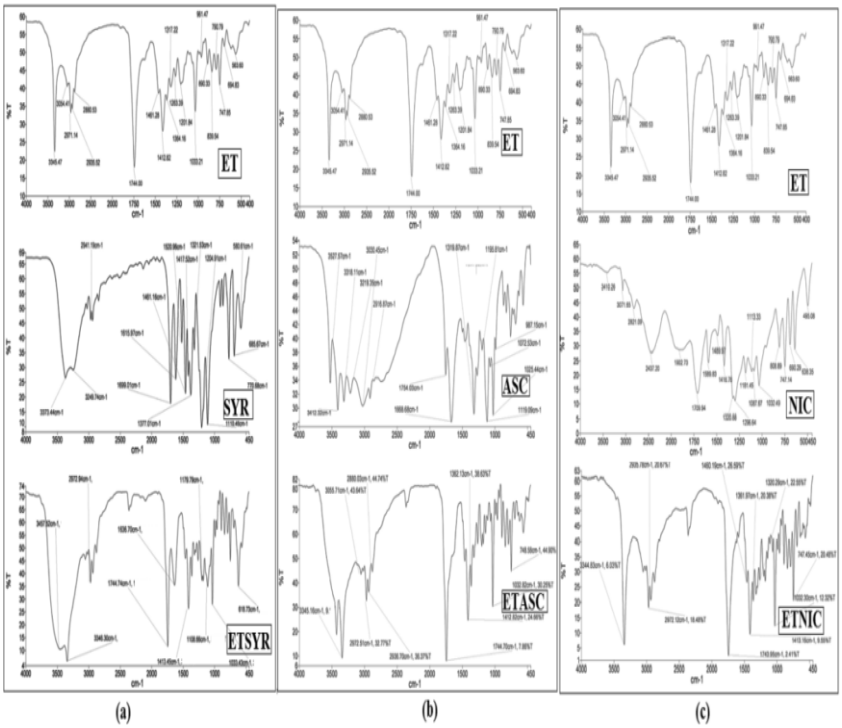

Figure 16: FTIR spectra of Etodolac (ET), Coformers (SYR, ASC, and NIC), and corresponding eutectics (ETSYR, ETASC, and ETNICA)

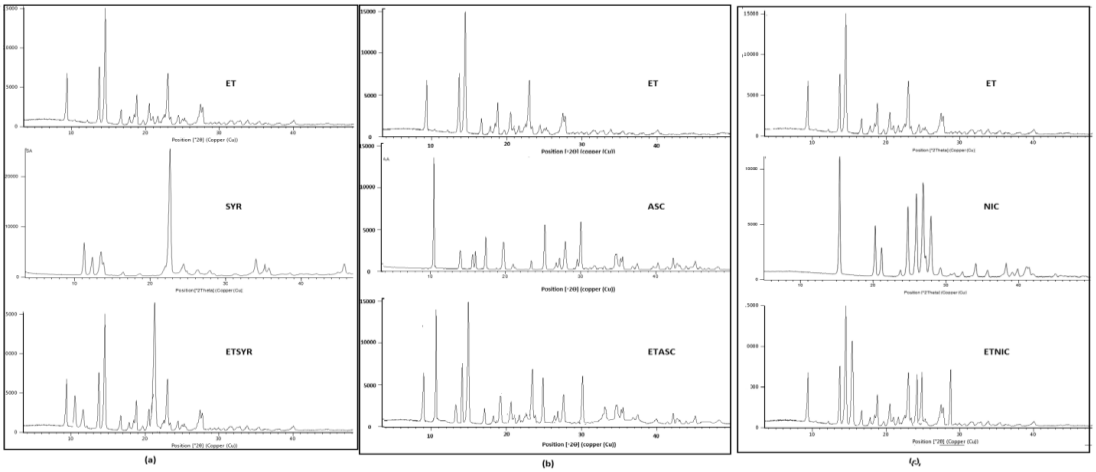

Figure 17: PXRD pattern of Etodolac (ET), Coformers (SYR, ASC, and NIC), and corresponding eutectics (ETSYR, ETASC, and ETNICA)

Scanning Electron Microscopy

The SEM image results perfectly illustrate the morphological characteristics of etodolac, the coformers (syringic acid, ascorbic acid, and nicotinic acid) as against the eutectics which have specifically different morphology offers a beneficial tool in identifying the eutectics as distinct entities from their original molecules (11). Figure 18 represents variable particle shapes *viz.* aggregated flaky, irregular cluster-shaped crystals (ET) and a size ranging from 15-20 µm in size. Similarly, syringic acid (SYR) is seen as a small needle shape with sharp edges of around 5-20 µm in size, ascorbic acids as plate crystal (ASC) which varies from 20-100 µm and nicotinic acid as elongated columnar Globular type crystal which varies in 100-200 µm. The analysis of the eutectics under a scanning

electron microscope displayed adequate changes as compared to the parent molecule. The crystals of ETSYR shows an irregularly shaped cluster of crystal in the size range of 5-10 µm, and ETASC and ETNICA appear to the agglomerates of irregularly shaped crystals with no well-defined shape ranging from 20-100 µm in size.

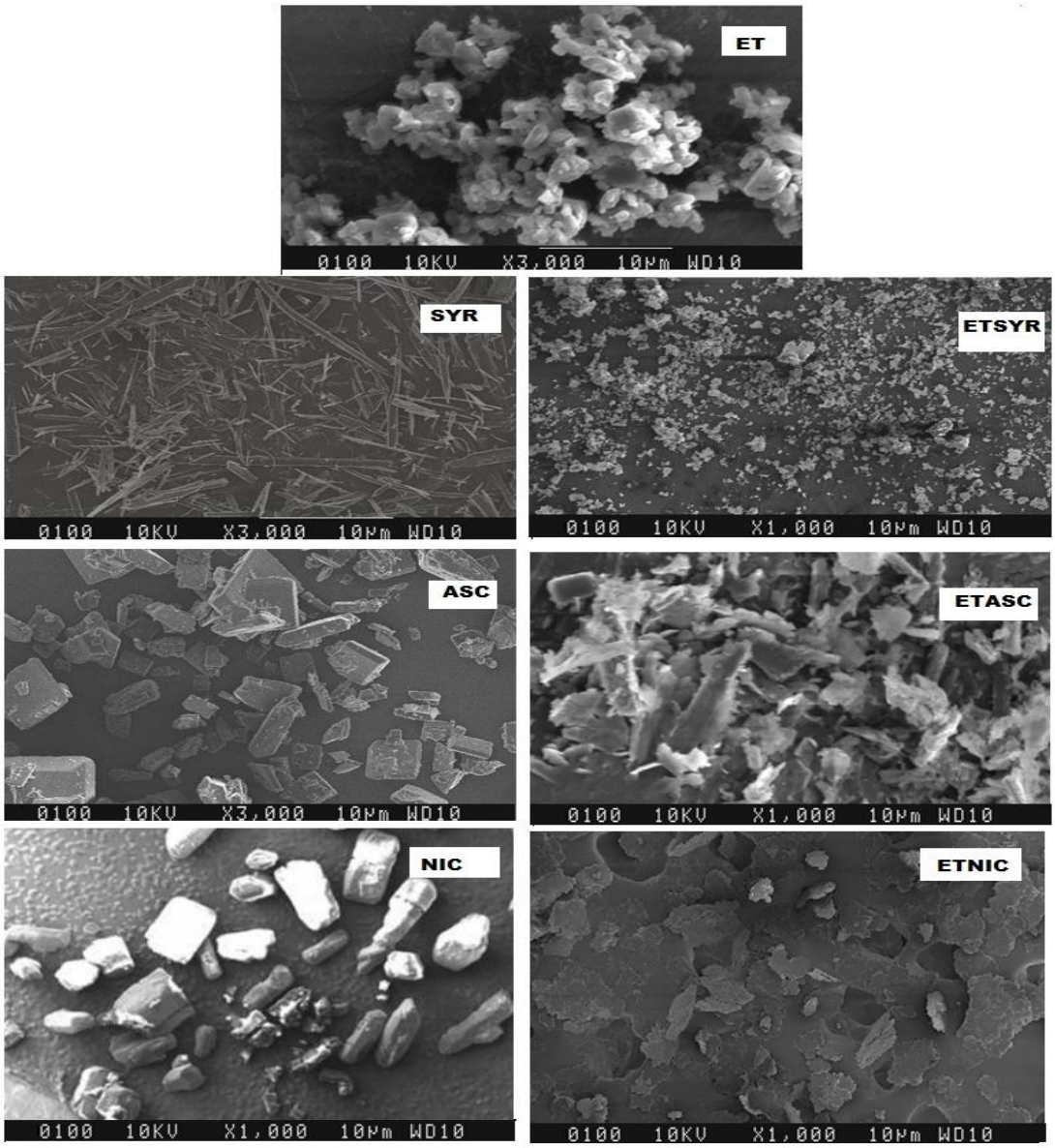

Figure 18: Scanning electron microscopy images of Etodolac (ET), Coformers (SYR, ASC, and NIC), and corresponding eutectics (ETSYR, ETASC, and ETNICA)

Apparent solubility and dissolution studies

Apparent solubility and dissolution studies of the eutectic mixtures of ET were performed in phosphate buffer pH 6.8 at 37°C. Maximum absorption of etodolac during oral administration is from the intestine and therefore this condition imitates the intestinal condition of humans. Quantification of ET and its eutectic mixture was done by HPLC as discussed in the experimental section. All EMs showed significant solubility improvement and IDR which follows the order: ETNICA>ETASC>ETSYR >ET. The solubility studies reveal that the ETNICA eutectic is almost 8.7 times more soluble than parent ET followed by the ETASC eutectic which is 6.1 times more soluble. It is followed by ETSYR which is 4.1 times more soluble throughout most of the experiment. Maximum solubility (S_{max}) and dissolution profile are given in Figure 19 and Figure 20) whereas numerical values of solubility are mentioned in Table 1. The results of solubility studies were

determined after 4 hours as well as after 24 hours. The maximum solubility levels were achieved for the eutectic after 180 mins for ETASC, and ETSYR whereas maximum solubility for ETNICA was observed after 200 mins. This is associated with the surplus thermodynamic functions of eutectics due to high free energy, weaker intermolecular interactions, and greater molecular mobility between the binary constituents. The difference in increased solubilities in different eutectics mixtures is attributed to the differential intrinsic solubility of the coformer. Similarly significant improvement in the dissolution rate in EMs is attributed to the dispersibility of the drug in the hydrophilic coformer and enhanced wettability owing to the solubilization of the coformer that accelerates faster dissolution of the drug in the media. Coformer intrinsic solubility has a greater influence on the solubility of the complex in a multi-component system. In the present study, coformer with high aqueous solubilities such as NIC exhibited a better solubility profile of eutectic mixtures as compared to other coformers (ASC and SYR).

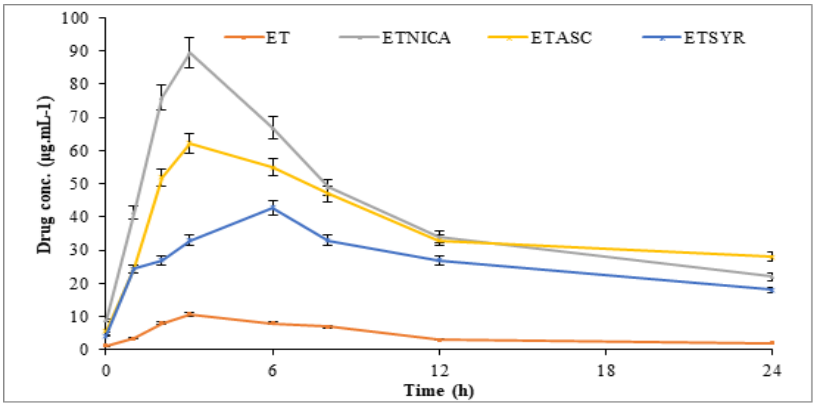

Figure 19: Apparent solubility of etodolac and its respective eutectics

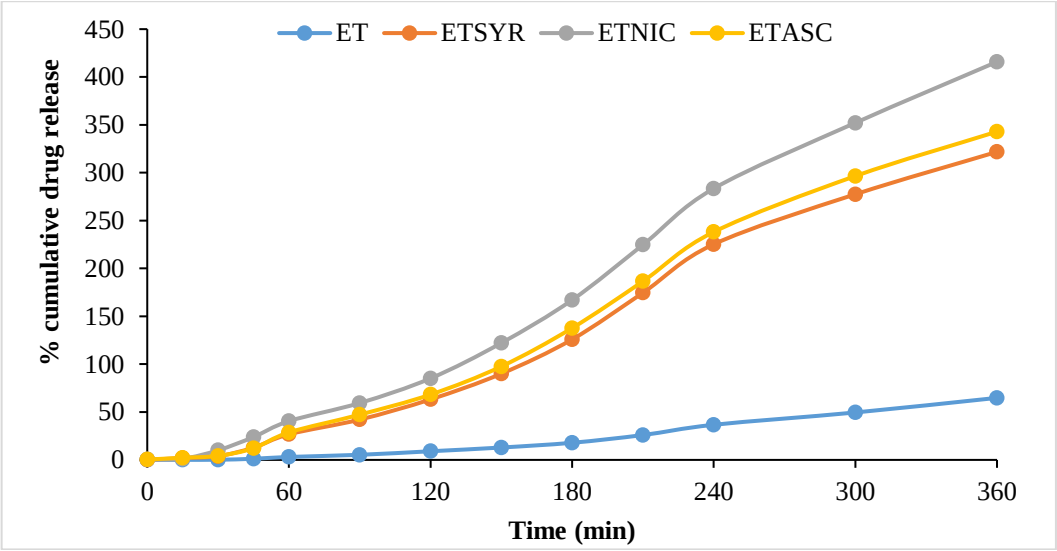

Figure 20: Dissolution profile of etodolac and its respective eutectics

Table 1: Solubility of etodolac and its respective eutectics

Drug/eutectic mixture	Solubility (µg/ml)
ET	10.3±0.02
ETNICA	90.1±0.12
ETASC	61.09±0.3
ETSYR	42.1±0.12

Conclusion

The current study has successfully utilized a mechanochemical approach to create three different eutectic mixtures (EMs) of etodolac, incorporating antioxidant coformers namely syringic acid, ascorbic acid, and nicotinic acid. The absence of molecular interactions and structural barriers led to the formation of eutectic blends between the two components, a conclusion supported by FTIR and PXRD analyses. These EMs, representing multi-component solid configurations of irbesartan, offer a twofold benefit: enhanced biopharmaceutical attributes and significant antioxidant properties compared to the unmodified drug form.

The promising outcomes from this preclinical investigation serve as a motivating factor and suggest the potential for further exploration through extensive clinical trials. It's important to note that significant endeavors will be required to transition these EMs to a commercial scale. Notably, the twin screw extrusion technique has recently emerged as an effective alternative to mechanochemical synthesis, enabling the production of various high-quality pharmaceutical products. Consequently, this method could play a pivotal role in upscaling the production of these EMs.

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